10 July 2018
EMA/450315/2018

Report from EMA industry survey on Brexit preparedness

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Executive summary

On 29 March 2017, the United Kingdom (UK) submitted the notification of its intention to withdraw from the European Union (EU). This means that unless a ratified withdrawal agreement establishes another date, all EU primary and secondary law ceases to apply to the United Kingdom from 30 March 2019 at 00:00h (CET) and the UK becomes a 'third country'.

Subject to any transitional arrangement in a possible withdrawal agreement, as of this 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 European Economic Area (EEA));
- Some activities must be performed in the EU (or EEA), related for example to pharmacovigilance, batch release, quality control etc.

As a consequence, marketing authorisation holders may be required to adapt processes and consider changes to the terms of the marketing authorisations of their medicines in order to ensure that they remain valid once the UK leaves the EU.

In January 2018, the European Medicines Agency (EMA), as part of its Brexit preparations, launched a survey in order to gather information from companies on their Brexit preparedness plans and to identify any particular concerns with regard to medicines supply that may impact public or animal health.

EMA contacted over 180 marketing authorisation holders (MAHs) of 694 human and veterinary centrally authorised medicinal products that are located in the UK, or who have quality control, batch release, and/or importation sites or a qualified person for pharmacovigilance (QPPV) or pharmacovigilance system master file (PSMF) in the UK, on their plans to submit transfers, notifications or variations to their marketing authorisations in the context of the UK's withdrawal from the EU.

Highlights from the feedback[1] received:

- There was a **high response rate**; EMA received feedback from MAHs on over 90% of centralised authorised products (CAPs) that were subject to the survey.
- Overall the survey results show that MAHs of centrally authorised medicines **are taking steps to make the necessary changes to their marketing authorisations** to prepare for the Withdrawal from the EU.
- 400 medicines require a **transfer of the marketing authorisation** to a MAH based in the EU27 or an EEA Member State. According to the industry responses, the large majority of companies (94%) plan to submit transfer applications in due time;27 (6%) might be submitted after 30 March 2019.
- 335 centrally authorised medicinal products (human and veterinary) require a change to the location of the **QPPV**; 282 (84%) of those are expected to be submitted on time and 53 (16%) at a later time point.

[1] It should be noted that these figures/percentages are combined for human and veterinary medicinal products apart from PSMF, which is only for human medicinal products.

- For 376 medicines for human use, a change to the location of the **PSMF** will be necessary; the majority of the responders, 224 (60%), indicated that the change might not be made on time. The timing of the change request is unknown for 4% of these medicines.
- The **batch release sites** of 119 medicines need to be transferred to a location within the EU27 or an EEA Member State; timely submission of change requests are expected for 96 (81%) of these medicines. The remaining 23 (19%) may not be submitted on time.
- **Quality control sites** for 41 medicines need to be relocated to the EU27 or an EEA Member State; for 35 (85%) of these medicines MAHs are planning submission in due time and for 6 (15%), MAHs have either not responded or indicated submission at a later time point.
- **Importation sites** for 18 medicines need to be relocated to the EU27 or an EEA Member State; only half of the companies responded to this question (9 out of the 18) and of those only 4 (22%) indicated that they will be submitting before the March 2019 deadline.

Impact on medicines supply

Of all affected products (694), for 108 (16%) medicines (88 human and 20 veterinary), all, or a major part of, the above steps are carried out in the UK only and changes may not be submitted in time according to companies' current plans. This raises major concerns that if plans are not adapted, these products may no longer be available on the EU market.

Impact on workload

Results from the survey indicate that the majority of the submissions of the required change requests to the Agency are scheduled for Q1 2019 which is at the time when EMA will be relocating to the Netherlands, where its new headquarters will be located. Pharmaceutical companies are therefore being strongly advised to submit the necessary changes for the continued maintenance of their marketing authorisations to EMA as early as possible and before the end of Q4 2018 to ensure processing in due time.

Follow-up to survey

EMA is following up individually with all non-responders to the survey.

EMA will also follow up directly with the MAHs that have batch release, quality control and/or importation sites located in the UK only and that have indicated in the survey that they do not plan to submit changes required before 30 March 2019, as this could potentially lead to supply disruptions.

In addition, EMA will monitor and track the submissions of required changes for the affected centrally authorised medicines and workload analysis will be used to ensure adequate resource planning within EMA and the EU medicines regulatory network, where relevant.

Introduction

The Agency is responsible for the scientific evaluation, supervision and safety monitoring of medicines. EMA protects public and animal health currently across 28 EU Member States, as well as the countries of the EEA , by ensuring that all medicines available on the EU market are safe, effective and of high quality. EMA serves a market of over 500 million people living in the EU.

On the 2nd May 2017, the European Commission issued a "Notice to Marketing Authorisation Holders (MAHs) of centrally authorised medicinal products for human and veterinary use", which stated:

"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 establishes another date, 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'.

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 submitted in due time, considering the procedural timelines foreseen in the regulatory framework."

In order for EMA to gather information on the status of industry's preparedness for the consequences of the UK's withdrawal from the EU, a Brexit industry survey was launched in January 2018. The survey was sent to the MAHs of both human and veterinary centrally authorised medicinal products, comprising more than 180 companies. These MAHs, responsible for 694 human and veterinary centrally authorised medicinal products, were located in the UK, or had quality control, batch release, and/or importation sites or a QPPV or PSMF in the UK.

The aim of this survey was two-fold. Firstly, to identify those companies where there is a need for concerted action to address medicines supply concerns due to Brexit in order to protect human and animal health, and secondly to help the Agency and the European Commission plan resources in the areas where these submissions will be processed.

The survey was launched on 23 January 2018 with a deadline for response of 9 February 2018.

Methodology

The survey was a web based survey using the European Commission's EU Survey tool and format. See enclosed link: https://ec.europa.eu/eusurvey/

Two questionnaires were sent, one intended to gather information on MAH transfer, PSMF, QPPV, orphan designation and veterinary Minor Use Minor Species (MUMS) designation changes. A second questionnaire gathered information on certain manufacturing sites (batch release, importation, batch control, and Official Medicines Control Laboratory (OMCL) testing arrangements).

Survey findings: highlights

Transfers of marketing authorisations, changes to location of QPPV for human and veterinary medicinal products and PSMF for human medicinal products

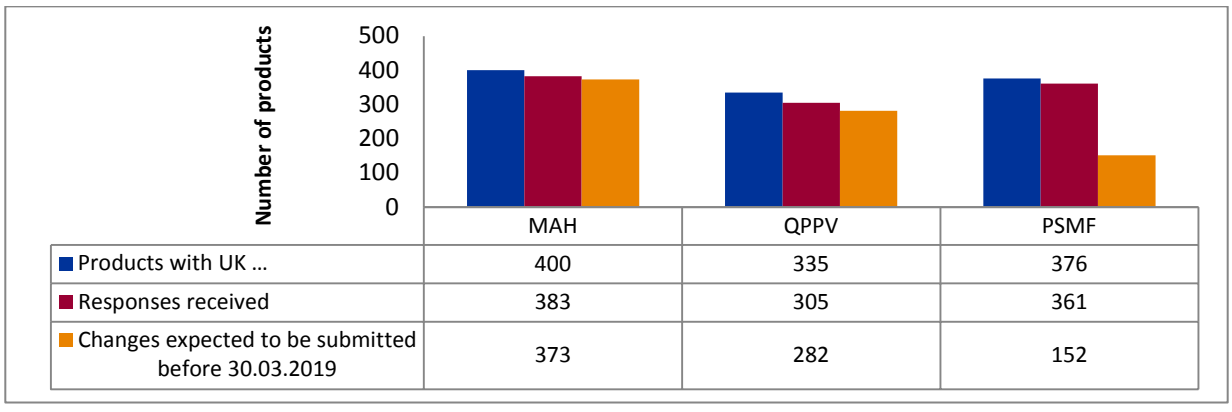
Transfer of marketing authorisation

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 MAH will therefore need to **transfer** its **marketing authorisation** to a holder established in the Union (EEA). The transfer of the marketing authorisation must be fully completed and implemented by the marketing authorisation holder before 30 March 2019 (see EC-EMA Q&A, question 1).

EMA databases indicate that 400 CAPs have their MAHs registered as being established in the UK. Such marketing authorisations will, therefore, need to be transferred and implemented before 30 March 2019 to a holder established in the Union (EEA). Out of those targeted 400, 373 informed the Agency of their intention to submit such **transfer application of marketing authorisation** within the previously mentioned set deadline, See **Fig. 1.**

Fig. 1: MAHs' intention to change UK based MAHs, QPPVs and PSMF location in the Union/EEA for CAPs

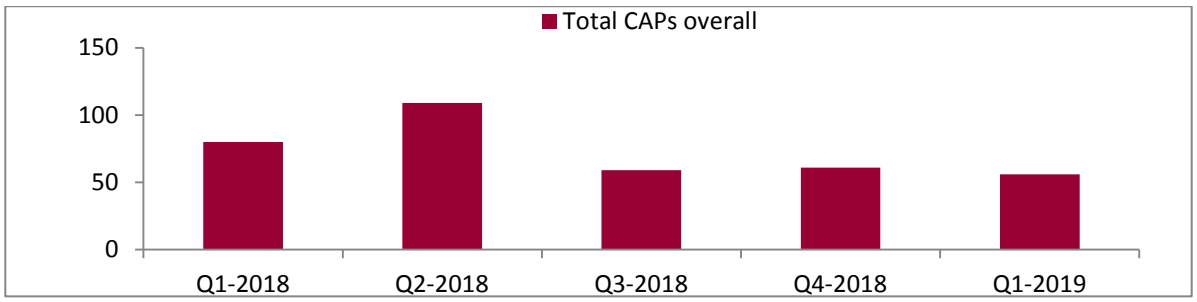


	MAH	QPPV	PSMF
Products with UK …	400	335	376
Responses received	383	305	361
Changes expected to be submitted before 30.03.2019	373	282	152

Overall, industry has been active in planning such transfers in advance of the UK withdrawal from the Union (EEA) for human medicinal products. According to the responses received, the large majority of companies (94%) plan to submit transfer applications in due time. For 27 centrally authorised medicinal products (6%) no responses were received. The concerned MAHs will be contacted by the EMA to obtain feedback on their status of readiness.

In terms of intended submission dates, the majority of transfers for human medicinal products are expected to take place by Q2 2018 but they will continue through Q4 2018 and Q1 2019, when EMA will be relocating to the Netherlands. See **Fig. 2** for further details.

Fig. 2: MAHs intent to submit transfer applications –CAPs for human use



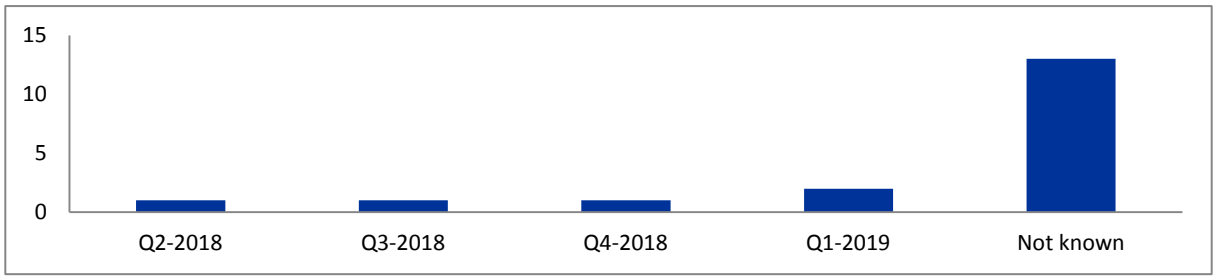
The MAH transfer submissions linked to 'Brexit' represent an approximately a ten -fold increase compared to EMA's average annual submission levels. 'Brexit' variations represent an increase of 22% of Type IA and 10% of quality Type II variation submissions. The responses provided as part of the survey show that the related workload will be spread over the period between Q1 2018 to Q1 2019. The main workload peaks are expected to be Q4 2018 and Q1 2019 with an approximately 50% and 30% monthly increase in Type IA and Type II quality submissions respectively over this period.

For **veterinary medicines**, 18 centrally authorised veterinary medicinal products are located in the UK and the MAH will need to transfer their marketing authorisation to a new MAH based in one of the EU/EEA Member states. This represents a five-fold increase in the average number of transfer applications submitted annually.

It should, however, be noted that the majority of these veterinary MAHs have not yet decided when these submissions would be made.

In terms of intended submission dates for the veterinary transfers, for the majority this is unknown and of those who provided timelines, requests are mainly expected to be submitted in Q1 2019, which coincides with the timing of EMA's relocation, see **Fig. 3**.

Fig. 3: MAHs intent to submit transfer applications –CAPs for veterinary use



Qualified Person for Pharmacovigilance (QPPV) and Pharmacovigilance System Master File (PSMF) changes

To fulfil its obligations, the MAHs of human and veterinary medicines are required by European law to nominate a QPPV who resides and carries out his/her tasks in the Union (EEA)[2]. For human medicinal products, the PSMF[3] must also be located within the Union.

At the time of completion of this survey, MAHs of 335 centrally authorised medicinal products (both human and veterinary) have indicated that their QPPVs are based in the UK. For the PSMF (for human medicines only) 376 are based in the UK. Based on responses received, 282 (84%) and 152 (40%) of QPPVs and PSMFs respectively were confirmed as on track for the requisite changes to be made by the deadline of 30 March 2019. However, it should be noted that these figures may be subject to change depending on the further feedback obtained from MAHs.

[2] 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).
[3] 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).

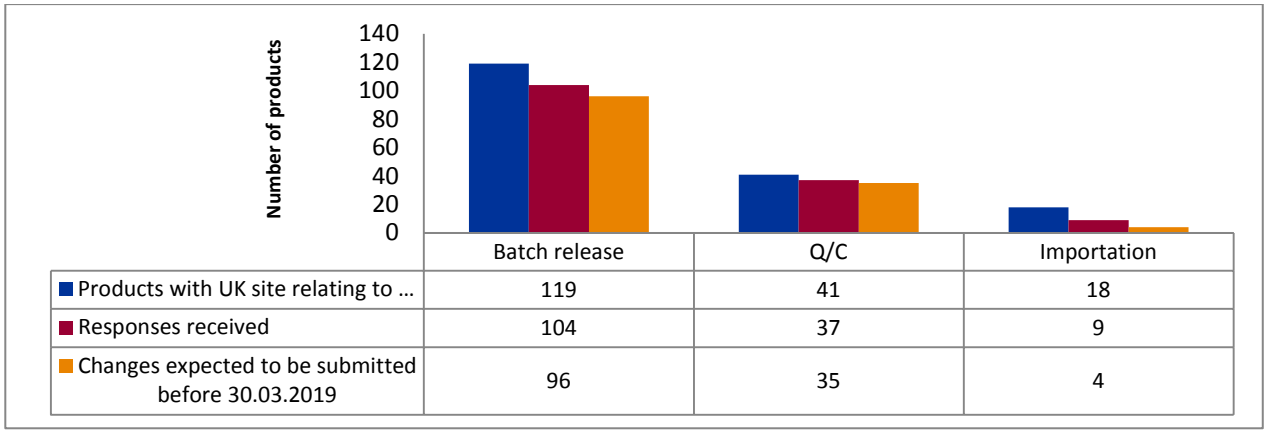
Changes in quality control, batch release and importation sites for human and veterinary medicinal products[4]

Batch release site location changes

To control the quality of the medicinal products circulating within the EU, 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 for certifying that each batch of medicinal product intended to be placed on the EEA market was manufactured in accordance with EU Good Manufacturing Practice (GMP) requirements and the marketing authorisation. The batch release site has to be located in the Union (EEA). By the time of the UK withdrawal date from the Union, the MAH will therefore need to transfer any current UK-based site of batch release to a location established in the Union.

From the responses received to the survey, the Agency was informed that the large majority of the batch release sites currently located in the UK would be changed to a site in the EU/EEA in due time i.e. 96 of 119 (81%). 23 (19%) of the variations needed to change the batch release sites currently located in the UK to another Union (EEA) Member State, might not be in time for the changes to be in place prior to 30 March 2019, see **Fig. 4**. This includes 15 products for which no response was received.

Fig. 4: CAPs' MAHs intention to change their UK-only based quality control, batch release and importation sites in the Union/EEA



	Batch release	Q/C	Importation
Products with UK site relating to …	119	41	18
Responses received	104	37	9
Changes expected to be submitted before 30.03.2019	96	35	4

Quality control site location changes

In accordance with Article 51(1)(b) of Directive 2001/83/EC and Article 55(1)(b) of Directive 2001/82/EC the MAH 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 MAH will need to change the location of any current UK-based site of batch control to a location established in the Union (EEA) and submit the corresponding variation.

Further to the analysis of the survey responses, 41 variations for quality control changes need to be submitted. For 35 (85%) of these medicines, MAHs are planning submission in due time and for six (15%) MAHs have either not responded or indicated submission at a later time point, see **Fig. 4**.

[4] The figures included in this section are only focusing on the medicines which have only UK sites.

Importation site location

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.

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 into 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 GMP and control of the plant are equivalent to those in the Union (EEA).

In addition, 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).

MAHs will therefore need to specify an authorised importer established in the Union (EEA) and submit the corresponding variation.

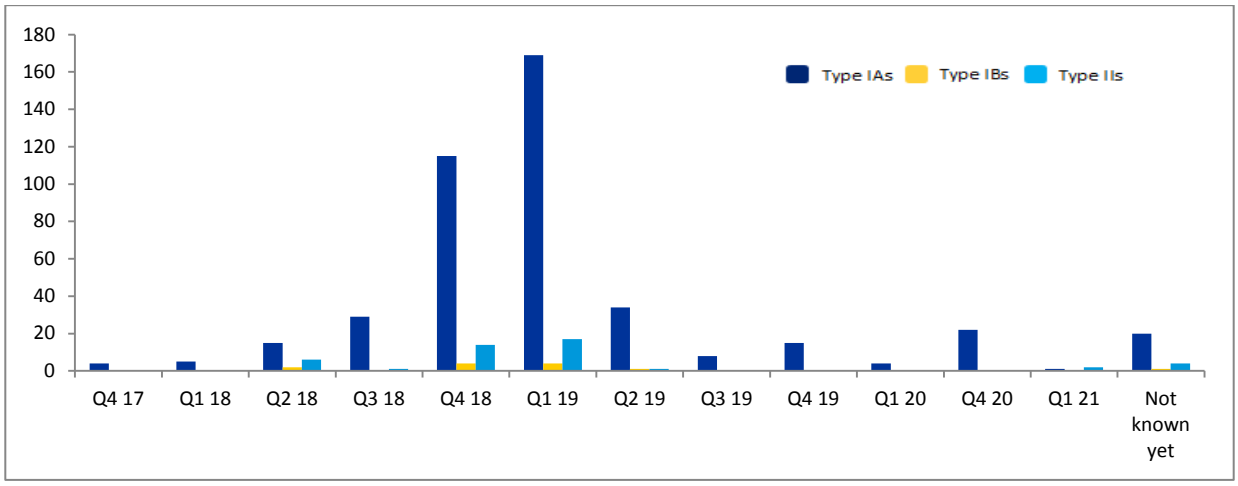
The survey analysis for centrally authorised products showed that of the 18 importation sites identified as needing to be changed from the UK to a new site in the Union/EEA, responses were not received for half of these. Of the nine responses, only four (22%) indicated that they will be submitting before the March 2019 deadline. See **Fig. 4** for further details.

In addition, it should be noted that there are 139 and 201 centrally authorised human and veterinary medicinal products which have respectively batch release and quality control sites located in the Union/EEA and also in the UK. For 106 of these products, changes to their batch release or quality control testing sites might not be submitted before 29 March 2019.

Furthermore, the majority of the changes related to the above-mentioned batch release, quality control and importation site changes are expected to be submitted as **minor variations**, except when related to biologicals (see further details in EMA "Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure", question 2).

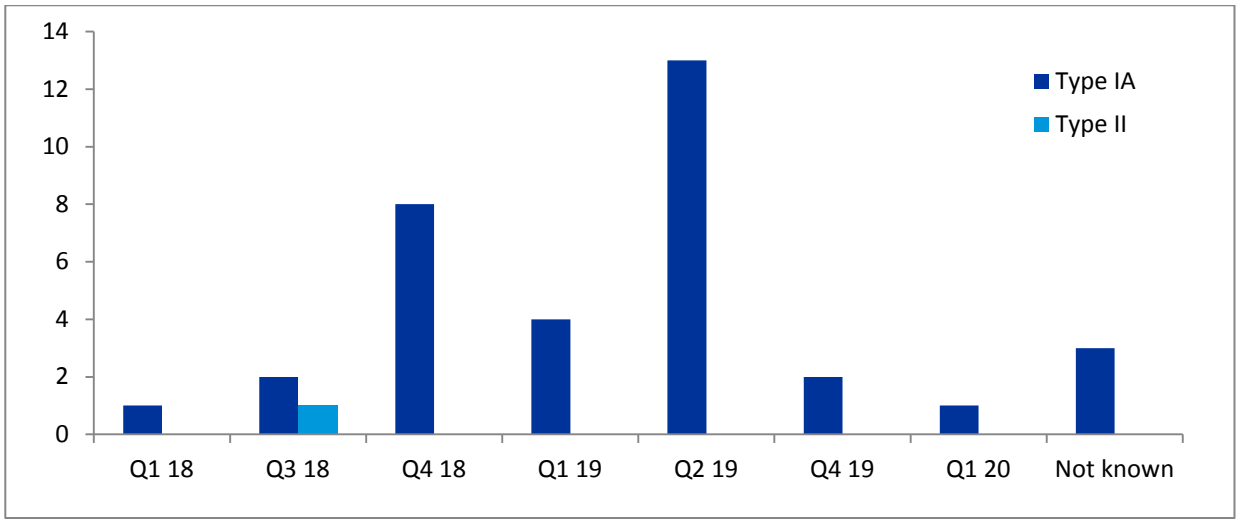
The survey analysis showed that for the **centrally authorised human medicinal products** the required -Brexit'-related variations are estimated to comprise 441 Type IAs, 12 Type IBs and 45 Type IIs. For the Type IAs and Type IIs, the main part of the workload is expected in Q4 2018 and Q1 2019. This will represent an approximately 40-50% increase in Type IA submissions and a 20-30% increase for quality Type IIs during this period, see **Fig. 5**.

Fig. 5: Human CAPs' MAHs variations submissions



For **veterinary centrally authorised medicinal products**, 'Brexit' variations are estimated to comprise 34 Type IA variations and 1 Type II variation. This represents an approximately 14% increase in Type IAs. The main workload is expected between Q4 2018 and Q2 2019, which will be a critical time point for EMA in view of its relocation to the Netherlands. See **Fig. 6**.

Fig. 6: Veterinary CAPs' MAHs variations submissions



Survey outcome in terms of potential impact on supply of medicines

In line with the initial objectives set for this survey, an analysis of the responses provided by the MAHs has enabled the Agency to define a list of potentially 'critical' centrally authorised medicinal products.

Of the 694 centrally authorised medicinal products which were subject of the survey, 108 medicines (88 human and 20 veterinary) i.e. 16% of those identified to have all, or a major part of, previously described function or sites in the UK only and for which not all changes are expected to be submitted in time, were considered to be 'critical' in terms of supply and access to patients in Europe.

It should be noted that any conclusions drawn from this survey on criticality are reliant on the quality of the information provided by the MAHs, and are valid at the time when the survey was completed. It is recognised that companies' plans may be subject to change.

Conclusions and next steps

- EMA received feedback from MAHs on over 90% of CAPs that were subject to the survey. EMA is in the process of following- up individually with all non-responders.
- Overall, the survey results indicate that the MAHs of centrally authorised medicines are taking steps to make the necessary changes to their marketing authorisations to prepare for the UK's withdrawal from the EU.
- Analysis of the survey responses has resulted in the identification of 108 centrally authorised medicinal products (88 human and 20 veterinary medicinal products) at potential risk of critical supply.
- The majority of the change requests required for centrally authorised products are expected to be submitted from Q4 2018 to Q1 2019. The latter quarter will be a challenging time for the Agency in terms of processing high numbers of requests as it coincides with the Agency's relocation to the Netherlands, where its new headquarters will be based.
- For veterinary medicinal products, there was a high level of non-responders to the question on marketing authorisation transfers and it is therefore not possible to formulate conclusions at this stage.
- A high level of uncertainty also still exists as to where the new sites for PSMF, QPPV and batch release will be located post-Brexit, and consequently further information will be needed for EMA and EU network inspectorates to plan their workload and resources.
- Some MAHs have informed the Agency that they do not plan to change their UK only sites, including OMCLs.

In view of the above findings, EMA will follow-up directly with the MAHs that have batch release, quality control and/or importation sites located in the UK only and that have indicated in the survey that they do not plan to submit the changes required before 30 March 2019, as this could potentially lead to supply disruptions.

In addition, EMA will monitor and track the submissions of required changes for the affected centrally authorised medicines and workload analysis will be used to ensure adequate resource planning within EMA and the network, where relevant.

Pharmaceutical companies are being strongly advised to submit the necessary changes for the continued maintenance of their marketing authorisations to EMA as early as possible and before the end of Q4 2018 to ensure processing in due time.

Annex I

LIST of KEY EMA AND EUROPEAN COMMISSION 'BREXIT' RELATED DOCUMENTS and WEB LINKS

- EMA web page on the United Kingdom's withdrawal from the European Union ('Brexit') [link].
- EMA web page on Brexit-related guidance for companies [link].
- Notice to marketing authorisation holders of centrally authorised medicinal products for human and veterinary use [link].
- 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 [link].
- Practical guidance for procedures related to Brexit for medicinal products for human and veterinary use within the framework of the centralised procedure [link].