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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**

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

In this regard, marketing authorisation holders of centrally authorised medicinal products for human and veterinary use are reminded of certain legal consequences that need to be considered in a timely manner. Preparing for the consequences of the UK's withdrawal from the Union is not just a matter for European and national administrations, but also for private parties.

This list of Questions and Answers (Q&As) has been drafted jointly by the European Commission and EMA. This version is a first update of the initial list of Q&As published on 31 May 2017 and it replaces that initial list of Q&As. The new text introduced in this version of Q&As 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. **(NEW:)** The transfer of the marketing authorisation must be fully completed and implemented by the marketing authorisation holder before 30 March 2019.

#### **1a. What if I am an applicant established in the UK? (NEW 1 December 2017)**

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



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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*)**

If the sponsor/applicant is established in the UK, the MUMS incentives 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 MUMS outcome letter document reference number.

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). **(NEW:)** 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



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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).



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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 EU GMP requirements and the marketing authorisation. **(NEW:)** 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 company's commercial register. 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.



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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? (NEW 1 December 2017)**

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).

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.<sup>1 2</sup>

### **11. Can medicinal products used in bioequivalence studies be sourced in the UK? (NEW 1 December 2017)**

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 EU or EEA for not less than eight years. According to Article 10(2)(b) of Directive 2001/82/EC and Article 13(2)(b) of Directive 2001/83/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.

Bioequivalence studies 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.<sup>3</sup>

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<sup>1</sup> 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.

<sup>2</sup> 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](https://ec.europa.eu/commission/publications/position-paper-goods-placed-market-under-union-law-withdrawal-date_en).

<sup>3</sup> 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



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**12. How does UK's withdrawal from the Union affect my biosimilar marketing authorisation or biosimilar marketing authorisation application? (for medicines for human use) (1 December 2017)**

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? (NEW 1 December 2017)**

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<sup>4</sup> to the same MAH. The GMA is accompanied only by a single regulatory data protection period<sup>5</sup> which applies both to data relating to the original medicinal product 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? (NEW 1 December 2017)**

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

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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.

<sup>4</sup> [C-629/15P](#), para. 72.

<sup>5</sup> [C-629/15P](#), para. 65.



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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.

**15. How does UK's withdrawal from the Union affect traditional herbal medicinal products (traditional-use registration)? (for medicines for human use) (NEW 1 December 2017)**

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) (NEW 1 December 2017)**

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? (NEW 1 December 2017)**

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? (NEW 1 December 2017)**

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



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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? (NEW 1 December 2017)**

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.

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