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DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

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Questions and Answers related to the United Kingdom's withdrawal from the European Union with regard to the medicinal products for human and veterinary use within the framework of the Centralised Procedure

This list of Questions and Answers (Q&As) complements the "*Notice to stakeholders - withdrawal of the United Kingdom and EU rules for medicinal products for human use and veterinary medicinal products*".[1]

(NEW) This list of Q&As addresses a situation where the United Kingdom becomes a third country on 30 March 2019 ("the withdrawal date") without a withdrawal agreement and hence without a transition period provided for in the draft Withdrawal Agreement.

This list has been drafted jointly by the Directorate-General for Health and Food Safety of the European Commission and EMA. This version is an update of the initial list of Q&As published on 31 May 2017 as subsequently amended and it replaces all previous versions of Q&As. The new text introduced in this version of Q&As "Rev 04" is indicated by the word "**NEW**". The Q&As may be further updated and complemented in the future. The advice below applies equally to medicinal products for human or veterinary use, unless otherwise indicated in the heading to the question.

1. What if I am a marketing authorisation holder established in the UK?

According to Article 2 of Regulation (EC) No 726/2004 the marketing authorisation holder must be established in the Union. Through the EEA Agreement this is extended to include also Norway, Iceland and Liechtenstein.

For centrally authorised medicinal products the marketing authorisation holder will therefore normally need to transfer its marketing authorisation to a holder established in the Union (EEA) (see Commission Regulation (EC) 2141/96 and EMA Q&A on transfer). This means that the addressee of the marketing authorisation decision changes to the new addressee. The transfer of the marketing authorisation must be fully completed and implemented by the marketing authorisation holder before 30 March 2019.

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[1] https://ec.europa.eu/info/brexit/brexit-preparedness/preparedness-notices_en#sante

1a. What if I am an applicant established in the UK?

Any marketing authorisation applicant must be established in the Union (EEA). Therefore, for marketing authorisation applications (MAAs) that are expected to receive a Commission Decision after 29 March 2019, applicants established in the UK will need to change to a non-UK applicant established in the Union (EEA) before 30 March 2019. It is strongly recommended that applicants established in the UK consider such change, where possible, in advance of the submission of the MAA.

2. What if I am an orphan designation holder established in the UK? (*for medicines for human use*)

According to Article 2 of Regulation (EC) No 141/2000 the sponsor of an orphan medicinal product designation must be established in the Union (EEA).

For designated orphan medicinal products the holder will therefore need to transfer its designation to a holder established in the Union (EEA) (see Checklist for sponsors applying for the transfer of Orphan Medicinal Product (OMP) designation and the corresponding template) or it will need to change its place of establishment to a Member State of the Union (or EEA) and submit the corresponding documentation through a change of name and/or address of the orphan designation holder procedure provided the legal entity remains the same (see 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, 27.03.2014).

3. What if I am a UK company with a MUMS (Minor Use Minor Species/limited market) status for my product? (*for veterinary medicines*)

According to Article 79 of Regulation (EC) No 726/2004, the Management Board of the European Medicines Agency should, in the case of veterinary products which have limited markets, or in the case of veterinary medicinal products intended for diseases with a regional distribution, adopt the necessary measures to provide assistance to companies at the time of submission of their applications. This activity supports applicants for marketing authorisations, which in accordance with the general rules have to be established in the Union (EEA) (see Question 1a above).

If the sponsor/applicant is established in the UK, the MUMS incentives provided on the basis of Article 79 of Regulation (EC) No 726/2004 would no longer be applicable with effect from the date of the UK's withdrawal from the Union, as a sponsor/applicant established within a third country cannot seek and receive MUMS/limited market classification in the Union (EEA). However, MUMS/limited market classification is connected to the product/indication and therefore transferable together with the product.

To formally acknowledge the transfer, the EMA requires a letter from the original sponsor/applicant officially informing the EMA of the transfer of the classification product and the MUMS/limited market classification from the original sponsor/applicant to a sponsor/ applicant established in the Union (EEA). This letter should state the document reference number of the MUMS outcome letter confirming the MUMS classification.

For already authorised MUMS/limited market veterinary medicinal products it is important to note that a transfer of marketing authorisation does not include a transfer of an MUMS/limited designation as this is subject to a different procedure. Therefore, for those authorised MUMS/limited market veterinary medicinal products the marketing authorisation holder needs to transfer the marketing authorisation (see: "What if I am a marketing authorisation holder established in the UK (H + V)?") and separately the MUMS/ limited market classification (see above). The five year period of validity for MUMS/limited market classification is not affected by the transfer of classification.

4. What if my Qualified Person for Pharmacovigilance (QPPV) resides and carries out his/her tasks in the UK?

According to Article 8 of Directive 2001/83/EC and Article 74 of Directive 2001/82/EC, the qualified person responsible for pharmacovigilance must reside and carry out his/her tasks in a Member State of the Union (EEA). The QPPV will therefore need to change his/her place of residence and carry out his/her tasks in the Union (EEA) or a new QPPV residing and carrying out his/her tasks in the Union (EEA) will need to be appointed. Changes in the QPPV, including contact details (telephone, and fax numbers, postal address and email address) may, for medicinal products for human use, be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline C.I.8). Regarding medicinal products for veterinary use the changes should be updated through a variation (see Variation Guideline (2013/C 223/01), classification C.I.9).

5. What if my Pharmacovigilance System Master File is located in the UK (PSMF)? (*for medicines for human use*)

According to Commission Implementing Regulation (EU) No 520/2012, the PSMF must be located within the Union (EEA). The supervisory authority for pharmacovigilance is the competent authority of the Member State in which the pharmacovigilance system master file is located. The marketing authorisation holder will therefore need to change the location of the PSMF to a Member State within the Union (EEA). Changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation) (see Variation Guideline (2013/ C 223/01), classification C.I.8).

6. What if my manufacturing site of the active substance is located in the UK?

As of the date of the withdrawal of the UK from the Union, active substances manufactured in the UK will be considered imported active substances.

Directive 2001/83/EC and Directive 2001/82/EC state that manufacturing authorisation holders are obliged to use, as starting materials, only active substances that have been manufactured in accordance with the detailed guidelines on GMP for starting materials.

In addition, pursuant to Article 46b(2) of Directive 2001/83/EC, active substances for medicinal products for human use shall only be imported in the Union (EEA) if, inter alia, the active substances are accompanied by a written confirmation from the competent authority of the exporting third country which, as regards the plant manufacturing the exported active substance, confirms that the standards of good manufacturing practice and control of the plant are equivalent to those in the Union (EEA).

7. What if my manufacturing site of the finished product is located in the UK?

As of the date of the withdrawal of the UK from the Union, medicinal products manufactured in the UK will be considered imported medicinal products.

The competent authorities of the Union (EEA) shall ensure that the **import** of medicinal products into their territory is subject to an authorisation in accordance with Article 40(3) of Directive 2001/83/EC and Article 44(3) Of Directive 2001/82/EC. The authorisation is granted when a number of conditions, as defined in Articles 41 and 42 of Directive 2001/83/EC and Articles 45 and 46 of Directive 2001/82/EC, are fulfilled (e.g. availability of a qualified person within the Union (EEA), GMP inspection).

For centrally authorised medicinal products the marketing authorisation holder will therefore need to specify an authorised importer established in the Union (EEA) and submit the corresponding variation (see Variation Guideline (2013/ C 223/01), classification B.II.b.2).

In addition, in accordance with Article 51(1)(b) of Directive 2001/83 and Article 55(1)(b) of Directive 2001/82 the marketing authorisation holder will need to specify a site of **batch control** in the Union (EEA) where each production batch can undergo upon importation a full qualitative analysis, a quantitative analysis of at least all the active substances and all the other tests or

checks necessary to ensure the quality of medicinal products in accordance with the requirements of the marketing authorisation.

For centrally authorised medicinal products the marketing authorisation holder will need to change the location of its current UK based site of batch control to a location established in the Union (EEA) and submit the corresponding variation (see Variation Guideline (2013/ C 223/01), classification B.II.b.2).

8. What if my batch release site is located in the UK?

In accordance with Article 51(1) of Directive 2001/83/EC and Article 55(1) of Directive 2001/82/EC, the qualified person of the manufacturing and importation authorisation holder is responsible to certify that each batch of medicinal product intended to be placed on the EEA market was manufactured in accordance with the Union GMP requirements and the marketing authorisation. The batch release site has to be located in the Union (EEA).

For centrally authorised medicinal products the marketing authorisation holder will therefore need to transfer its current UK based site of **batch release** to a location established in the Union (EEA) and submit the corresponding variation (see Variation Guideline (2013/ C 223/01), classification B.II.b.2).

9. I am a UK based SME, would I still have access to financial and administrative assistance in accordance with Commission Regulation (EC) No 2049/2005 (the 'SME Regulation')?

In order to be eligible for financial and administrative assistance, companies must be established in the Union (EEA) and meet the definition of an SME.

As of the date of the withdrawal of the UK from the Union, the guidance for non-EEA based companies shall apply also to UK based companies:

- to apply for SME status once the company has established a legal entity in the Union (EEA). For proof of establishment, the SME office requires a copy of the certificate of incorporation in the commercial register of the companies. In such cases, the SME declaration can be submitted in the name of the newly established subsidiary with details of the parent company to be declared.
- to indirectly benefit from the SME incentives through an Union (EEA) established SME regulatory consultancy. SME regulatory consultancies may seek to benefit from the provisions of the SME Regulation on behalf of non-EEA based clients, only if both they and the client meet the SME criteria (i.e. fall below headcount and financial thresholds). In this case, both the regulatory consultancy and the non-EEA based company should submit SME declarations. If successful, the regulatory consultancy would receive an SME notification and the non-EEA based company would be listed in an annex to that notification as an SME client company. It is not possible for an SME regulatory consultancy to be considered eligible if they are acting on behalf of non-SME clients, as this would be contrary to the objectives of the SME Regulation.

Further information is available on the EMA website (link) and in the SME User Guide (link).

10. How does UK's withdrawal from the Union affect my generic or hybrid marketing authorisation or application based on a reference product authorised in the UK?

A generic or hybrid application in accordance with Article 10 of Directive 2001/83/EC or Article 13 of Directive 2001/82/EC refers to information that is contained in the dossier of a reference medicinal product (RefMP) that is or has been authorised in the Union (EEA).[2]

Generic/hybrid marketing authorisations granted before 30 March 2019 referring to a RefMP authorised by the UK (UK RefMP) remain valid.

Generic/hybrid applications for which marketing authorisations will be granted after 29 March 2019 should refer to a RefMP that is or has been authorised in a EU-27 Member State or a contracting state of the EEA.[3] [4] Applicants are advised to take this into account already at the time of submission of the application.

11. Can medicinal products used in bioequivalence studies be sourced in the UK?

According to Article 10(1) of Directive 2001/83/EC or Article 13(1) of Directive 2001/82/EC the applicant can submit an abridged application if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised in the Union or EEA for not less than eight years. According to Article 10(2)(b) of Directive 2001/83/EC and Article 13(2)(b) of Directive 2001/82/EC generic medicinal product means a medicinal product which has the same qualitative and quantitative composition in active substance and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.[5]

(NEW) Pivotal studies (bioequivalence, in vitro dissolution tests or therapeutic equivalence studies, as appropriate) that have been conducted with a medicinal product sourced in the UK can be used in generic/hybrid marketing authorisation applications only if the marketing authorisation for that application will be granted before 30 March 2019.[6]

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[2] See also the electronic application form for marketing authorisation applications, section 1.4.2.2 or 1.4.3.2

[3] This will also facilitate management of generic/hybrid product's life cycle in the post-authorisation phase, considering for example the need to implement changes to the product information of the EEA RefMP also for the generic/hybrid products.

[4] The (exceptional) situation where a RefMP is or has been authorised in the UK only is addressed in the EU's "Position paper on Goods placed on the Market under Union law before the withdrawal date" (footnote 7): https://ec.europa.eu/commission/publications/position-paper-goods-placed-market-under-union-law-withdrawal-date_en .

[5] See also the electronic application form for marketing authorisation applications, section 1.4.2.3 or 1.4.3.3

[6] In exceptional cases where bioequivalence studies are intended for use in new applications which will be submitted before 30 March 2019 and if these bioequivalence studies have been already completed the applicants may consider contacting the competent authority to discuss the particular circumstances of their application in order to avoid unnecessary repetition of studies in humans or animals. **(NEW)** In cases where bioequivalence studies have been conducted with a reference product sourced in the UK before 30 March 2019 and when this product is the same as an EU27 reference product, authorised either via the centralised procedure or mutual recognition or decentralised procedure based on the same dossier, the applicants may consider contacting the competent authority to discuss the particular circumstances of their application also in cases when the application cannot be submitted before 30 March 2019, in order to avoid unnecessary repetition of studies in humans or animals.

12. How does UK's withdrawal from the Union affect my biosimilar marketing authorisation or biosimilar marketing authorisation application? (*for medicines for human use*)

The considerations described under questions 10 and 11 regarding the choice of RefMP are also applicable to biosimilars.

The Guideline on similar biological medicinal products should however be consulted for the available scientific guidance when considering using a non-EEA authorised comparator (i.e. a non-EEA authorised version of the reference medicinal product) in the development of a biosimilar. Batches of the RefMP released by the UK after 29 March 2019 will not be considered as a Union (EEA) authorised comparator.

13. How does UK's withdrawal from the Union affect the Global Marketing Authorisation (GMA) concept?

The concept of 'global marketing authorisation within the meaning of Article 6(1) of Directive 2001/83/EC and Article 5(1) of Directive 2001/82/EC covers the initial marketing authorisation and all subsequent developments of the original medicinal product, irrespective of their authorisation procedures, namely variation or grant of a separate MA[7] to the same MAH. The GMA is accompanied only by a single regulatory data protection period[8] which applies both to data relating to the original medicinal product[9] and to data presented for any subsequent developments. That regulatory data protection period begins with the grant of the initial marketing authorisation in the Union (EEA).

Marketing authorisations granted before 30 March 2019 by the UK can still be considered as the initial marketing authorisation.

14. How does UK's withdrawal from the Union affect well-established use applications?

According to Article 10a of Directive 2001/83/EC and Article 13a of Directive 2001/82/EC it is possible to replace results of the pre-clinical and clinical trials by detailed references to published scientific literature if it can be demonstrated that the active substances of a medicinal product in the claimed therapeutic indication and (for veterinary products) target species have been in well-established use within the Union (EEA) for at least ten years, with recognised efficacy and an acceptable level of safety. In this regard, the provisions of Annex I of Directive 2001/83/EC or Annex I of Directive 2001/82/EC shall apply.

Data sourced from the UK, while the UK was a Member State of the Union, can be taken into account to demonstrate that the active substances of a medicinal product in the claimed therapeutic indication and (for veterinary products) target species have been in well-established use within the Union (EEA) for at least ten years, with recognised efficacy and an acceptable level of safety.

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[7] C-629/15P, para. 72.
[8] C-629/15P, para. 65.
[9] See also the electronic application form for marketing authorisation applications, section 1.4.2.1 or 1.4.3.1

15. How does UK's withdrawal from the Union affect traditional herbal medicinal products (traditional-use registration)? (*for medicines for human use*)

The traditional-use registration procedure allows the registration of herbal medicinal products without requiring particulars and documents on tests and trials on safety and efficacy, provided that there is sufficient evidence of the medicinal use of the product throughout a period of at least 30 years, including at least 15 years in the Union (EEA).

Data sourced from the UK, while the UK was a Member State of the Union, can be taken into account to demonstrate that the product has been in medicinal use throughout a period of at least 15 years within the Union (EEA).

16. How does UK's withdrawal from the Union affect the prevalence for orphan drug designation? (*for medicines for human use*)

For applications for orphan designations or for its maintenance submitted after 29 March 2019, patients in the UK should no longer be taken into account in the calculation of the prevalence of the disease in order to meet the requirements for orphan drug designation as set out in Regulation (EC) No 141/2000 i.e. a condition affecting no more than 5 in 10 thousand persons in the Union (EEA).

17. How does UK's withdrawal from the Union affect the local representative located in the UK, if also nominated for Member States other than the UK?

The local representative mentioned in the product information should be located in the Union (EEA). Therefore, any local representative located in the UK and nominated for Member States other than the UK will have to be changed to a local representative located in the Union (EEA).

The corresponding amendments to labelling and package leaflet must be fully completed and implemented by the marketing authorisation holder before 30 March 2019, either as part of a regulatory procedure affecting the annexes (e.g. variation, renewal), or through a notification under an Article 61(3) of Directive 2001/83/EC or (for veterinary products) through a Type IAIN variation (see Variation Guideline (2013/ C 223/01), classification C.II.6.a).

17a. How does UK's withdrawal from the Union affect the local representative for UK mentioned in the product information?

After 29 March 2019, the mentioning of the local representative for UK in the product information will become obsolete.

The deletion of the local representative for UK in the product information will need to be incorporated as part of a future regulatory procedure affecting the annexes (e.g. variation, renewal) and the earliest opportunity after 29 March 2019 should be used.

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

According to Article 24(4) to (6) of Directive 2001/83/EC, Article 28(4) to (6) of Directive 2001/82/EC and Articles 14(4) to (6) and 39(4) to (6) of Regulation (EC) No 726/2004 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 or on the Union market will cease to be valid. When an authorised product previously placed on the market in the authorising Member State or in the Union 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.

In case a centrally authorised medicinal product has only been marketed in the UK, the placing on the UK market, while UK was a Member State of the Union, will be taken into account to determine the applicability of the sunset clause for the medicinal product concerned. In this respect, if after

the UK withdrawal from the Union, the medicinal product is not placed on any other market of the remaining Member States, the three year period for the sunset clause will start running from the last date the medicinal product was placed on the UK market, while UK was a Member State of the Union.

19. What if my product is subject to Official Control Authority Batch Release (OCABR) and is currently tested by a UK Official Medicines Control Laboratory (OMCL)?

According to Article 114 of Directive 2001/83/EC and Article 82 of Directive 2001/82/EC, Member States may require the marketing authorisation holder of a human immunological medicinal product or a medicinal product derived from human blood or plasma or immunological veterinary medicinal product to submit samples from each batch of the bulk and/or the medicinal product for examination by an Official Medicines Control Laboratory (OMCL) or a laboratory that a Member State has designated for that purpose before the release on the market. This is referred to as Official Control Authority Batch Release (OCABR).

According to the EU Administrative Procedure for Official Control Authority Batch Release[10], prior to marketing in the Union (EEA), batches of medicinal products subject to independent testing should obtain an Official Control Authority Batch Release Certificate common to all Member States. This shall demonstrate that the batch of medicinal product has been examined and tested by an OMCL within the Union (EEA) in accordance with this procedure and with Official Control Authority Batch Release guidelines pertaining to the medicinal product and that it is in compliance with the approved specifications laid down in the relevant monographs of the European Pharmacopoeia (Ph. Eur.) and in the relevant marketing authorisation.

For products placed on the market as of the withdrawal date,[11] OCABR cannot be carried out by an OMCL located in the UK. OCABR will need to be carried out by an OMCL located within the Union (EEA) or by a country officially recognised by the Union for mutual recognition of batch release. The marketing authorisation holder will therefore need to identify a OMCL located in the Union (EEA) for official batch release or an officially recognised partner (as stated above) for official batch release. A list of the OMCLs that may be in a position to provide the Union OCABR certificates for different products is available to manufacturers from the European Directorate for the Quality of Medicines & Healthcare (EDQM) on request at batchrelease@edqm.eu.

19a. Can I, as of the withdrawal date, import a medicinal product into the Union (EEA) on the basis of a certificate issued before the withdrawal date by the UK OMCL? (NEW)

No. As of the withdrawal date, the mutual recognition of Official Control Authority Batch Release (OCABR) stops.

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[10] Guideline for the administrative procedure to be followed by the competent OMCL authorities for the implementation of Directive 2001/83/EC Article 114 as amended by Directive 2004/27/EC, available at https://www.edqm.eu/en/batch-release-human-biologicals-vaccines-blood-and-plasma-derivatives

[11] For goods placed on the EU market *before* the withdrawal date, the EU is trying to agree solutions with the United Kingdom in the withdrawal agreement. The essential principles of the EU's position on goods placed on the market under Union law before the withdrawal date are available here: https://ec.europa.eu/commission/publications/position-paper-goods-placed-market-under-union-law-withdrawal-date_en. The concept of placing on the market refers to each individual product, not to a type of product, irrespectively of whether it was manufactured as an individual unit or in series

However, the Official Medicines Control Laboratory (OMCL) of an EU27 or EEA Member State may take account of the certificate issued by the UK OCML when issuing a certificate.

19b. Does the change of the marketing authorisation holder due to the UK's withdrawal impact on the validity of the Official Control Authority Batch Release issued by a Official Medicines Control Laboratory (OMCL) of an EU27 or EEA Member State? (NEW)

No. The Official Control Authority Batch Release (OCABR) of the OMCL of an EU27 or EEA Member State remains valid even if the marketing authorisation holder changes.

20. What if my product is subject to Official Batch Protocol Review (OBPR) and evaluation is done by a UK Competent Authority? (*for veterinary medicines*)

According to Article 81 of Directive 2001/82/EC Member States may require the marketing authorisation holder for immunological veterinary medicinal products to submit to the competent authorities copies of all the control reports signed by the qualified person in accordance with Article 55 of Directive 2001/82/EC in order to verify that control tests were carried out in accordance with the methods laid down for the purposes of marketing authorisation. This is referred to as an 'Official Batch Protocol Review' (OBPR). OBPR may be carried out by a Competent Authority within the Union (EEA) or in a country officially recognised by the Union for mutual recognition of batch release (e.g. Switzerland).

For products placed on the market as of the withdrawal date,[12] OBPR cannot be carried out by a UK Competent Authority. The marketing authorisation holder will therefore need to identify another Competent Authority located in the Union (EEA) or an officially recognised partner (as stated above) for official batch protocol review.

21. How does UK's withdrawal from the Union affect the status of inspection outcomes by the UK competent authority?

It is expected that findings of inspections, in particular to determine compliance with good manufacturing practice, good clinical practice and pharmacovigilance obligations, conducted by the UK competent authority before 30 March 2019 are implemented by the inspected entities in accordance with the applicable legislation, in particular Directive 2003/94/EC, Commission Delegated Regulation (EU) No 1252/2014 and Directive 91/412/EEC with regard to good manufacturing practice, Directive 2001/20/EC and Commission Directive 2005/28/EC with regard to good clinical practice and Regulation (EC) No 726/2004, Directive 2001/83/EC and Commission Implementing Regulation (EU) 520/2012 with regard to pharmacovigilance obligations.

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[12] For goods placed on the EU market *before* the withdrawal date, the EU is trying to agree solutions with the United Kingdom in the withdrawal agreement. The essential principles of the EU's position on goods placed on the market under Union law before the withdrawal date are available here: https://ec.europa.eu/commission/publications/position-paper-goods-placed-market-under-union-law-withdrawal-date_en. The concept of placing on the market refers to each individual product, not to a type of product, irrespectively of whether it was manufactured as an individual unit or in series

22. How does UK's withdrawal from the Union affect CE certification of medical devices by UK notified bodies?

This issue is addressed in the **Commission Notice on the withdrawal of the United Kingdom and EU rules in the field of industrial products** that also covers medical devices.

23. How does UK's withdrawal from the Union impact the CHMP scientific opinion for ancillary medicinal substances in medical devices requested by UK notified bodies?

According to Article 1(4) of Directive 93/42/EEC where a device incorporates, as an integral part, a substance which, if used separately, may be considered to be a medicinal product within the meaning of Article 1 of Directive 2001/83/EC and which is liable to act upon the body with action ancillary to that of the device, that device shall be assessed and authorized in accordance with Directive 93/42/EEC. In accordance with Annex I of Directive 93/42/EEC for a new medical device, the notified body acts as the applicant in an initial consultation procedure with EMA concerning the scientific opinion on the ancillary medicinal substances incorporated in the medical devices.

Union product legislation requires Notified Bodies to be established in a Member State and be designated by a Member State notifying authority.

From the withdrawal date, UK notified bodies will lose their status as the Union notified bodies. They will no longer be able to be an applicant in an initial consultation procedure with EMA and EMA will not be able to issue a scientific opinion to them as notified bodies of a third country.

24. How does UK's withdrawal from the Union impact on the possibility to market a multi-country pack which includes the 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 Directive 2001/83/EC in Title V or Directive 2001/82/EC in Title V and requires that the summary of product characteristics is the same in all the markets concerned.

(NEW) 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 in a restricted area (the so-called "blue box") 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 labelled in the "blue box". 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).

25. What if Qualified Person's for Pharmacovigilance (QPPV) back-up arrangements are in the UK?

According to Article 2 of Commission Implementing Regulation (EU) No 520/2012 back-up arrangements shall apply in the absence of the QPPV. As the tasks of QPPV need to be carried in a Member State of the Union (EEA), the back-up arrangements for cases of absence of the QPPV, which replace such tasks, also need to be performed in the Union (EEA).

Where a MAH relies on the services of a deputy QPPV as part of its back-up arrangements in the absence of the QPPV, those arrangements should ensure that the deputy QPPV is established and performs his/her tasks in the Union (EEA).

For veterinary medicines, reference is made to the EMA Brexit practical guidance.

26. Who will take over supervision of the manufacturing sites of medicinal products in third countries (including UK after the Withdrawal date) previously supervised by UK authorities and when will the next GMP inspection be conducted? (NEW)

According to Articles 18 and 43 of Regulation (EC) No 726/2004, in case of medicinal products imported from third countries the supervisory authorities shall be the competent authorities of the Member State or Member States that granted the authorisation provided for in Article 40(3) of Directive 2001/83/EC or Article 44(3) of Directive 2001/82/EC respectively to the importer of the concerned medicinal product.

As of the withdrawal date, UK authorities will no longer undertake the role of a supervisory authority.

The new Union supervisory authority responsible for supervision of manufacturing sites located in UK and third country sites previously inspected by UK will decide, using a risk-based approach, when an inspection of the site(s) concerned will be required, in order to confirm or re-confirm GMP compliance.

27. Can I continue to use after 29 March 2019 a manufacturing site for which the Union GMP certificate has been issued by UK authorities?(NEW)

All medicinal products for human and veterinary use manufactured or imported into the Union (EEA), including medicinal products intended for export, are to be manufactured in accordance with the principles and guidelines of good manufacturing practice.[13] [14] A certificate of good manufacturing practice ("GMP certificate") is issued to a manufacturer if the outcome of the inspection shows that the manufacturer complies with the principles and guidelines of good manufacturing practice as provided for by the Union legislation.[15] [16]

While the Union legislation does not require a Union GMP certificate issued by a Member State for issuing a marketing authorisation[17] or importation of a medicinal product,[18] in practice GMP certificates issued by the Union competent authorities are used to confirm the Union GMP compliance in regulatory submissions (e.g. marketing authorisation applications) and for imports from third countries. This means that GMP compliance of manufacturing sites in third countries may also be confirmed through other means, based on a risk-based approach (e.g. based on information on GMP compliance from third country regulatory authorities). GMP certificates issued by the UK competent authority before 30 March 2019 should therefore be considered as such information on GMP compliance from the third country regulatory authority.

[13] Commission Directive 2003/94/EC, Recital (1).
[14] Commission Directive 1991/412/EEC.
[15] Directive 2001/83/EC, Article 111(5).
[16] Directive 2001/82/EC, Article 80(5).
[17] Article 8(3)(ha) of Directive 2001/83/EC.
[18] Article 51(1)(b) of Directive 2001/83/EC, Article 55(1)(b) of Directive 2001/82/EC.

28. Shall the information about the unique identifier uploaded to the UK repository between 9 February 2019 and 29 March 2019 be transferred to another repository in the Union? (for medicines for human use)(NEW)

Article 33(1) of Commission Delegated Regulation (EU) 2016/161 requires marketing authorisation holders to ensure that unique identifiers and related information are uploaded to the Union repository system before a product is released for sale or distribution. Any information uploaded to the Union hub or a national repository should be transferred and stored in all national or supranational repositories serving the territory of Member State(s) where the product is intended to be placed on market. Therefore, the information on products released on the market before the withdrawal date will be already present in the national repositories where the product is intended to be placed on the market and there is no need to transfer information from the UK repository.

29. Can activities related to safety features take place in the UK? (for medicines for human use)(NEW)

The manufacturer placing the safety features, as referred to in Articles 14 and 15 of the Commission Delegated Regulation (EU) No 2016/161, is the manufacturer actually affixing the unique identifier and anti-tampering device on the packaging. There is no requirement that such a manufacturer has to be located in the Union (EEA). However, if a manufacturer is not in the Union (EEA), then the obligation to ensure that Articles 14 and 15 of the Delegated Regulation (EU) No 2016/161 are complied with lies with the importer.

The Qualified Person at the batch release site in the Union (EEA) will have to ensure that the safety features have been affixed to the packaging (Article 51(1) of Directive 2001/83/EC). This task may be delegated to appropriately trained personnel or third parties, as set out in Annex 16 to the EU GMP guidelines (section 1.7). For general GMP requirements on outsourced activities, refer to Chapter 7 of the EU GMP guidelines.

The responsibility for ensuring that the information is uploaded in the repositories system lies with the MAH (or the person responsible for placing on the market medicinal products which are parallel distributed/parallel imported). The Delegated Regulation does not prohibit MAHs from subcontracting or delegating data-upload tasks to on-boarding partners (OBPs) acting on their behalf. However, the infrastructures, hardware and software used for data upload must be physically located in the EEA (see question 7.19 in Questions and Answers on Safety Features for Medicinal Products for Human Use).

30. Can parallel trade of medicinal products sourced in the UK and supplied to the EU(27) or EEA continue as of the withdrawal date?(NEW)

Parallel trade of medicinal products in the internal market is possible in particular because of (i) the rules in the internal market for the exhaustion of trade mark rights; and (ii) the fact that the summary of product characteristics and the labelling of medicinal products are – apart from issues of language used – identical.

As of the withdrawal date, the rules for exhaustion of trade mark rights in the Union (EEA) no longer apply in respect of products placed on the UK market. Moreover, the terms of the marketing authorisation will over time differ.[19]

Hence, parallel trade of medicines sourced in the UK is in practice no longer possible as of the withdrawal date.

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[19] To this may add national rules on parallel trade of medicinal products with third countries.

However, from the point of view of Union pharmaceutical law, medicines that have been sourced in the UK, and brought into the territory of the EU27 (EEA) before the withdrawal date can continue to circulate on the EU27 (EEA) market if they are authorised.

31. Does, as of the withdrawal date, Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 continue to apply to parallel trade of medicinal products sourced in the UK?(NEW)

Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 address the distribution of a centrally authorised medicinal product from one Member State to another by a pharmaceutical company independent of the marketing-authorisation holder ("parallel distribution"; in the context of this legislation, this notion is to be distinguished from "parallel imports" of nationally authorised products). It does not cover export or import of the product from third countries. Moreover, as of the withdrawal date, central marketing authorisations cease to be valid in the UK. As of the withdrawal date, Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 no longer apply to medicinal products sourced in the UK for the purpose of parallel distribution in EU27 (EEA). However, it is recalled that, as set out in the previous Q&A pair, parallel trade of medicinal products sourced in the United Kingdom will anyhow no longer be possible as of the withdrawal date.

32. Will parallel distribution notices under Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 with UK as the Member State of destination remain valid as of the withdrawal date?(NEW)

Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 address the sourcing of centrally authorised medicinal products in Member States and their distribution in other Member States (to be distinguished from parallel imports of nationally authorised products). It does not cover export or import of the product from third countries. Moreover, as of the withdrawal date, central marketing authorisations cease to be valid in the UK. Therefore, as of the withdrawal date, notices with the UK as the only destination country will become obsolete, whereas, notices with several destination countries will remain valid with respect to EU27 destination countries.

33. Will parallel distribution notices under Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 for a parallel distributor located in UK remain valid as of the withdrawal date?(NEW)

Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 address the sourcing of centrally authorised medicinal products in Member States and their distribution in other Member States (to be distinguished from parallel imports of nationally authorised products). It does not cover export or import of the product from third countries. Moreover, as of the withdrawal date, central marketing authorisations cease to be valid in the UK. Therefore, as of the withdrawal date, notices to distributors in the UK will become obsolete.

Please note that the transfer of parallel distribution notices to another entity is not foreseen and a change of address is possible only in case the legal entity remains the same.

34. Will parallel distribution notices under Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 with a re-packaging site located in UK remain valid as of the withdrawal date?(NEW)

Article 76(4) of Directive 2001/83/EC and Article 57(1)(o) of Regulation (EC) No 726/2004 address the sourcing of centrally authorised medicinal products in Member States and their distribution in other Member States (to be distinguished from parallel imports of nationally authorised products). It does not cover export or import of the product from third countries. Therefore as of the

withdrawal date the UK sites will have to have been removed, in order for these notices to remain valid as of the withdrawal date.

35. What will change regarding reporting requirements into EudraVigilance of Individual Case Safety Reports (ICSRs) from the UK? (for medicines for human use) (NEW)

According to Article 107 of Directive 2001/83/EC **suspected serious adverse reactions** have to be reported no matter if they occurred in the Union (EEA) or in third countries.

Suspected non-serious adverse reactions occurring in third countries do not have to be reported in the Union (EEA). Thus, as of the withdrawal date

- non-serious adverse reactions that have occurred in the UK before the withdrawal date have to be reported;

- it is no longer mandatory to submit to EudraVigilance reports of suspected non-serious adverse reactions that have occurred in the UK as of the withdrawal date.

For individual cases originating from UK and submitted to EudraVigilance before the withdrawal date, when a follow-up information is received by the marketing authorisation holder as of the withdrawal date, it should be continued to be submitted to EudraVigilance when third country reporting criteria apply.

As of the withdrawal date, UK authorities will no longer have access to EudraVigilance. Marketing authorisation holders are therefore reminded that they will need to submit into EudraViglance information that they might receive from UK authorities regarding cases occurring in the UK, in line with the reporting requirements for non-EU/EEA cases.

36. What will be the impact of UK's withdrawal on referral procedures? (NEW)

Referral procedures ongoing on the withdrawal date will continue, irrespective of the Member State that triggered the referral, with the exception of MRP/DCP referral procedures on applications with UK as the reference member state[20].

As of the withdrawal date, UK products will formally no longer be part of Union referral procedures. As a consequence, as of the withdrawal date assessment reports will no longer be shared with marketing authorisation holders/applicants for UK products that were previously concerned by the referral procedure. Nevertheless, all data submitted in the referral procedure, including data submitted on UK products before the withdrawal date, will be taken into account during the assessment.

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[20] As stated in question 1b of the Questions and Answers published by the Coordination Group for Mutual Recognition and Decentralised Procedures - Human and Questions and Answers published by the Coordination Group for Mutual Recognition and Decentralised Procedures – Veterinary http://www.hma.eu/fileadmin/dateien/Veterinary_medicines/CMDv_Website/Brexit/QAs_UK_withdrawal_from_EU_national_authorised_medicinal_products.pdf, with regards to MRP/DCP procedures with UK as the reference member state "For new marketing authorisation applications, if the procedure is not completed before 30 March 2019 (i.e. agreement of the concerned Member States [..] or decision of the Commission [..]) the procedure is stopped and the applicant needs to submit a new application to a new Reference Member State.". Therefore MRP/DCP referral procedures on applications with UK as the reference member state will not continue after 29 March 2019.

A scientific opinion issued as of the withdrawal date, as well as Commission Decisions adopted as of the withdrawal date, will not include UK products. The Commission Decision will only be addressed to the EU27 (EEA) Member States.

The fees for referrals are determined at the start date of procedure. For medicinal products for human use the fees for Pharmacovigilance referrals are calculated based on products authorised in the Union (EEA) (as recorded in 'Article 57 database') at that time. Until the withdrawal date this includes UK nationally approved products.

37. How do I handle, as of the withdrawal date, data from UK in the Periodic Safety Update Reports? (NEW)

Periodic safety update reports (PSURs) should present cumulative and interval summaries of global safety data obtained from various sources worldwide. Relevant safety data obtained from UK sources as of the withdrawal date should therefore continue to be included in PSURs as per usual requirements for third country data.

For the calculation of exposure from marketing experience by region, patients exposed in the UK until the withdrawal date should be included in the EU/EEA estimate. Thereafter, UK patient exposure should be considered as part of the non-EU/EEA regions.