Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human

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

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 published by the European Commission

The below Practical Guidance aims to provide procedural and practical guidance regarding submission of changes. It addresses the implications of the withdrawal agreement and the transition period provided for therein.

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

Implications of the IE/NI protocol are addressed separately in the CMDh Practical Guidance on the implementation of the Protocol on Ireland/Northern Ireland for medicinal products for human use approved via MRP/DCP.

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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. 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 end of the transition period. All Brexit-relevant changes may be grouped (http://www.hma.eu/96.html).

7. How to classify Brexit-related changes impacting 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 comprising the batch release testing recognition. For products manufactured outside the EEA, also an authorised importation site in the EEA is required.

Finished products intended for the EEA market for which batch release and quality control testing sites are located in the UK will have to undergo batch release and batch release testing in sites located in the EEA. 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 and intended for the EEA market an importation site (in EEA) will need to be introduced in the MA.

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**	**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

[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.*

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	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		
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:

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.

[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.*

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)

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 the end of the transition period?

Certain changes that have to be fully implemented before the end of the 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 the transition period provided that the MAH is established in the Union (EEA) by that time.

Type-IA variations requiring immediate notification ('IAIN') 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 the transition period, 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 taken 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, or change from UK to UK(NI) can be included as part of a future regulatory procedure (e.g. variation, renewal) affecting the package leaflet. The earliest opportunity after the end of the transition period 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 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.

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 the end of the transition period, 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:

- 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 the end of the transition period, 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.

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, 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 national procedures 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 of a marketing authorisation application or variation 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 EU27/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.

The GMDP Inspectors Working Group have agreed a harmonised risk-based approach for the use of GMP Certificates issued by UK authorities after the end of the transition period to confirm GMP compliance for the purpose of regulatory submission and importation from third countries. This approach may be used by the EU competent authorities of the EU without prejudice to national legislation. As such, valid GMP certificates for sites located in Great Britain and in other 3rd countries issued by UK authorities after the end of the transition period can be submitted by companies for the purposes of demonstrating GMP compliance in the context of regulatory submissions and/or importation requirements.

In applying the risk based approach, the EU Supervisory Authority will verify the submitted UK GMP certificate to ensure that the scope encompasses the facilities, dosage forms and/or manufacturing processes for which it is being submitted and whether other GMP compliance or non-compliance information is available from other EU or international authorities. The EU supervisory authority will assess and confirm the GMP compliance of the site. In accordance with Article 111 of Directive 2001/83/EC and Article 80 of 2001/82/EC, each Supervisory Authority can decide, at any moment in time, to perform an inspection of a manufacturer if it considers that there are grounds for suspecting GMP non-compliance.

The GMDP Inspectors Working Group will re-assess the applicability of this risk-based approach periodically.

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

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 national procedures 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.

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 the transition period?

According to Article 6(1a) of Directive 2001/83/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.

24. What will change in submission into EudraCT of clinical studies conducted in UK?

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?

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 EU27/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[3].

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

26. 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?

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 the transition period this includes UK nationally approved products.

27. 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.

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

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 transition period this includes participating marketing authorisation holders of UK nationally approved products.

28. What will happen to renewals, variations and worksharing procedures with the UK as RMS/reference authority when they are ongoing after March 29, 2019?

There are no ongoing procedures with the UK as RMS/reference authority after 31 January 2020. Renewals, variations and worksharing procedures with the UK as RMS/reference authority were automatically stopped and have to be submitted with a new RMS/reference authority.

29. What will happen to DCP procedures with the UK as RMS when they are ongoing after March 29, 2019?

[Question removed as there are no ongoing procedures with the UK as RMS after 31 January 2020.]

30. Can I still place my product on the market when the MAH, batch release site, batch control site, local representative, QPPV or PSMF will still be located in the UK after the end of transition period?

After the end of the transition period products with the activities of MAH, local representative, QPPV or PSMF still located in the UK may no longer be placed on the market in the EU/EEA, Member states will take the necessary action on these products that are no longer compliant with the EU legislation.

With respect to batch release and QC testing, after the transition period, products may no longer be placed on the market unless these activities are located within the EU/EEA/UK(NI). However, for MR/DCP procedures which include the MS IE, CY, MT, or UK(NI), continued use of sites for batch control and batch release may be permitted temporarily under the conditions for the exemption as stated in Commission Notice C/2021/450 (OJ C 27, 25.1.2021, p. 11–16) and if granted by the competent authorities of IE, CY, MT or UK(NI) for supply to their markets only.

Marketing authorisation holders have to submit variations to replace these activities from the UK site to an EU/EEA site or UK(NI) site, as appropriate. Only after the activities have been transferred to sites in the EU/EEA or UK(NI) as appropriate, the products may be placed on the market in the EU/EEA again, (unless the above exemption applies).

Products with these activities still located in the UK but already released and placed on the market on the territory of the EU/EEA or UK before the end of the transition period, may be further made available on the market of the EU/EEA in line with Art 41 of the Withdrawal Agreement and do not have to be re-called from the market.

31. What will happen to my ongoing DCP marketing authorisation applications when the applicant, future MAH, batch release site, batch control site, local representative, QPPV or PSMF will still be located in the UK after the end of transition period?

The procedures will not stop automatically but can be further processed by the RMS until the EoP. For all activities as mentioned above the procedure might go on until Day 210 with further possibilities for the applicant to change these activities to an EU site. The respective changes may be submitted with

the Day 106 or Day 160 response documents. For changes submitted outside of these official responses it is up to the RMS to accept these changes or not.

Unless all UK sites/activities (applicant, future MAH, local representative, QPPV, PSMF) and/or UK(GB) sites (batch release site, batch control site) have been removed/replaced by Day 210, the procedure will be closed negatively as the application is not compliant with the EU legislation.

When such procedures have already been positively finalised on Day 210 before the end of the transition period but the national phase is still ongoing the necessary variations should be submitted to all member states in line with the classification guideline and also updated translations should be submitted, if applicable, during the national phase. Only after transfer of all these activities to the EU MAs might be issued.

32. 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.]

33. Where should I address questions regarding continuation of a multi-country pack involving UK?

Multi-country packs are medicinal products that are labelled to allow their placing on the market in several Member States with the same packaging. This possibility is subject to the requirements set out in in Title V of Directive 2001/83/EC and requires that the summary of product characteristics is the same in all the markets concerned.

Article 57 and Article 62 of Directive 2001/83/EC and Article 63 of Directive 2001/82/EC allow Member States to require inclusion of certain additional labelling information (the so-called "blue box" concept) provided that all the strict conditions for application of Article 57 or Article 62 of Directive 2001/83/EC and Article 63 of Directive 2001/82/EC are fulfilled.

In applying these provisions, multi-country packs with the UK market are only possible if

- the product information is exactly the same in the United Kingdom as in the EU27 (EEA); and
- the Member State has allowed additional information according to the "blue box" concept. This additional information must be limited to certain administrative information

In any event the product labelling and package leaflet must be fully in line with the summary of product characteristics as authorised in the Union (EEA).

For any questions regarding continuation of multi-country packs involving UK, the marketing authorisation holders are encouraged to consult with national competent authorities of respective EU27/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.

34. Can I use a reference medicinal product (RefMP) authorised in the UK for my generic/hybrid/biosimilar application?

For generic (Art 10.1) and hybrid (Art. 10.3) applications the RefMP is mentioned in three subsections of section 1.4.2 or 1.4.3. in the application form. The advice for use of a UK RefMP is presented in accordance with these subsections:

- **Medicinal product which is or has been authorised in accordance with Union provisions in force for not less than 6/8/10 years in the EEA**

Marketing authorisations granted before the end of the transition period by the United Kingdom can continue to be used in this subsection also for generic/hybrid applications submitted after the end of the transition period.

- **Medicinal product authorised in the Union/Member State where the application is made or European reference medicinal product**

  In case the medicinal product has not been authorised in the Union/Member State where the application is made, the applicant can refer to a European reference medicinal product (ERP).

  Generic/hybrid applications for which marketing authorisations will be granted during or after the transition period (regardless if they are submitted before or after the end of the transition period): Applicants are advised to refer to an ERP that is or has been authorised in an EU-27/EEA Member State. In the exceptional situation where the RefMP is or has been authorised in the UK only, it can be used as ERP provided it was authorised in the UK before the end of the transition period.

- **Medicinal product which is or has been authorised in accordance with Union provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies/used for the demonstration of bioequivalence (if applicable) and/or in other studies**

  Generic/hybrid applications submitted before but finalised after the end of the transition period (MRP/DCP): If studies with a UK RefMP have already been completed (final study report) before the end of the transition period, NCAs will accept submission of such studies.

  Generic/hybrid applications submitted after the end of the transition period via MRP or RUP: CMS will accept submission of studies with a UK RefMP provided that the studies were completed (final study report) before the end of the transition period.

  Generic/hybrid applications submitted after the end of the transition period (DCP): If studies with a UK RefMP have already been completed (final study report) before the end of the transition period, NCAs will accept submission of such studies also after the end of the transition period, but only if the UK RefMP was authorised via a European procedure (MRP, DCP or the centralised procedure).

  The advice in this section applies to all pivotal studies (bioequivalence, in vitro dissolution tests or therapeutic equivalence studies, as appropriate) in generic or hybrid applications.

The advice above is also applicable to biosimilar (Art. 10.4) applications. The Guideline on similar biological medicinal products is however to be consulted for the available scientific guidance when considering using a non-EU authorised comparator (i.e. a non-EU authorised version of the reference medicinal product) in the development of a biosimilar.

35. What will be the effect of UK's withdrawal on authorisations granted in accordance with Article 126(a) of Directive 2001/83/EC on the basis of Marketing Authorisations issued by the UK?

According to Article 126(a) of Directive 2001/83/EC, in the absence of a marketing authorisation or of a pending application for a nationally authorised medicinal product authorised in another Member State, a Member State may for justified public health reasons authorise the placing on the market of the said medicinal product. Traditionally, some of these authorisations have been granted on the basis of national marketing authorisations granted by the UK.

Authorisations granted by EU27 (EEA) national competent authorities on the basis of Article 126a before the end of the transition period will remain valid. However, new authorisations on the basis of

Article 126a referring to the national marketing authorisations granted by the UK cannot be granted after the end of the transition period as the UK will become a third country.

In any event, if the products placed on the market on the basis of Article 126a are sourced from the UK after the end of the transition period they will be considered as products imported from a third country and will need to comply with all the requirements of the EU law for imported products.

36. How does the UK's withdrawal from the Union affect the sunset clause?

According to Article 24(4) to (6) of Directive 2001/83/EC any authorisation which within three years of its granting is not followed by the actual placing on the market of the authorised product in the authorising Member State market will cease to be valid. When an authorised product previously placed on the market in the authorising Member State is no longer actually present on the market for a period of three consecutive years, the authorisation for that product will cease to be valid.

As such there will be no effect of UK's withdrawal from the Union on national marketing authorisations approved in EU/EEA-Member States.

37. For existing authorisations, if I still have UK sites mentioned in the dossier after the end of the transition period in addition to EU sites, e.g. alternative batch release or batch control sites, should I remove these?

Yes. Alternative sites still located in the UK(GB) should be removed from the MA using the respective variation procedure according to the classification guideline. This should be done at the earliest opportunity for all procedures except for procedures where the competent authorities of IE, CY, MT and/or UK(NI) have granted an exemption for their markets. UK(GB) sites may be permitted temporarily under the conditions for the exemption as stated in Commission Notice C/2021/450 (OJ C 27, 25.1.2021, p. 11–16) and if granted by the competent authorities of IE, CY, MT or UK(NI) for their markets (for a period of 12 months until the end of 2021).