EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guidance on preparing for Brexit in the centralised procedure

SME info day: Regulatory toolbox for medicines and combined devices developers

Presented by Leonor Enes on 26 October 2018
SME Office, Stakeholders and Communication Division

An agency of the European Union

Agenda

1. Available guidance
2. UK based SMEs: Qualification/Incentives
3. Aspects related to the centralised procedure:
   a. development of medicines
   b. ongoing MAA (Marketing Authorisation Application): UK applicant
   c. marketing authorisation: UK MAH (Marketing Authorisation Holder)
4. Implementation of the redistribution of the UK centrally authorised products portfolio
5. Key messages

Available guidance

EC and EMA 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).

Questions and Answers Document (Q&A) published jointly by EMA & EC. Provides a legal interpretation of principles to be applied in a consistent manner across the pharmaceutical network (human and veterinary) and across sectors

EMA Practical Guidance. Provides more practical guidance and complements the EC-EMA Q&A. Covers submission of applications for changes and related fees in centralised procedure

I am a UK based SME:

how can I continue to benefit from SME incentives?

Guidance for **non-EEA** based companies will apply after 29 March 2019

Two possible ways:

a) Establish a new legal entity in the Union (EEA) and apply for SME status directly

b) Indirectly through an Union (EEA) established SME regulatory consultancy. Both Non-EEA company and EEA consultant need to meet the SME criteria (i.e. fall below headcount and financial thresholds). The regulatory consultancy receives an SME notification and the non-EEA based company is listed in an annex to that notification as an SME client company

EMA SME figures as of October 2018

1861 total SMEs registered with EMA

286 *(15,3%)* UK based SMEs registered with EMA

15 UK based SMEs have already created a EU27/EEA subsidiary due to Brexit (***10*** qualified and ***5*** qualifications ongoing).

Aspects related to the development of medicines - Transfer of orphan designation

Need to transfer the designation to a sponsor established in the Union (EEA) or change the place of establishment to the Union (EEA)

Free of charge. An application must be submitted for each designation.

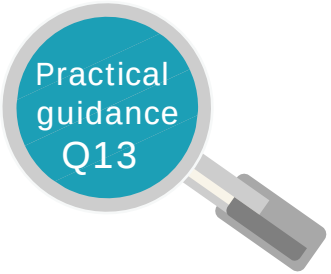
Guidance

- 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,
- Checklist for sponsors applying for the transfer of Orphan Medicinal Product (OMP) designation, and the corresponding templates.

Contact point: orphandrugs@ema.europa.eu

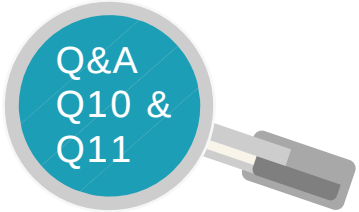
Aspects related to the development of medicines: Paediatric Investigation Plans (PIPs) and waivers

No requirement for Paediatric Investigation Plan/ Waiver addressee to be established in the EU/EEA



Aspects related to the development of medicines: generic, hybrid and biosimilar products

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



MAs granted before 30 March 2019

Remain valid even if reference product is authorised in UK

MAs granted after 29 March 2019

Reference product is or has been authorised in EU27/ EEA

Aspects related to ongoing MAA

For MAAs to be granted after 29 March 2019, the applicant needs to be **changed** to non-UK applicant established in the Union (EEA)

Practical guidance Q10

Detailed guidance on requesting change of the applicant

Other updates: UK Qualified Person for Pharmacovigilance (QPPV), Pharmacovigilance Master File (PSMF), batch release and batch control sites, intended Official Medicines Control Laboratory (OMCL) and nominated local representatives may also need to be changed.

Practical guidance Q11

SMEs statistics as of October 2018

UK MAA / total MAA	OD in UK	PSMF UK	QPPV UK	Batch control UK only	Batch Release UK only	Importation UK only
10/16	*5*	*13*	*12*	*9*	*4*	*1*

Aspects related to Marketing Authorisations

Changes required include

UK MAH

UK QPPV and PSMF located in UK

UK batch control site

UK Batch release site

Importation for manufacturing site in UK

SMEs statistics as of October 2018

UK MAA / total MAA	OD in UK	PSMF UK	QPPV UK	Batch control UK only	Batch Release UK only	Importation UK only
20/31	*3*	*18*	*16*	*4*	*9*	*1*

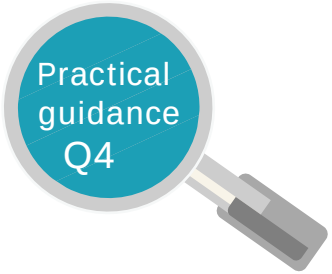
Aspects related to Marketing Authorisations: MAH transfer

MA **transfer** to a Holder in the Union (EEA) **required**

Orphan drugs: need to **transfer** the designation to a sponsor established in the Union (EEA) or change the place of establishment to the Union (EEA)

Transfer to be fully completed and implemented before 30 March 2019

Contact point: matransferquery@ema.europa.eu



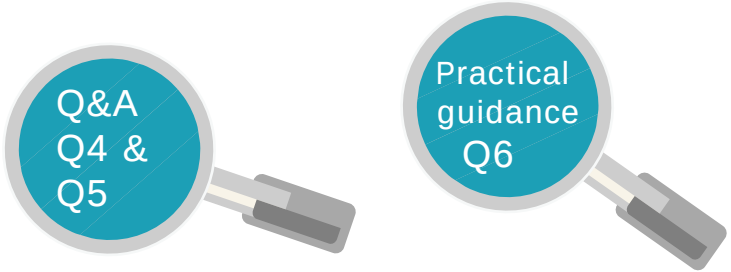
Aspects related to Marketing Authorisations: UK Qualified Person for Pharmacovigilance (QPPV) and Pharmacovigilance Master File (PSMF) located in UK

QPPV must reside and carry out his/her tasks in an EEA Member State

PSMF must be located within EEA

- *Guidance:* See question: How to inform the authorities of a change in the summary of the pharmacovigilance system?

Notification through Article 57 database



Aspects related to Marketing Authorisations: manufacturing and supply

Manufacturing	UK batch control site	UK Batch release site	OMCL
• 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)**	• Upon importation ***batch release*** needs to be done **in the Union (EEA)**	• Official Control Authority Batch Release ***(OCABR)*** needs to be conducted by an OMCL in the Union (EEA)

Changes to manufacturing and supply (1)

1. Importation of finished product

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

2. Importation of APIs (Active Pharmaceutical Ingredient)

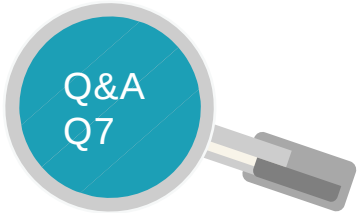
APIs manufactured in the UK will need to be accompanied by a written confirmation from MHRA confirming GMP compliance

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

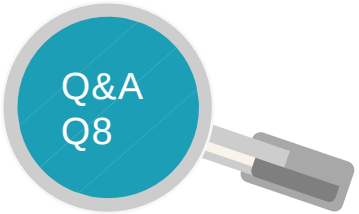


Changes to manufacturing and supply (3)

3. Batch release

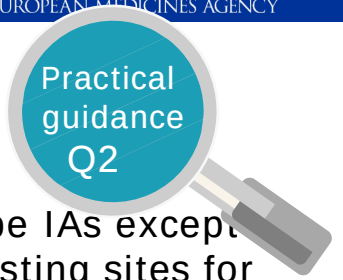
Each batch of medicinal product manufactured in third countries needs to be certified by a QP that each batch of medicinal product was manufactured in accordance with GMP and the marketing authorisation

- **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.

Changes to manufacturing and supply (4)

4. Official Medicines Control Laboratory (OMCLs)

For products for which Official Control Authority Batch Release (OCABR) is required, this needs to be carried out by an OMCL located within the Union (EEA) or by a country officially recognised by the EU for mutual recognition of batch release

- **Finished product currently controlled by a UK OMCL** -> a new OMCL needs to be identified and notified by the MAH to conduct OCABR before 30th March 2019

Aspects related to Marketing Authorisations: medical devices

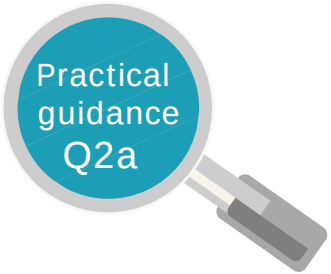
CE marking of medical devices

- EC Notice on industrial products
- CE marking supported by UK Notified body - need to apply for a **new certificate issued by an EU-27 Notified Body** or arrange for a transfer

Information in the dossier

- For **medicinal products that are co-packaged** with a medical device CE marked based conformity assessment by UK Notified Body – need to update the documentation or remove/replace device

Variations for changes related to medical devices



Medical device forming a single integral product with the medicinal product	Medical device is co-packaged with the medicinal product
Same medical device is maintained, but the Notified Body supporting the CE marking is changed	
Variation not required (CE marking not mandatory), but if documentation in the dossier is updated: Type IA_{IN} (B.IV.1.a)	Type IA_{IN} (B.IV.1.a)
Replacement of the medical device with an alternative CE marked medical device	
Replacement not required (CE marking not mandatory), but if replacement is made: Type II (B.IV.1.c)	For device without significant impact on the delivery of the active substance: Type IA_{IN} (B.IV.1.a) For device with significant impact on the delivery of the active substance: Type II (B.IV.1.a)
Removal of the medical device from the pack	
Not applicable	Type IA_{IN} (B.IV.1.b)

Implementation of the redistribution of the UK centrally authorised products portfolio

- New (Co)-Rapporteurships were communicated to MAHs.
- The new (Co)-Rapporteurs will only take full responsibility for the re-allocated medicinal products as of 30 March 2019 when the UK withdraws from the Union and becomes a third country. The MHRA will be accountable for the medicinal products for which they are (Co)-Rapporteurs until 29 March 2019
- However, the new (Co)-Rapporteurs may be required to handle, from Q4 2018 onwards, post-authorisation procedures when it is envisaged that the procedures may be still under evaluation after the 30 of March 2019
- The decision is taken at procedure level and depending on the average length of the procedure
- Cut-off dates for each procedure are published at EMA website (here) taking into consideration the deadline of 30 March 2019

Key messages: prepare for BREXIT

- Work on a scenario that UK will be a “third country” on 30/03/19
- Use available published guidance
- Use pre-submission meetings (offered as a teleconference) to discuss details related to BREXIT preparedness
- For product related queries liaise with the procedure manager as early as possible
- Submit changes promptly
- Submit general questions via AskEMA
- Contact the SME Office for support to continue to benefit from SME incentives

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Any questions?

Further information

See: supporting SMEs

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Post-meeting slide

Link to the NOTICE TO STAKEHOLDERS on the WITHDRAWAL OF THE UNITED KINGDOM AND EU RULES IN THE FIELD OF CLINICAL TRIALS mentioned during the Q&A.