29 March 2018
EMA/167192/2018

Industry Stakeholder meeting/webinar on Brexit and operation of the centralised procedure for human medicinal products

23 March 2018

**General notes *(see also slides circulated on 28/03)***

**Withdrawal agreement / transition period / future relationship (Olga Solomon, DG Santé)**

Working bottom line UK will become a 3rd country, from 30 March 2019, get prepared for that. It is a joint responsibility on companies and regulators to address the challenge and opportunity for EU MS to take over workload of MHRA. Issues are more complex for nationally authorised products, given the higher volume, but HMA and CMDh are working on this. Withdrawal agreement is winding down of UK membership. Transition period the full acquis will apply (e.g. MAH adopted in this period will also apply to the UK, or any other changes). UK will no longer participate in the EMA management board, CMDh and CHMP, no longer act as leading assessment authority (RMS, Rapporteur) and full role of court of Justice would apply. However, the political progress still ongoing and agreement still has to be ratified. Do NOT rely on the transition period for preparedness/business planning (expected October 2018).

**Submissions of BREXIT changes (Tony Humphreys, Head of Scientific Committees Regulatory Science Strategy)**

10% of EMA resource has been diverted to focus on relocation activities. Expected staff loss is expected to be quite high. For EMA this is the main uncertainty in context of relocation. Please avoid Q1-2019 in submitting variations, no guarantee the system will be as efficient as one expects it to be.

**Re-distribution of Rapporteurships (Monica Dias, Policy and Crisis Management)**

Methodology of re-allocation building on existing knowledge: 1) procedures are either allocated to the current Co-Rapporteur, 2) peer reviewer of the initial MAA, allocation expertise based on ATC code. In cases of different products of a MAH with same INN, these will be allocated to the same Rapporteur.

Implementation: allocation has been completed. Companies will be informed of the new Rapporteur allocation on April 30, 2018. UK will remain lead until March 2019, in the meantime the new Rapporteur will work together with UK in parallel as shadow Rapporteur, after which the new Rapp. will take over.

Knowledge transfer: EMA will support the new Rapporteur by creating a knowledge transfer package for products. Companies are expected to play a role in this process of knowledge transfer (including understanding of upcoming procedures - forecast).

**EMA survey**

Analysis still ongoing (EMA received 91% response feedback), they are currently following up with those companies in case of incomplete responses. After this is done EMA will share an overview of initial findings/summary report (expected early May). A second survey will be launched soon, to check for authority capacity for MRP/DCP. Results to be expected ready Q2 2018.

**Updated Q&A / practical guidance**

Still being discussed (scope not clear /shared), but expected in Q2-2018 for consultation.

**Product specific queries**

Companies were further encouraged to reach out the EMA in case of product specific questions or alignment of upcoming submissions. Especially in the case of MAH transfers in parallel to ongoing procedures it is considered important to agree on the best strategy to obtain the Commission Decision.

**List of questions from industry associations**

| **Industry stakeholders organisations** | **Theme** | **Topic** | **Date** | **Questions** |
| --- | --- | --- | --- | --- |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | MAH | Changing MAH due to BREXIT as a Variation | 13/03/17 | 1. The annexed document further outlines the regulatory / legal rationale that appointing a legal entity from the same family of companies as the new MAH due to Brexit can be notified as a variation as opposed to a transfer of an MA under Regulation 2141/96. The document also explains why making these changes as a variation rather than an MA Transfer will have a positive impact on the use of resources needed to make this administrative change (see Annex)

**Response:** EC retain their view that this is not a variation. Transfers are from one legal entity to another legal entity and the MAH transfer procedure should be used. Concept of same MAH is used in certain clearly defined situations.EMA took into account the legal analysis from industry, and therefore have proposed simplifications to the transfer process. Companies are allowed to have a combined version of all documents submitted. Mock up requirements have been waived. Implementation period is very flexible, not exceeding 29th of March. Parallel variations/procedures (also renewals, notifications) are allowed. FMD/serialisation can be incorporated into MA transfer plans.It is recommended for companies to contact EMA transfer queries for advice and for pre-checking of submissions. Use the special mailbox for questions.  |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | MAH | Transfer of MAHs | 13/03/17 | Given the high volume of products impacted there is a need to agree on a pragmatic way to update artworks with the Brexit related change in MAH with other ongoing activities such as manufacturing changes and serialisation.2. We acknowledge that the current EMA guidance permits that implementation of the change in artwork can be longer than 6 months but must be prior to March 2019. For procedures where the MAH change is administrative i.e. the MAH remains within the same company so there is no material change per se. Could EMA consider longer implementation time-lines e.g. one year from Commission Decision? **Response:** Implementation must be complete by 29 March 2019 (i.e. product QP released after 29 March 2019 must have new packaging)3. In the situation where an MAA is approved before the planned submission of the change in MAH but the launch is not planned until after the change in MAH is approved (so the product is approved but not yet marketed), can these procedures also follow the same implementation date agreement as above? The standard MA transfer process for a product not yet marketed requires that the proposed date of implementation should be the day on which the Commission Decision on the Transfer is issued. This does not allow the same flexibility with regard to implementation dates as marketed products.**Response:** If launch would be after transfer, launched product would haveto reflect new MAH. EMA will discuss alternatives in very exceptional cases. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | MAH | Ongoing MAAs – Brexit related MAH change process | 13/03/17 | 4. Clarification would be appreciated on the process to update an ongoing MAA with a Brexit related change to the MAH name and/or address? Can it occur at day 120/180?**Response:** yes, but implemented by 29 March 2019. A new MAH can be introduced to ongoing MAA but this must be prior to 30 March 2019 and cannot create a duplicate MAA. Make sure that you do the transfer of Orphan designation before transfer of applicant. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | MAH | MAH transfer national requirements | 13/03/17 | 1. Industry is encountering additional national requirements following an MAH Transfer for a centralised product (e.g. requirements for submission of a national variation to implement the opinion). These undermine the agreed position within the CHMP opinion and EC Decision. Can EMA support engagement with HMA/CMDh to confirm that no additional steps are needed at a national level?

**Response:** No further discussions. EMA will discuss with CMDh and HMA Task Force. EMA are not aware of this situation and companies are advised to share any examples. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | Manufacturing and Supply | Products placed on the marketMultipacks | 13/03/17 | It has already been stated that products that have been placed on the market prior to the date that the UK leaves the EU can remain on the market.1. We presume that ‘placed on the market’ means the product has been QP-released by the manufacturer and placed into the distribution chain, can the EMA/COM confirm this interpretation is correct?

**Response:** The “green section” of the draft withdrawal agreement states that product placed on the market prior to the UK leaving the EU can stay on the market. Definition of placed on the market: when a product enters distribution chain after QP release it can stay on the market, this includes named patient supplies.1. Is there a potential for an arrangement for continuation of multi-country packs after UK leaves the EU? This would support public health in the EU especially in smaller markets such as Ireland, Malta and Cyprus.

**Response:** no prior example of having a third country on the packaging of an EU product.  EMA is exploring whether this could be possible but only when labelling remains fully harmonized – EMA will communicate to industry when a final decision is reached. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | Manufacturing and Supply | Inspectorate Q&A | 13/03/17 | 1. In various meetings EMA mentioned the publication of a Q&A with EU inspectorate sections to clarify in writing some question like acceptance of UK GMP certificate after Brexit, how re-inspection program will be conducted, impact on renewal if EU GMP has not been granted prior a UK GMP expires, etc... Please clarify status and timelines for this Q&A.

**Response:** GMP certificates issued by UK after 30 March 2018 will be from a third country and so can only be considered as supporting information, and won’t be able to replace EU- GMP certificates. However, it can be used as part of a risk based approach / planning. EMA is drawing up a list of 3rd country sites currently inspected by the UK where EU GMP certificates will need to be issued on expiry of the current certificates issued by the UK.Arrangements for the transition period meaning of “UK acquis” is too uncertain. Remind that actual negotiations on future relationship will only be ratified upon withdrawal. We prepare for a withdrawal date of 29-03-2018. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | Certificate of pharmaceutical product (CPP) | Recognition of the EMA signatories | 13/03/17 | 1. We understand that EMA CPP signatures are not recognized in the Netherlands and therefore each CPP issued by the EMA will also have to be sent to the Ministry of Foreign Affairs (MOFA) before being legalized. This would be an additional unnecessary step which will have an impact on costs and increase the processing timeline, potentially delaying regulatory submissions. Can the EMA advice if they will be seeking to gain recognition of the EMA signatories in the Netherlands?

**Response:** EMA don’t believe that CPPs need legalisation. Companies are requested to share further info.  |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | Certificate of pharmaceutical product (CPP) | EMA legal entity on certificates/CPPs | 13/03/17 | 1. Taking into account the upcoming relocation of EMA and issuing certificates/CPPs could EMA advice when will be the effective date of the move from London to Amsterdam and to which address?

**Response:** CPP is effective on the date on which it is issued. On the date a certificate is issues it will contain the current address on that date (please refer also to EMA relocation tracker on the website). |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | CP operational aspects | EMA timeline for review | 13/03/17 | 1. Given the volume of submissions and other ongoing activities, can the EMA confirm that they still expect the review timelines to remain the same?

**Response:** EMA have put measures in place through their BCP to maintain their core activities. Relocation in Q1 2019, Advice to industry don’t wait till last minute to make changes, don’t leave submission to Q1 2019 as EMA will be preparing to relocate. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | CP operational aspects | Reallocation of (Co)-Rapporteurships | 13/03/17 | 1. Although it has been indicated that EMA is of the intention to communicate the re-allocation plans to MAHs around the end of 1Q, it would be helpful to have a better understanding of what the reallocation plans are, including expected timelines.

**Response:** Rapporteur reassignment for planned MAAs is still under discussion and will be communicated separately (see general notes / EMA slides). Companies are informed end of April; UK will remain responsible until 29 March 2019. There might be a possibility for the MAH to meet the future Rapporteur as part of the knowledge transfer (also to discuss forecast –planning of procedures). |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | CP operational aspects | Scientific advice | 13/03/17 | 1. Can we get confirmation that UK scientific advices will still be recognized for future applications? For some products these advices have already been obtained, while applications are still to come in future.

**Response:** Reminded that scientific advice is not binding. SA from UK can still be provided as supporting information as it is not prohibited to include non EU Scientific Advice in application. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | CP operational aspects | EMA meetings with individual companies | 13/03/17 | 1. From EMA correspondence around their Brexit preparedness survey, it seemed that EMA intends for Brexit-related discussions with companies to be handled in the context of Business Pipeline meetings. The need for - and EMA participation at – meetings to discuss companies’ Brexit plans should be prioritised and should be based on potential issues and questions identified by companies in respect of their products.

**Response:** For product specific issues, contact the product manager. For broader discussions, these will be organised through Pipeline meetings. If none is schedules the company is requested to reach out with a specific request and what needs to be discussed. |
| EFPIA, EBE, Vaccines Europe, AESGP, EUCOPE, EuropaBio, Medicines for Europe, EuropharmSMC | Pharmacovigilance | Deputy QPPV | 13/03/17 | 1. In follow-up to recent discussions, could EMA/COM provide confirmation that there will be no change to back-up procedures to meet the QPPV’s legal obligations (deputy QPPV), once the UK has left the EU?

**Response:** deputy and back-up procedures should occur inside the EU. If transition period adopted uncertain if UK based QPPV still be recognized during that time - strongly encouraged to make change by 30 March 2019 but some uncertainty which needs follow up. |
| EIPG | Transitional period | Transitional period | 11/03/18 | 1. If the terms of the “European Commission Draft Withdrawal Agreement on the withdrawal of the United Kingdom of Great Britain and Northern Ireland from the European Union and the European Atomic Energy Community” were to remain as currently proposed by the European Union, can it be confirmed that during the transitional period, post March 2019, medicinal product can move from UK to the rest of Europe, and vice versa, under current conditions and regulations.

**Response:** Yes, if transition period is agreed as part of Withdrawal Agreement, this would also include clinical trials materials. |
| EIPG | Manufacturing | QP/ReleaseTransfer MAHs/Multi-packs | 11/03/18 | 1. Ireland has many joint packs with the UK and if the legal entity address is in the UK, they will need to be transferred to an address in the EU 27. This is another variation with diverging regulations and associated implementation timelines which may be challenging to implement for small volume products such as niche products or older but medically necessary products. No doubt this kind of product will have to be withdrawn from the Irish market as plants have minimum order quantities and Irish only packs will be non-viable.

If a product physically moves from the European mainland to Ireland by road through the UK there is concern that the product will need to be QP released again in Ireland. If products are in a sealed truck with shrink wrapped pallets, will products still require double QP release?**Response:** Same rules will apply as to current 3rd countries. If product transits via a 3rd country then customs rules will apply. In the above scenario products will be handled as goods that have transited through a third country. |
| EIPG | FMD/Manufacturing | FMD/Manufacturing/QP | 11/03/18 | 1. Regarding NMVO/EMVO, in the event of a "hard Brexit", assuming that any product brought into the European Union from the UK is an import:

a) Can the safety features be placed on the product by a manufacturing site in the UK? b) If yes, for the purposes of the Delegated Regulation, who is “the manufacturer placing the safety features” – the UK manufacturer or the importer?c) What tasks (not responsibilities) would the EU QP be able to delegate to the UK manufacturer under the cover of appropriate technical agreements, and what tasks would he/she be expected to ensure that are performed by the importer?d) In the presence of appropriate agreements, could the UK manufacturer upload the data to the repositories system, provided this is done before the importer’s QP releases the product for sale?**Response:** 1. There is nothing to stop UK site applying safety features.
2. As per the FMD Reg, the manufacturer placing the safety features is the manufacturer. If this is done in a3rd country, importer must ensure compliance, similar to manufacturing in other 3rd countries.
3. QP to ensure that safety features are implemented. They can delegate their task to trained personal (fall under GMP chapter 7).
4. MAH is responsible for ensuring data upload, but can delegate the task to someone else. UK will be treated as any other 3rd country.
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| EIPG |  | QP release of Clinical trials materialsEudravigilance Access | 11/03/18 | 1. a) There is a large number of Europe-wide ongoing trials in the UK. Past experience has shown that batch release of trial materials exported to third countries from the UK is delayed by paper work. Is it considered that there are enough Qualified Persons in Europe to cover the extra release work which will be involved?

b) Please clarify whether there will be access for the UK to the EudraVigilance data base following a "hard Brexit"**Response:** 1. Not within remit of EMA to answer. QP release has to be done in EU. Regarding export of IMPS from UK to EU no retest is required but need batch release including GMP.
2. Art.7 of Withdrawal Agreement says that UK will cease to have access to EU databases. UK ADRs will still need to be submitted to Eudravigilance during the transition period although MHRA will not have access.
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| EIPG | Manufacturing | Published [EMA Practical guidance document, December 2017](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/11/WC500239369.pdf)  [Q2] | 11/03/18 | 1. Q2 - "Products that only have batch release and quality control testing sites for finished product in the UK will have to change the batch release and testing sites. For products that have other batch release and testing sites the MAH may choose to delete the site(s) or may choose to replace them. For finished products manufactured in the UK an importation site (in EEA) will need to be introduced."

Does this mean that there would be an expectation for provisional release in the UK before shipment, followed by QP release at an EEA site? If provisional release is required, can we assume that would still be via a QP in the UK. Can this be confirmed please?**Response:** please refer to Q&A. If companies have specific issues, they should discuss with EMA. |
| EIPG | Manufacturing | Published [EMA Practical guidance document, December 2017](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/11/WC500239369.pdf)  [Q2] | 11/03/18 | 1. Q7 & Q8 - Same clarification required as per the comment above on provisional release.

Q10 & Q11 The answer to Question 10 says that MA granted according to Art. 10 (generic and hybrid) after 29 March 2019 should have a RefMP that is or has been authorised in one of the EU-27 Member States (UK, without specific agreements, is therefore excluded). The answer to Question 11 says that Bioequivalence studies performed with a UK sourced product can be used in generic/hybrid Marketing Authorization applications only if the MA for that application will be granted before 29 March 2019. The above situation will prevent applicants running repeat use, MRP or duplicate DCP procedures having a UK RefMP or supported by bioequivalence studies using a UK sourced product if these procedures had not been completed (MA granted) before 29 March 2019. Given the timelines of some of the above mentioned procedures, an applicant is already prevented from starting such procedures. Please clarify. Q12 & Q16 - This states 29 Mar 2019 as a cut off, whereas other answers state 30 Mar 2019. What is the rationale for this? **Response:** please refer to Q&A.   |
| EIPG | Generic MPs | Published [EMA Practical guidance document, December 2017](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/11/WC500239369.pdf)  [Q2] | 11/03/18 | 1. Q10 & Q11 The answer to Question 10 says that MA granted according to Art. 10 (generic and hybrid) after 29 March 2019 should have a RefMP that is or has been authorised in one of the EU-27 Member States (UK, without specific agreements, is therefore excluded). The answer to Question 11 says that Bioequivalence studies performed with a UK sourced product can be used in generic/hybrid Marketing Authorization applications only if the MA for that application will be granted before 29 March 2019. The above situation will prevent applicants running repeat use, MRP or duplicate DCP procedures having a UK RefMP or supported by bioequivalence studies using a UK sourced product if these procedures had not been completed (MA granted) before 29 March 2019. Given the timelines of some of the above mentioned procedures, an applicant is already prevented from starting such procedures. Please clarify.

**Response:** please refer to Q&A. (Discussions on MRP/DCP are outside of the scope of the meeting. Refer to Q& A document and plan studies accordingly. There may be flexibility where studies have been completed and application is planned to be submitted prior to March 19. Commission commented that each situation would be evaluated on a case by case basis. Also considering “legislation refers to Reference product not Global Reference Product” |
| EIPG | Dates UK Withdrawal | Published [EMA Practical guidance document, December 2017](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2017/11/WC500239369.pdf)  [Q2] | 11/03/18 | 1. Q12 & Q16 - This states 29 Mar 2019 as a cut off, whereas other answers state 30 Mar 2019. What is the rationale for this?

**Response:** Distinction between things that need to be done before UK withdrawal and things that will happen afterwards |
|  | AOB |  |  | **Question**: Can there be adjusted fees for Brexit related changes? **Response**: No, same fees apply |
|  | AOB |  |  | **Question:** Do UK testing/release sites need to be deleted from MAs?**Response:** Without a transition, if the MA after March 2019 includes sites located in the UK for activities where EU law requires EU sites (e.g. release), the MA would not be in line with EU law.Until Brexit the EMA cannot force Industry to take the UK sites out. Depending on the future relationship, they might be kept in the files. If not, they should be deleted by variation. Redundant UK sites: will need to be deleted. Can delete/replace all UK sites as a single Type 1A variationConcerns raised that after removal of UK sites the UK national licence extracted from the CP will not have the required UK release and QC testingBrendan Cuddy (EMA Inspections) noted that he did not have a personal issue with inactive UK sites not being deleted immediately after Brexit, but commented out that any listed sites could be subject to inspection. |