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Practical guidance for procedures related to Brexit for medicinal products for human use approved via MRP/DCP

On June 19, 2018, the European Commission and CMDh published an updated **Notice** to marketing authorisation holders of national authorised medicinal products for human 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 a ratified withdrawal agreement[1] establishes another date, 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'."

Preparing for the withdrawal is therefore not just a matter for EU and national authorities, but also for private parties.

In view of the considerable uncertainties, in particular concerning the content of a possible withdrawal agreement, marketing authorisation holders of national authorised medicinal products for human use are reminded of certain legal repercussions, which need to be considered when the United Kingdom becomes a third country.

In order to consider the necessary changes, a list of Questions and Answers (Q&As) has been drafted by the CMDh and published on the HMA website taking into account the European Commission's and EMA's Questions and Answers on the same issues within the framework of the centralised procedure 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 medicinal products for human use approved via MRP/DCP approved via MRP/DCP need to ensure that the necessary changes are made by the 30 March 2019, unless indicated otherwise in the guidance below or subject to the terms of any withdrawal agreement. This guidance is also in line with the EMA's Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure but adapted to nationally authorised products approved under MRP/DCP.

This document complements the CMDh Q&A to provide procedural and practical guidance regarding the submission of changes.

1. For the switch of the RMS is it sufficient to have the DCP/MRP/RUP finalised or is it necessary to have already received a MA? If so, is it

sufficient to have the MA in the proposed new RMS available or is a MA needed in all CMS?

It is sufficient to have the DCP/MRP/RUP finalised with EoP.

2. How can I submit my RMS switch request?

The CMDh has provided a template for a request to switch the RMS (http://www.hma.eu/90.html). The template should be sent to the proposed new RMS. Email addresses are available from the contact points list, "Requests for RMS switch" (http://www.hma.eu/69.html).

3. When can I apply for a switch of the RMS and when can the switch be implemented?

The switch can be applied for at any point in time after the EoP in a new MAA. However, for the implementation of the switch all other pending regulatory procedures, e.g. variations, renewals, etc., have to be closed. MAHs should preferably discuss the availability and timing beforehand with the proposed new RMS.

4. What can I do if not all strengths have been approved in the proposed single new RMS?

The new RMS can only take over procedures for which a MA is approved in this country. If single strengths are missing in the proposed new RMS there is the possibility to add these MAs by applying for a RUP in the current RMS. Otherwise, the missing strengths have to be switched to a different RMS. It should be assured that the smallest possible number of new RMS is chosen. Furthermore, a worksharing variation could be envisaged to keep the harmonisation.

5. If there are several MAHs in one MRP/DCP which of them can apply for the switch of the RMS?

According to the definition all MAHs within the same procedure are regarded as the same MAH. Generally, it is the task of the MAH in the current RMS to initiate the process.

6. 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. All Brexit-relevant changes may be grouped (http://www.hma.eu/96.html).

7. 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		

[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.

Manufacturing process	Non-biological / non-immunological product	Biological or immunological product
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 6 “Can I group Brexit-related variations?”

8 What variation(s) shall I submit in case of a change of Notified body (previously from UK) for a medical device included in the pack?

For medicinal products that are co-packaged with medical devices (but do not form a single integral product at the time of placing on the market) it is required to include in their dossier evidence demonstrating that the device is CE marked.

The Notice from the European Commission to Stakeholders on Withdrawal of the United Kingdom and EU Rules in the Field of Industrial Products states the following:

> *Where economic operators hold certificates issued by a UK Notified Body prior to the withdrawal date and plan to continue placing the product concerned on the EU-27 market as from the withdrawal date, they are advised to consider either applying for a new certificate issued by an EU-27 Notified Body or arranging for a transfer – on the basis of a contractual arrangement between the manufacturer, the UK Notified Body, and the EU27 Notified Body - of the file and the corresponding certificate from the UK Notified Body to an EU-27 Notified Body, which would then take over the responsibility for that certificate.*

Therefore, for medicinal products that are co-packaged (but do not form a single integral product) with a medical device for which the conformity assessment to support the CE marking was performed by a UK Notified Body, it will be necessary to either update the MA dossier with evidence supporting the CE marking by a new Notified Body, or remove the medical device from the pack, or replace the device with an alternative medical device with a valid CE mark.

A medical device forming a single integral product with the medicinal product does not require a CE mark, therefore no submission of a new CE marking documentation is required.

The following scenarios, although not exhaustive, may apply to medicinal product packs containing medical devices for which the conformity assessment to support CE marking was performed by a UK Notified Body:

Medical device forming a single integral product with the medicinal product	Medical device is co-packaged with the medicinal product
Same medical device is maintained, but the Notified Body supporting the CE marking is changed	
Variation not required (CE marking not mandatory), but if documentation in the dossier is updated: Type IA_{IN} (B.IV.1.a)	Type IA_{IN} (B.IV.1.a)

[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.

Medical device forming a single integral product with the medicinal product	Medical device is co-packaged with the medicinal product
Replacement of the medical device with an alternative CE marked medical device	
Replacement not required (CE marking not mandatory), but if replacement is made: Type II (B.IV.1.c)	For device without significant impact on the delivery of the active substance: Type IA_{IN} (B.IV.1.a) For device with significant impact on the delivery of the active substance: Type II (B.IV.1.a)
Removal of the medical device from the pack	
Not applicable	Type IA_{IN} (B.IV.1.b)

9. 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 approved grouping examples (http://www.hma.eu/96.html):

- 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.

10. When should I submit Brexit related type IA ("do and tell") variations that have to be implemented before 30 March 2019?

Certain changes that have to be fully implemented before 30 March 2019 can be submitted as type IA variations. Considering the regulatory nature of type IA variations ("do and tell"), and in order to avoid the need to implement such changes even earlier, it is acceptable that corresponding notification of

type IA variation(s) is submitted no later than within 2 months after 29 March 2019 provided that the MAH is established in the Union (EEA) by that time.

Type-IA variations requiring immediate notification ('IA_{IN}') must in any case be notified (submitted) immediately following implementation of the change.

The MAHs are reminded that actual implementation of such changes must in any case take place before 30 March 2019, irrespective of the variation type.

11. 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 NCAs of changes to the QPPV or PSMF location by submitting a variation except in cases where there is a transfer of the MA to a new MAH. In those cases the new summary of the pharmacovigilance system still has to be submitted by a type IA IN variation under C.I.8.a. A variation to submit the summary of the pharmacovigilance system will not be necessary in cases where the MA is transferred within companies belonging to the same parent company and the same PSMF will continue to be used. (see Q/A 2.8 on variations - http://www.hma.eu/20.html). 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.

12. What do I need to take into account when I change the PSMF location from UK to a Member State within the Union (EEA)?

In accordance with Article 7(1) of Commission Implementing Regulation (EU) No 520/2012 the pharmacovigilance system master file shall be located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site in the Union where the qualified person responsible for pharmacovigilance operates. This requirement should be take into account if the Pharmacovigilance System Master File (PSMF) is located in the UK and the marketing authorisation holder needs to change the PSMF location to a Member State within the Union (EEA).

13. Do I need to change the UK-based addressee of a PIP or waiver decision?

The EU Pharmaceutical legislation does not require the addressee of a PIP or waiver to be established in the EU/EEA. It is therefore not necessary to request a change of an addressee of a PIP or waiver that is located in the UK.

14. What Brexit-related changes to the Product Information can I include as part of other procedures affecting the Product Information?

A change of MAH or of batch release manufacturer require dedicated procedures (MA transfer or variation, respectively), during which any related update within the Product Information should be made, i.e. such amendments cannot be postponed till other, unrelated procedures.

An update of the package leaflet to delete the name of the product in the UK can be included as part of a future regulatory procedure (e.g. variation, renewal) affecting the package leaflet. The earliest opportunity after 29 March 2019 should be used.

Changes to the local representative mentioned in the product information are dealt with at a national level.

15. How should I notify the change of Official Medicines Control Laboratory (OMCL) currently in the UK?

For products subject to Official Control Authority Batch Release (OCABR) this activity needs to be conducted by a designated OMCL located in the Union (EEA) or a country covered by a mutual recognition agreement that includes recognition of OCABR. Products that currently have OCABR conducted only by UK OMCL will have to change their OMCL. For products that have other designated OMCL(s) the MAH may choose to remove the UK OMCL.

When designating a new OMCL and/or removing a previously designated OMCL located in the UK, the Marketing Authorisation Holders should notify such change to the RMS or relevant NCA in writing through submission of a letter in a new eCTD sequence.

16. How shall I reflect UK national scientific advice in submissions made after 29 March 2019?

National scientific advice from UK competent authorities will be regarded, as of the withdrawal date, as a scientific advice from a third country. Information on any third country scientific advice can be included in the application dossier, as appropriate.

17. How can I change the UK based applicant to a non-UK based applicant for an ongoing marketing authorisation application?

For marketing authorisation procedures that are expected to be closed after 29 March 2019, the applicant must be established in the Union (EEA). Where the application was initially planned for a UK based company and it has not been possible to change the applicant to a non-UK entity prior to the submission of the MAA, such change will need to be made during the procedure.

Making such change to an ongoing MA application is possible at certain procedural milestones in case the change of applicant will not create a ‘duplicate application’ to another pending application or authorised product.

In order to request a change of the applicant, the following documents need to be submitted as part of the Day 106 or Day 160 responses in the decentralised procedures or Day 40 responses for mutual recognition procedures so that by 29 March 2019 the change is implemented:

- A letter requesting the change of applicant and signed by both the previous and the new applicant.

- A confirmation (as part of the cover letter) that complete and up-to-date file concerning the medicinal product or a copy of this file has been made available to or has been transferred to the new applicant.
- Updated application form and affected annexes (includes proof of establishment of the new applicant within the Union (EEA) issued in accordance with national provisions and which should be no older than 6 months and the power of attorney for a person communicating on behalf of the new applicant).
- Updated summary of the pharmacovigilance system.
- Any other documents of the marketing authorisation dossier affected by the change of applicant, as relevant (e.g. an updated Letter of Access for an application that includes an Active Substance Master File).

The applicants are encouraged to request the changes as early as possible as the acceptability of the proposed changes will need to be assessed.

18. Should I update my ongoing MA application with regards to other entities or activities currently located in the UK?

For marketing authorisation procedures (MAAs) that are expected to be closed after 29 March 2019, the future MAH, QPPV, batch release sites, batch control sites, intended OMCL (if applicable) and nominated local representatives for Member States other than UK must be located in the Union (EEA). Where it has not been possible to amend the application in this regard prior to the submission of the MAA, such change will need to be made during the decentralised procedure.

In order to request the above listed changes, a cover letter highlighting the proposed changes and updated affected dossier documents (e.g. updated product information and mock-ups, if applicable) will need to be submitted as part of the Day 106 or Day 160 responses in the decentralised procedures. The change of future MAH should be accompanied with an updated Summary of the Pharmacovigilance System.

The applicants are encouraged to request the changes as early as possible, in particular with regards to manufacturing sites, as the acceptability of the proposed changes will need to be assessed.

For MRP, necessary updates should be made via the appropriate variation procedure in advance of submitting the application to the CMS. During an ongoing MRP any necessary update of the application should be made with the Day 40 responses and is limited to issues not covered by the variation regulation like the future MAH.