EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

3. Impact of Brexit on Veterinary applications/marketing authorisations

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EC/EMA Questions and Answers

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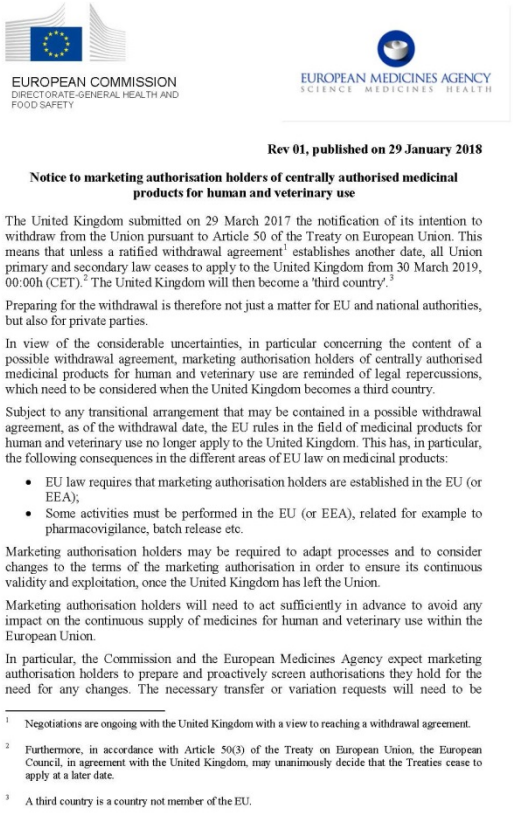
2017 publication of EC Q&A update – EMA procedural guidance

2017 Publication of EC Q&A update - EMA procedural guidance – EMA Survey	
02.05.17	**Publication of EC/EMA** Notice **to marketing authorisation holders** of centrally authorised medicinal products for human and veterinary use
31.05.17	**Publication of EC/EMA** Q&A 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 *
24.11.17	**Publication EMA** Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure
01.12.17	**Publication** of **updated EC/EMA** Q&A 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
29 January 2018	**Revised Notice, revised EC/EMA** Q&A **and revised EMA** Practical guidance published

EC/ EMA Notice to MAHs

- EC and EMA published a **Notice to MAHs** of centrally authorised medicines products for human and veterinary use
- Unless a ratified withdrawal agreement establishes another date, **UK** will become a **'third country**' from 30 March 2019, 00:00h (CET).
- Companies reminded to **plan in advance in order to avoid any impact on the continuous supply of medicines** for human and veterinary use within the Union (EEA).



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DIRECTORATE-GENERAL HEALTH AND FOOD SAFETY

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Rev 01, published on 29 January 2018

Notice to marketing authorisation holders of centrally authorised medicinal products for human and veterinary use

The United Kingdom submitted on 29 March 2017 the notification of its intention to withdraw from the Union pursuant to Article 50 of the Treaty on European Union. This means that unless a ratified withdrawal agreement[1] establishes another date, all Union primary and secondary law ceases to apply to the United Kingdom from 30 March 2019, 00:00h (CET).[2] The United Kingdom will then become a 'third country'.[3]

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

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

Subject to any transitional arrangement that may be contained in a possible withdrawal agreement, as of the withdrawal date, the EU rules in the field of medicinal products for human and veterinary use no longer apply to the United Kingdom. This has, in particular, the following consequences in the different areas of EU law on medicinal products:

- EU law requires that marketing authorisation holders are established in the EU (or EEA);
- Some activities must be performed in the EU (or EEA), related for example to pharmacovigilance, batch release etc.

Marketing authorisation holders may be required to adapt processes and to consider changes to the terms of the marketing authorisation in order to ensure its continuous validity and exploitation, once the United Kingdom has left the Union.

Marketing authorisation holders will need to act sufficiently in advance to avoid any impact on the continuous supply of medicines for human and veterinary use within the European Union.

In particular, the Commission and the European Medicines Agency expect marketing authorisation holders to prepare and proactively screen authorisations they hold for the need for any changes. The necessary transfer or variation requests will need to be

[1] Negotiations are ongoing with the United Kingdom with a view to reaching a withdrawal agreement.

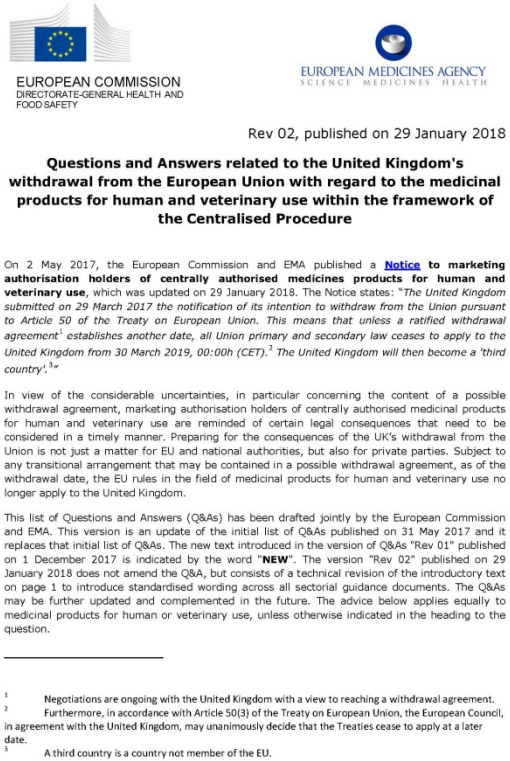
[2] Furthermore, in accordance with Article 50(3) of the Treaty on European Union, the European Council, in agreement with the United Kingdom, may unanimously decide that the Treaties cease to apply at a later date.

[3] A third country is a country not member of the EU.

EC/EMA Q&As

- Questions and Answers Document published jointly by EMA & EC covers both human and veterinary medicinal products
- Provides a **legal interpretation** of principles to be applied in a consistent manner across the pharmaceutical network (human and veterinary)
- Corresponding guidance for MRP/DCP has been published in parallel by CMDh/CMDv

- Several updates since the initial version in May 2017; further updates expected



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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Rev 02, published on 29 January 2018

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**, which was updated on 29 January 2018. The Notice states: "*The United Kingdom submitted on 29 March 2017 the notification of its intention to withdraw from the Union pursuant to Article 50 of the Treaty on European Union. This means that unless a ratified withdrawal agreement[1] establishes another date, all Union primary and secondary law ceases to apply to the United Kingdom from 30 March 2019, 00:00h (CET).[2] The United Kingdom will then become a 'third country'.[3]*"

In view of the considerable uncertainties, in particular concerning the content of a possible withdrawal agreement, 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 EU and national authorities, but also for private parties. Subject to any transitional arrangement that may be contained in a possible withdrawal agreement, as of the withdrawal date, the EU rules in the field of medicinal products for human and veterinary use no longer apply to the United Kingdom.

This list of Questions and Answers (Q&As) has been drafted jointly by the European Commission and EMA. This version is an 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 the version of Q&As "Rev 01" published on 1 December 2017 is indicated by the word "**NEW**". The version "Rev 02" published on 29 January 2018 does not amend the Q&A, but consists of a technical revision of the introductory text on page 1 to introduce standardised wording across all sectorial guidance documents. 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.

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[1] Negotiations are ongoing with the United Kingdom with a view to reaching a withdrawal agreement.
[2] Furthermore, in accordance with Article 50(3) of the Treaty on European Union, the European Council, in agreement with the United Kingdom, may unanimously decide that the Treaties cease to apply at a later date.
[3] A third country is a country not member of the EU.

EMA Procedural Guidance

- Provides more **practical guidance** and complements the EC-EMA Q&A; will be updated accordingly.
- Covers submission of applications for changes and related fees in centralised procedure
- Covers both human and veterinary medicinal products
- Aimed at, where possible, a simplified approach nevertheless respecting legal requirements.

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29 January 2018
EMA/478309/2017 Rev. 1[1]
Human Medicines Evaluation Division
Veterinary Medicines Division

Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure

On 2 May 2017, the European Commission and EMA published a **Notice** to marketing authorisation holders (MAHs) 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 view of the considerable uncertainties, in particular concerning the content of a possible withdrawal agreement, MAHs 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 a significant matter for European and national administrations, and also equally important for private parties. Subject to any transitional arrangement that may be contained in a possible withdrawal agreement, as of the withdrawal date, the EU rules in the field of medicinal products for human and veterinary use no longer apply to the United Kingdom.

In order to consider the necessary changes, a list of Questions and Answers (Q&As) 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 drafted jointly by the European Commission and EMA is available on the EMA website.

The below Practical Guidance has been developed taking into consideration that as of 30 March 2019 the United Kingdom will become a third country. As a result, MAHs and applicants of centrally authorised products for human or veterinary use need to ensure that the necessary changes are made by the 30 March 2019, unless indicated otherwise in the guidance below.

This document complements the EC-EMA Q&A to provide procedural and practical guidance regarding submission of changes and related fees.

[1] Revision 1 does not amend the guidance, but revises only the introductory text on this page, aligning it with the amended introductory text in corresponding EC-EMA Q&A.

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Establishment/location requirements (1/4)

UK MAH

- MA **transfer** to a Holder in the Union (EEA) **required**
- To be fully completed and implemented before 30 March 2019

UK Applicant

- For MAAs to be granted a MA after 29 March 2019 need to be **changed** to non-UK applicants established in the Union (EEA)
- Recommended to change in advance of MAA submission

UK based SME

- Guidance for **non-EEA** based companies will apply after 29 March 2019
- New legal entity (SME) in the Union (EEA) or benefit indirectly through SME consultancy in Union (EEA)

Establishment/location requirements (2/4)

UK company with MUMS status for its medicinal product

- MUMS (Minor Use Minor Species/limited market) incentives will no longer be applicable after 29 March 2019
- Not yet authorised products with MUMS/limited market classification: classification is connected to the product/indication; thus classification transferable together with the product.
- Authorised products with MUMS/limited market classification: transfer of the MA does not include a transfer of a MUMS/limited market classification = done through different procedure.

Establishment/location requirements (3/4)

UK QPPV

- The Qualified Person for Pharmacovigilance (QPPV) will need to change place of residence and carry out tasks in the Union (EEA) or a new QPPV in the Union (EEA) will need to be appointed

Local Representative located in the UK

- Nominated for Member States other than the UK: will have to be changed to a local representative located in the Union (EEA)
- Nominated for UK: After 29 March 2019 becomes obsolete

Establishment/location requirements (4/4)

Manufacturing site in UK	UK batch control site	UK Batch release site
• Active substances and medicinal products manufactured in the UK will be considered as ***imported*** *after 29 March 2019*	• Upon importation batch control needs to be conducted (repeated) in a site **in the Union (EEA)**	• Needs to be changed to a site **in the Union (EEA)**

Impact on generic and hybrid products

Generic/ hybrid products rely on data of the reference medicinal product that is or has been authorised in the Union (EEA).

Generic / Hybrid MAs granted before 30 March 2019

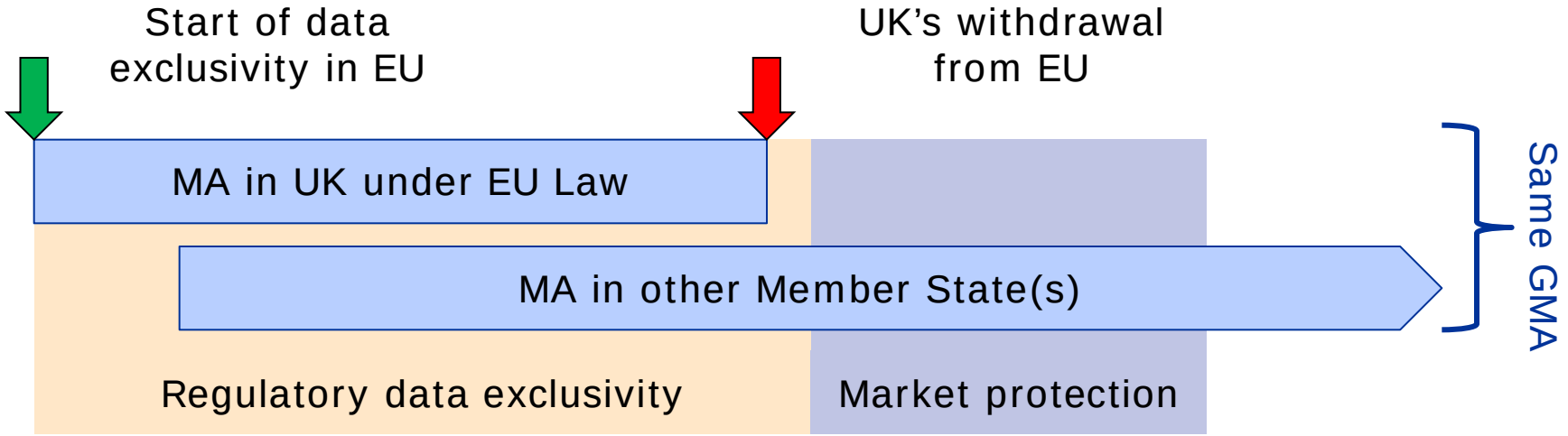
Remain valid even if reference product is authorised in UK

Generic / HybridMAs granted after 29 March 2019

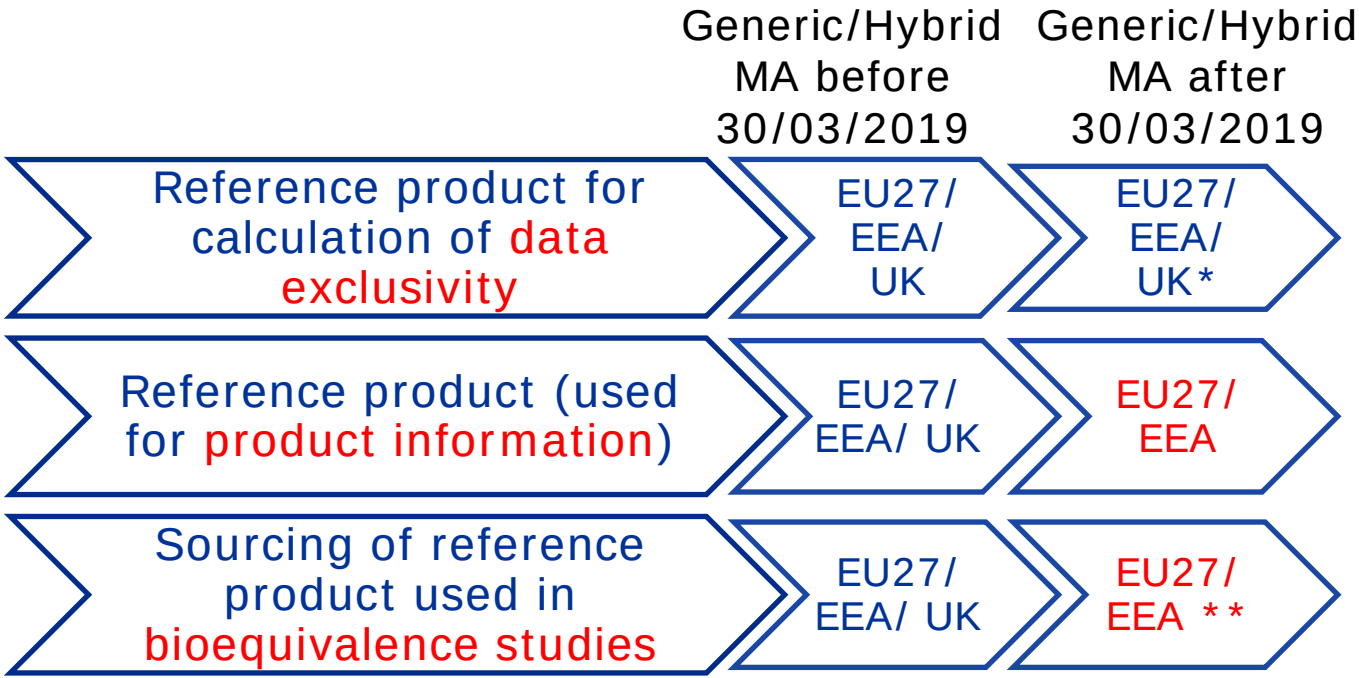
Reference product must be authorised in EU27/ EEA

Global marketing authorisation (GMA)

MAs granted before 30 March 2019 by UK can still be considered as the initial MA for the purpose of calculating data exclusivity and marketing protection periods



Various reference products in the application form



* Granted by UK before 30 March 2019

** Exceptions possible for applications pending on 29 March 2019

Other aspects

Well-established use applications	UK data from before 30 March 2019 can be used as EU/EEA data
Sunset clause	If marketed only in UK – timer starts from last placing on UK market before 30 March 2019
Contact persons	Expectation that contacts for product defects/recalls are in EU/EEA. Recommended also for applicant/MAH.

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EMA Practical Guidance, including post-authorisation aspects and impact on manufacturing and supply

Presented by: Beyhan Mustafov, Veterinary Regulatory and Organisational Service, EMA
Andrei Catalin Spinei, Manufacturing and Quality Compliance Service, EMA

MA transfers for centrally authorised veterinary medicinal products (1/3)

- 20 MA transfers for centrally authorised veterinary medicinal products are expected.
- Need to smoothen the procedural handling while maintaining the regulatory and legal requirements (i.e. 1 MA transfer submitted for each MA).
- Need for increased flexibility on MA transfers with regards to other ongoing procedures.
- Need to increase flexibility on the implementation period for the new MAH.

MA transfers for centrally authorised veterinary medicinal products (2/3)

- Mock-ups requirements waved when only the MAH's name & address change.
- Implementation period longer than 6 months (but not exceeding 29 March 2019).
- Any other regulatory procedures can run in parallel to transfers.
- Single opinion document per MA transfer.

MA transfers for centrally authorised veterinary medicinal products (3/3)

- All MAHs are advised to get in touch as soon as possible with vet.applications@ema.europa.eu

- Close interactions with MAHs to advise on the best use of the simplifications in order to optimise the smooth running of the transfers
  - ✓ Preparatory TCs, pilot submissions, pre-submission checks

- Experience so far…….

Update of local representatives in the product information for centrally authorised veterinary medicinal products

- Any UK local representative that is nominated as representative for other EU/EEA MS for the product needs to be changed **before 30th March 2019**.
  - ✓ Update as part of any regulatory procedure affecting Annexes finalising before 30th March 2019 (e.g. Type IA, IB, II, renewal, PSUR-var) -> Preferred option
  - ✓ By submission of a Type IA_{IN} C.II.6.a
- Deletion of UK representative **after 29th March 2019**
  - ✓ At the earliest regulatory procedure affecting Annexes finalised after 29th March 2019 (e.g. Type IA, IB, II, renewal, PSUR-var)

Changes of QPPV

- The relocation of QPPV from UK to an EU/EEA Member State should be notified through the submission of a Type IA_{IN} (C.I.9.a) before 30th March 2019.

Transfer of minor use / minor species (MUMS) / limited market classification

- MUMS/limited market classification is connected to the product/indication (i.e. **transferable together with the product**), **but to formally acknowledge the transfer, a separate letter from the UK sponsor / applicant is required** officially informing the EMA of the transfer of the classification from the UK sponsor/applicant to a sponsor/applicant established in the Union (EEA).

Changes to manufacturing and supply (1)

1. Importation

Medicinal products manufactured in third countries need to be imported by an authorised importer established in the Union (EEA)

- ✓ **Finished product currently manufactured in the UK** -> an importation site in the Union (EEA) needs to be approved before 30th March 2019
- ✓ **Finished product manufactured in a third country and currently imported into UK** -> an importation site in the Union (EEA) needs to be approved before 30th March 2019

Changes to manufacturing and supply (2)

2. Batch control

Each batch of medicinal products manufactured in third countries needs to undergo a full qualitative and quantitative analysis in accordance with the registered specifications at an appropriately authorised quality control laboratory in the Union (EEA)

- ✓ **Finished product currently manufactured in the UK** -> a quality control site in the Union (EEA) needs to be approved before 30th March 2019
- ✓ **Finished product manufactured in a third country and currently batch controlled in UK** -> a batch control site in the Union (EEA) needs to be approved before 30th March 2019

Changes to manufacturing and supply (3)

3. Batch release

Each batch of medicinal product manufactured in third countries needs to be certified by a QP that each batch of medicinal product was manufactured in accordance with GMP and the marketing authorisation

- ✓ **Finished product currently manufactured in the UK** -> a batch release site in the Union (EEA) needs to be approved before 30th March 2019
- ✓ **Finished product manufactured in a third country and currently batch released in UK** -> a batch release site in the Union (EEA) needs to be approved before 30th March 2019

Changes to manufacturing sites

Manufacturing process	Non-biological/non-immunological product	Biological or immunological product
Addition or replacement of site		
The UK site is only a batch release site and/or importation site for the finished product	Type IA_{IN} (B.II.b.2.c.1)	Type IA_{IN} (B.II.b.2.c.1)
The UK site is a batch release and quality control site of the finished product	Type IA_{IN} (B.II.b.2.c.2)	Type IB (B.II.b.2.c.2) if the test methods performed at the site are not biological/immunological/immunochemical methods. Otherwise, it is Type II (B.II.b.2.c.3)
The UK site is only a quality control site of the finished product	Type IA (B.II.b.2.a)	Type IB (B.II.b.2.a) if the test methods performed at the site are not biological/immunological/immunochemical methods. Otherwise, it is Type II (B.II.b.2.b)
Deletion of a manufacturing site		
Deletion of site(s) for batch release, packaging, batch control[3]	Type IA (A.7)	Type IA (A.7)

- All variations are Type IAs except the addition of QC testing sites for biological methods, where a Type II is needed for the site transfer.
- Two strategies can be done by MAHs:
  - ✓ Replacement (add and delete of sites in the same variation)
  - ✓ Addition of sites and then deletion of UK sites through an A.7 scope.
- ✓ Any UK importation/batch control/batch release site should be deleted
- Multiple sites can be deleted in one A.7 scope.

Next steps?

- Future updates are planned

How to proceed with Brexit questions on CAPs?

- For **veterinary CAPs**: vet.applications@ema.europa.eu

- **General queries** – through AskEMA (suggest using web-form)