16 March 2020
EMA/478309/2017 Rev. 5[1]
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

This practical guidance complements **Notice** to stakeholders – withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products, which has been drafted jointly by the European Commission and EMA and is available on the EMA website.

The below Practical Guidance aims to provide procedural and practical guidance regarding submission of changes and related fees. It has been updated to address the implications of the withdrawal agreement and the transition period provided for therein. Additional considerations with regards to products placed on the market before the end of the transition period and the applicable rules in Northern Ireland after the end of the transition period are addressed in parts B and C of the EC/EMA Notice, respectively.

MAHs and applicants of centrally authorised products for human or veterinary use need to ensure that the necessary changes are made by the end of transition period, unless indicated otherwise in the guidance below.

[1] Revision 5 introduces revisions to reflect the implications of the withdrawal agreement.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of Contents

Variations

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 end of transition period.

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 Product Lead 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.

Differently from importation of finished products (including bulk finished products), it is not required to register importation of intermediate finished products undergoing further processing as a separate activity in the MA dossier. However, the respective site still needs to hold a Manufacturing and Importation Authorisation covering this activity.

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[2]	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[3]	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?"

[2] 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.
[3] 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.

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

2a. 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:

> *As of the end of the transition period, UK Notified Bodies will lose their status as EU Notified Bodies and will be removed from the Commission's information system on notified organisations (NANDO database). As such, UK bodies will not be in a position to perform conformity assessment tasks pursuant to Union product legislation as of the end of the transition period.*
>
> *When the applicable conformity assessment procedure requires or provides for the possibility of third party intervention, a certificate delivered by a body which is recognised as an EU Notified Body at the time of the placing of that product on the market will be required for products placed on the market as of the end of the transition period.*
>
> *It will therefore be necessary for economic operators to either apply for a new certificate issued by an EU Notified Body, or arrange for a transfer of the file and the corresponding certificate from the UK Notified Body to an EU Notified Body, which would then take over the responsibility for that certificate. This responsibility depends on the specific conformity assessment procedure required for the product concerned under the applicable product legislation set out in Annex. The transfer of certificates from a UK Notified Body to an EU Notified Body needs to take place before the end of the transition period, on the basis of a contractual arrangement between the manufacturer, the UK Notified Body, and the EU Notified Body..*

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)
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)

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 Product Lead or, for veterinary medicinal products, to vet.applications@ema.europa.eu.

3a. When should I submit Brexit related type IA ("do and tell") variations that have to be implemented before the end of transition period?

Certain changes that have to be fully implemented before the end of transition period 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 the end of transition period, 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 the end of transition period, irrespective of the variation type.

Transfer of marketing authorisation

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 the end of transition period.

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 Product Lead), 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?

[Question removed as currently there is no holder of an orphan marketing authorisation established in the UK.]

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

[Question removed as it was addressing the scenario of a large volume of transfer applications from one UK-based MAH to the same legal entity (Transferee) in EEA, which is no longer applicable in the current situation.]

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.

Transfer of orphan designation

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 end of transition period.

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).

5a. Is there any simplification possible in case of several transfers of orphan designations between the same sponsors? *(for medicines for human use)*

In order to facilitate handling of a large volume of orphan designation transfer applications from a current UK-based sponsor to a new sponsor in EEA, a combined version of each required supportive document (except product specific information) can be created covering all orphan designations affected. In such case the combined submission of transfer applications should consist of:

- A cover letter listing all orphan designations to be transferred and confirming that supportive documents are identical, with the exception of product specific transfer forms and translations;
- A proof of establishment of the new sponsor in the Union (EEA);
- A letter of authorisation from the new sponsor, when applicable;
- Separate product transfer form for each orphan designation;
- Separate translations document for each orphan designation, when applicable.

For further details on the procedural aspects of orphan designation transfer applications please also check the relevant guidance published on the dedicated page of Agency's website. Any pre-submission queries should be sent to orphandrugs@ema.europa.eu.

QPPV and the pharmacovigilance system

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.

7a. What do I need to take into account when I change the PSMF location from UK to a Member State within the Union (EEA)? *(for medicines for human use)*

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).

7b. What if Qualified Person's for Pharmacovigilance (QPPV) back-up arrangements are in the UK *(for veterinary medicines)*?

In relation to veterinary medicines, volume 9B of the Rules Governing Medicinal Products in the European Union applies and stipulates that the QPPV can delegate functions to a trusted deputy within the same organisation, in particular advice is provided to register the deputy in EudraVigilance Veterinary. In analogy with the requirement for the QPPV to reside within the EEA, the deputy who is deemed to perform tasks in absence of the QPPV or delegated to him/her, should also reside within the EEA.

Change of nominated contact persons

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 submitted via EMA Service desk by choosing from the "Type of question" drop down list <HUMAN - Change of contact – Post Auth> and attaching the filled-in template on company headed paper. Further information, please refer to Post-authorisation guidance for users of the centralised procedure, section 'Notifying EMA of changes to contact persons'.

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.

Ongoing initial marketing authorisation procedures

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

[Question removed as there are currently no UK based applicants in ongoing initial marketing authorisation procedures at EMA.]

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

For marketing authorisation applications (MAAs) that are expected to receive a Commission Decision after the end of transition period, the QPPV, PSMF (for medicines for human use), batch release sites, batch control sites, intended OMCL (if applicable) and nominated local representatives for Member States other than UK must be located in 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 procedure.

In order to request the above listed changes, a cover letter highlighting the proposed changes and updated affected dossier documents will need to be submitted as part of responses to the Day 120 List of Questions or Day 180 List of Outstanding Issues.

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, which may impact the timelines of the procedure.

For medicinal products for human use the applicants are advised to liaise with the Product Lead as early as possible or, for veterinary medicines, to contact vet.applications@ema.europa.eu.

CHMP scientific opinion under Article 58

12. Do I need to update the dossier for CHMP Scientific Opinion under Article 58 in light of UK's withdrawal from EU? *(for medicines for human use)*

The holder of a CHMP Scientific Opinion under Article 58 of Regulation (EC) No 726/2004 or their contact points must be established in the Union (EEA). Therefore, for CHMP Scientific Opinions under Article 58 held by an UK-based entity and with a UK-based (or non-EEA) nominated contact point, it will be necessary to complete before the end of transition period either of the following:

- Transfer the CHMP Scientific Opinion to a holder established in the Union (EEA) (by analogy to MA transfer procedure for centrally authorised medicines);
- Change the nominated contact point (by analogy to change of the contact person authorised to communicate on behalf of the MAH).

Paediatric investigation plans and waivers

13. Do I need to change the UK-based addressee of a PIP or waiver decision? *(for medicines for human use)*

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.

Contact point at the EMA

14. Who should be my primary contact point at the EMA regarding Brexit related activities?

For questions related to the (activities related to) UK's withdrawal from the EU, the applicants and marketing authorisation holders for medicinal products for human use should contact:

- In relation to orphan designations – orphandrugs@ema.europa.eu.
- In relation to MA applications – Product Lead for the concerned product.
- In relation to MA transfer procedures – matransferquery@ema.europa.eu.
- In relation to other post-authorisation procedures – Product Lead for the concerned product.

For questions related to the (activities related to) UK's withdrawal from the EU, the applicants and marketing authorisation holders for veterinary medicinal products should contact vet.applications@ema.europa.eu.

General questions should be submitted to the EMA using this contact form.

Impact on Rapporteurships

15. How will the change of the Rapporteurs currently from UK be conducted?

[Question removed as the change of Rapporteurs has been completed.]

Product Information

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

An update of the Package Leaflet to amend Local Representative(s) of the MAH can be included as part of any other regulatory procedure affecting MA Annexes (e.g. in a variation, in a renewal application, in an MA transfer application).

However, 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 to the MAH and/or batch release manufacturer information in MA Annexes cannot be postponed till other, unrelated procedures.

16a. Where should I address questions regarding continuation of multi-country packs involving UK? (NEW)

The requirements for use of multi-country packs are summarised in section 6.3 of the part A in EC/EMA Notice. For any questions regarding continuation of a multi-country packs involving UK, the marketing authorisation holders are encouraged to consult with national competent authorities of respective

EU/EEA Member State(s), in particular in case of doubts about acceptability of any UK specific information as part of the 'blue box' in that Member State.

Official Control Authority Batch Release

17. 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 EMA in writing through submission of a letter in a new eCTD sequence (for human medicinal products) or in the VNeeS dossier (for veterinary medicinal products). When submitting the letter via the eSubmission Gateway, the submission type should be "maa" and the submission-unit should be "additional-info".

National scientific advice issued by UK authorities

18. How shall I reflect UK national scientific advice in submissions made after the transition period?

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.

Compliance (GMP, GCP, GLP)

19. How will the UK's withdrawal affect ongoing applications that include manufacturing sites with GMP certificates issued by UK authorities?

According to Annex I of Directive 2001/83/EC the manufacturing process shall comply with the requirements of Article 4 of Commission Directive 2003/94 laying down the principles and guidelines of Good Manufacturing Practice (GMP) for medicinal products for human use, Article 4 of Commission Directive 1991/412 laying down the principles and guidelines of Good Manufacturing Practice for veterinary medicinal products and with the principles and guidelines on GMP, published by the Commission in The rules governing medicinal products in the European Community, Volume 4. GMP certificates issued by EU/EEA competent authorities are commonly used to confirm EU GMP compliance in regulatory submissions (e.g. marketing authorisation applications).

For Marketing authorisation and post-authorisation applications in centralised procedure that are under assessment at the time of UK's withdrawal from the Union a risk based approach will be applied by the assessing competent authorities concerning the sites with GMP certificates issued by UK. As part of the assessment it will be considered whether there is a need to request a GMP inspection by an EU/EEA

Competent Authority before concluding the procedure in question, or whether such inspection shall be conducted at a later stage in line with timing decided by the appointed EU/EEA supervisory authority.

20. How shall I reflect GMP certificates issued by UK authorities in regulatory submissions made after the transition period?

In regulatory applications submitted after the transition period any GMP certificates issued by UK authorities (regardless of the date of issuance) should be included as supportive information on GMP compliance. Such certificates should be listed in the respective application forms as a GMP certificate from a third country authority.

21. How will the UK's withdrawal affect applications relying on clinical studies for which GCP inspections have been conducted by UK authorities? *(for medicines for human use)*

According to Article 8(3)(ib) of Directive 2001/83/EC the marketing authorisation application shall be accompanied by a statement to the effect that clinical trials carried out outside the European Union meet the ethical requirements of Directive 2001/20/EC.

In accordance with Commission Directive 2005/28/EC it is necessary that inspectors ensure the practical effectiveness of the rules on good clinical practice.

As part of the assessment of applications in centralised procedure it will be considered in a risk based approach whether there is a need to request a GCP inspection by an EU/EEA Competent Authority before concluding the procedure in question.

22. How will the UK's withdrawal affect GLP status of non-clinical studies conducted in the UK?

According to Article 2 of Directive 2004/10/EC, when submitting results, the laboratories referred to in Article 1 of that Directive shall certify that the tests have been carried out in conformity with the principles of Good Laboratory Practice (GLP).

Following Decision C (97)186/Final of the OECD Council on the Mutual Acceptance of Data in the Assessment of Chemicals, data generated in the testing of chemicals in an OECD Member Country (including UK), in accordance with OECD Test Guidelines and the OECD principles of GLP, are accepted in other OECD Member Countries.

Responsibility about the product

23. Who will be responsible for the handling of market complaints, quality defects and recalls of batches that have been released by an UK site and supplied to the EU/EEA before the end of transition period?

According to Article 6(1a) of Directive 2001/83/EC and Article 5(2) of Directive 2001/82/EC, the marketing authorisation holder shall be responsible for marketing the medicinal product. The

designation of a representative shall not relieve the marketing authorisation holder of his legal responsibility.

The overall responsibility for a medicinal product therefore lies with the marketing authorisation holder. The marketing authorisation holders must ensure that market complaints, quality defects and product recalls are handled in accordance with EU requirements, if necessary taking over follow-up activities that otherwise would have been undertaken by the discontinued batch release site.

Submission of information into EMA databases

24. What will change in submission into EudraCT of clinical studies conducted in UK? (*for medicines for human use*)

The impact on the reporting requirements for protocol and result related information, as well as the establishment requirements are addressed in the European Commission Notice on the withdrawal of the United Kingdom and EU rules in the field of clinical trials.

25. What will change regarding reporting requirements to EudraVigilance (EVCTM) for suspected unexpected serious adverse reactions (SUSARs) related to clinical trials conducted in the UK? (*for medicines for human use*)

In accordance with Article 107 of Directive 2001/83/EC suspected adverse reactions occurring in the context of clinical trials shall be recorded and reported in accordance with Directive 2001/20/EC. SUSARs related to clinical trials occurring in the UK before the end of transition period should be reported by sponsors in accordance with chapter 7 "Reporting of Suspected Unexpected Serious Adverse Reactions by the Sponsor" of the Detailed guidance on the collection, verification and presentation of adverse event/reaction reports arising from clinical trials on medicinal products for human use ('CT-3').

Third country reporting requirements will apply for SUSARs occurring in the UK after the transition period. In accordance with paragraph 69 of chapter 7 of the Detailed guidance i.e. the sponsor of a clinical trial performed in at least one Member State (i.e. where an EU/EEA Member State is involved in the study) should report the following SUSARs:

- all SUSARs occurring in that clinical trial, irrespective of whether the SUSAR has occurred at a trial site in a Member State or at a trial site in a third country concerned,
- all SUSARs related to the same active substance (regardless of pharmaceutical form and strength or indication investigated) in a clinical trial performed exclusively in a third country or exclusively in another Member State, if that clinical trial, is
    - sponsored by the same sponsor, or
    - sponsored by another sponsor who is either part of the same mother company or who develops a medicinal product jointly, on the basis of a formal agreement, with that other sponsor[4].

[4] Provision of the IMP or information to a future potential marketing authorisation holder on safety matters should not be considered a joint development.

For sponsors conducting clinical trials with a medicinal product in UK, but not in any Union (EEA) Member State the reporting obligations to EudraVigilance for SUSARs will cease after the transition period.

26. What will change regarding reporting requirements into EudraVigilance Veterinary of adverse event reports from the UK? (*for veterinary medicines*)

Marketing authorisation holders should report adverse events occurring in UK before the end of transition period in line with reporting requirements for EU/EEA cases.

After the transition period, marketing authorisation holders should submit information they may receive on cases occurring in the UK through reports from animal owners, healthcare professionals or UK authorities in line with the reporting requirements for non-EU/EEA cases.

After transition period follow-up reports for adverse events having occurred in the UK and that were originally submitted to the UK authority prior to the end of transition period, should also be submitted in line with reporting requirements for non-EU/EEA cases taking due account that the original world-wide case reference is maintained.

UK nationally authorised products in European procedures

27. What will be the impact of UK's withdrawal on procedures for single assessment of periodic safety update reports that include UK nationally approved products and related fees? (*for medicines for human use*)

All data submitted for single assessment of periodic safety update reports (PSUSA), including data submitted before the withdrawal date on UK nationally approved products, will be taken into account during the assessment. However, after the transition period, UK products will formally no longer be part of any ongoing PSUSA procedure. As a consequence, after the transition period assessment reports will no longer be shared with marketing authorisation holders for UK products that were previously concerned by the PSUSA procedure. The outcome of the PSUSA procedure will only concern products authorised in the Union (EEA).

The fees for PSUSA procedures are determined based on products authorised in the Union (EEA) (as recorded in 'Article 57 database') at the start date of the procedure. Until the end of transition period this includes UK nationally approved products.

28. What will be the impact of UK's withdrawal on procedures for assessment of protocols and results of imposed non-interventional post-authorisation safety studies that include UK nationally approved products and related fees? (*for medicines for human use*)

After the transition period, UK products will formally no longer be part of procedures for assessment of protocols and results of imposed non-interventional post-authorisation safety studies (PASS). As a consequence, after the transition period assessment reports will no longer be shared with marketing authorisation holders for UK products that were previously concerned by the PASS procedure.

The PASS procedures fees for each study are determined on first submission of the study protocol and on first study results submission. In case of several marketing authorisation holders involved, the fee is split equally by participating marketing authorisation holders at the time of first submission (of protocol or results, accordingly). Until the end of withdrawal period this includes participating marketing authorisation holders of UK nationally approved products.

Marketing status

29. What do I need to do if before the end of transition period my product was placed only on the UK market?

In case a centrally authorised product at the end of transition period is only being placed on the UK market, the end of the transition period will lead to a cessation of placing of the product on the Union market. The marketing authorisation holders should report such situation to the EMA through the marketing status overview in the context of the "sunset clause monitoring".

For medicines for human use see questions "When and how to report the marketing status overview to the Agency?" and "What information should be reported to the Agency on the medicinal product marketing status?" in the EMA post-authorisation procedural advice for users of the centralised procedure.

For medicines for veterinary use see questions "What information should be reported to the Agency on the veterinary medicinal product marketing status?" and "When should the marketing authorisation holder report marketing status changes to the Agency?" in the EMA post-authorisation procedural Q&A.

Reference products from the UK

30. How to proceed if pivotal studies have already been conducted vis-à-vis UK sourced reference product and there are concerns that repetition of the study could be unnecessary?

Applicants for ongoing and upcoming applications (to be) submitted before but finalised after the end of transition period, in case they consider that an already conducted pivotal (e.g. bioequivalence) study using a UK sourced reference product should continue to be used, are advised to submit to the Agency a corresponding justification at the earliest opportunity but in any case before the withdrawal date. This also applies to cases where the application cannot be submitted before the end of transition period but the pivotal (e.g. bioequivalence) study has been conducted with a reference product that was sourced in the UK before the end of transition period and that is identical to the EU/EEA reference product, authorised either via the centralised procedure or mutual recognition or decentralised procedure based on the same dossier. For medicinal products for human use applicants are advised to contact the Product Lead for their application in order to discuss the arrangements for submitting such justification or, for veterinary medicines, to contact vet.applications@ema.europa.eu.

Exemption

31. Can I request a delay for transfer of batch control testing to the EU/EEA?

[Question removed as exemptions were foreseen until 31 December 2019 at the latest.]