Medicines & Healthcare products Regulatory Agency

No-deal Brexit Q&A

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CPRD NIBSC MHRA

Acronyms

- AE – Adverse Event
- CAP – Centrally Authorised Product
- CESP – Common European Submission Portal
- CHMP – Committee for Medicinal Products for Human Use
- CMS – Concerned Member State/s
- CoA – Change Of Ownership
- CP – Centralised Procedure
- CPP – Certificate of Pharmaceutical ProductDCP – Decentralised Procedure
- eAF – electronic Application Form
- eCTD – electronic Common Technical Document
- EMA – European Medicines Agency
- eMC – electronic Medicines Compendium
- GIS – Grandfathering Initiating Sequence
- HMRs – Human Medicines Regulations
- ICSR – Individual Case Safety Report
- MA – Marketing Authorisation
- MAA – Marketing Authorisation Application/s
- MHRA – Medicines and Healthcare products Regulatory Agency
- MIA – Manufacturer's Import Authorisation
- MIS – Minimal Initiating Sequence
- MLM – Medical Literature Monitoring
- MRDC – Mutual Recognition Decentralised Procedure
- MS – Member State
- PAM – Post Approval Measure
- PASS – Post-Authorisation Safety Study
- PI – Product Information
- PIL – Patient Information Leaflet
- PIP – Paediatric Investigation Plan
- PL – Product Licence
- PRAC – Pharmacovigilance Risk Assessment Committee
- PSMF – Pharmacovigilance System Master File
- PSUR – Periodic Safety Update Report
- PV – Pharmacovigilance
- QP – Qualified Person
- QPPV – Qualified Person Responsible for Pharmacovigilance
- QRD – Quality Review of Documents
- RIS – Regulatory Information Service
- RP – Reference Product
- SmPC – Summary of Product Characteristics
- SPS – Summary of Pharmacovigilance System
- TC – Teleconference
- WDA(H) – Wholesale Distribution Authorisation (for medicines for human use)
- WEU – Well Established Use

New Product Applications

1. Are there any restrictions (legal or otherwise) on filing national applications now in parallel to DCP applications with UK as CMS?

   While the UK is a Member State of the EU, applications in two or more Member States for the same medicinal product, must be submitted in accordance with Articles 28 to 39 of Directive 2001/83 (as amended). It is therefore not possible to submit a separate national application for the same medicinal product in the UK in parallel with other applications in a decentralised procedure when UK is (or is not) included as a CMS.

2. For a UK National Procedure, what access will the MHRA have to information and data on the EU reference product (RP)?

   In event of a no-deal Brexit, reference medicinal products for the purposes of UK abridged MA applications will be a product which is or has been approved in the UK based on a full MA dossier. These will also include relevant products that have been approved as a community marketing authorisation while UK was a MS of EU.

3. In which cases will it be allowed to continue with the European Reference Product? Will MHRA insist on switching to a UK RP, and if so when?

   Applications that are in process when UK departs the EU will be completed.

4. When will MHRA be issuing more detailed guidance on reference products for generic and hybrid applications?

   This information is was published on 22 October 2019 and can be found online here: https://www.gov.uk/guidance/comparator-products-in-bioequivalencetherapeutic-equivalence-studies-after-brexit.

5. What will be the requirements for well-established-use (WEU) applications post-Brexit? Currently for a WEU, the applicant needs to show widespread use in the EU, but it does not need to be specific to the UK. Post-Brexit, will there be a need to show predominantly WEU in the UK or will use within the community still be acceptable?

   In event of a no-deal Brexit, information on the use of the product in the EU will continue to be considered in applications claiming well established use in UK.

6. In order to ensure approval in 210 days or less, what milestones will MHRA put in the National Procedure to ensure predictable and reliable timelines (and to avoid multiple rounds of questions)?

   The MHRA will continue to monitor and publish compliance with high level performance targets.

7. Can MHRA guarantee that “in flight” DCPs with UK as CMS will be completed on time?

   MHRA will endeavour to complete ‘in-flight’ applications as soon as any outstanding issues have been resolved.

8. Will there be any requirements to manage procedures with UK as CMS that have been submitted (i.e. in validation) but have not yet started?

   There are no particular requirements. MRDC applications submitted to MHRA before exit day do not need to be resubmitted.

9. Can UK still run repeat use procedures?

   Repeat use procedures can continue to be run from UK while it remains a MS of EU, however these would require the receiving MS to agree to accept an expedited timetable.

10. Can companies request meetings with MHRA to discuss their new product pipeline regulatory strategies? If so, what is the best way to do that? Is there a less formal way to get advice on smaller issues?

    Companies can continue to contact MHRA to discuss their regulatory strategies. The first point of contact is available on gov.uk and enquires will be redirected as appropriate[1]*.*

[1] https://www.gov.uk/guidance/medicines-get-scientific-advice-from-mhra The first point of contact is Nathalie.Gilmore@mhra.gov.uk

Centralised Procedures

1. For Change of Ownership from an original CP MAH to a UK-based MAH, is the deadline for this still expected to be the end of 2020?

   The CoA should be submitted within 21 months of exit day.

2. If a centralised MAA is submitted prior to Brexit but does not reach day 120 before EU Exit occurs, is the MAH required to resubmit the entire MAA to MHRA, removing any reference to EU?

   A MAH is required to resubmit the entire MAA (all sequences) to MHRA in a technically valid eCTD format. It is not necessary to remove all references to the EU and if the applicant has opted for targeted assessment the dossier content should remain unchanged.

3. To maintain consistency with the EU paediatric article 45/46 regulation, could a variation application only be submitted when a product information (PI) update is proposed by the MAH or imposed by MHRA? In the situation where the MAH is not planning to update the PI as part of the initial appraisal submission and MHRA is asking to review the data, it is our expectation that a variation would initially not be required, but instead an "Art 46" procedure could be followed to provide the requested data in alignment with CMDh/EMA guidance. A standalone follow-up variation would be submitted if a PI update is requested as part of MHRA assessment of the data.

   On receipt of the cover letter for completed paediatric studies, MHRA will carry out an initial appraisal to decide on whether a full assessment is required. At that stage the applicant will have the opportunity to justify in the cover letter why a full assessment is not required, e.g. when:

   - the study will be included in a regulatory submission to vary the Marketing Authorisation in the next 6 months
   - the study has been reviewed in another regulatory procedure by MHRA or another competent authority and the review has not led to product information (PI) changes, or
   - another reason to defer the procedure.

   Moreover, the MHRA will consider undertaking a limited evaluation of the study data if the applicant provides robust justification that it is unlikely that PI changes will be necessary taking into account the strength of the generated data, for example when:
   - the study was conducted mainly in adult patients with limited paediatric patients included
   - the drug is already licensed in the paediatric study population and the study does not provide new efficacy or safety data
   - the study, due to its design, limited number of paediatric patients, discontinuation or other reason does not allow conclusions on efficacy or safety that would impact on the drug's benefit to risk ratio or be useful to prescribers and patients
   - only interim results from an ongoing study are available which will be assessed later in their totality
   - the study has been conducted in populations and/or diseases that are not applicable to UK (for example hay fever to specific seasonal pollen found in non-UK countries)
   - any other justification provided by the MAH as to why a detailed assessment is not required at this stage

In the above cases, a variation application will not be requested, as MHRA aims to help reduce burden to companies. A type II variation application will be required when the MAH proposes a PI update or when MHRA concludes after the initial appraisal, that a full assessment is needed to robustly conclude whether PI updates are warranted. The published MHRA guidance on Completed Paediatric Studies (https://www.gov.uk/guidance/completed-paediatric-studies-submission-processing-and-assessment-in-the-event-of-a-no-deal-scenario) will be updated shortly to provide this further clarification on cases where a type II variation application will not be required.

Baseline Submissions

1 Will MAHs receive an official approval letter or only an automated acknowledgement following the submission of an initiating sequence?

The system will generate and send a new MA grant letter (the usual grant letter template will be used). Please ensure your MHRA eComms details are correct.

2. What is the current MHRA Guidance regarding grandfathering?

The initiating sequence must contain the current granted EU patient information and, additionally, mock-ups of the UK patient information should be included or text-only versions. If text-only versions are provided, the MAH will need to submit a subsequent variation to approve mock-ups of the UK patient information within 2 years from exit date.

3. Is the submission of text-only versions of the product information applicable to both non-marketed and marketed products?

Yes, the requirement for text-only or full mock-ups applies to both non-marketed and marketed products. MHRA understand that current text-only versions may not be available or outdated for non-marketed products, but these are mandatory documents in order to establish the licence in the UK in the event of a no-deal.

4. MHRA guidance states that pending type IA & IB variations (submitted but not granted before exit day) should be included within the baseline submission, where pending variations are included as part of the initial baseline submission, is the MAH expected to receive separate approval letters for these variations?

Only pending type IA & IB variations conforming to the type and decision status listed, see online[2], can be included within the CAP Grandfathering Initiating Sequence (GIS). There will be no separate approval letter for these variations, the MA will be 'granted' with these variations already applied (see answer to 1 above). It is important to ensure the history document list all such variations accurately in this respect to avoid follow up questions or requests for information.

5. With reference to section 6 on variations, section 9 on renewals and section 12 of the CAP conversion guidance, it would be helpful to understand what is meant regarding the possibility to submit a variation, renewal or Article 61(3) notification before the data submission date if "there are other good reasons"? What can be considered a 'good reason'?

Examples of exceptional circumstances include but are not necessarily limited to a serious risk to patient safety or lack of availability of essential drugs if the submission of a variation, renewal or Article 61(3) notification would be unavoidably and excessively delayed due to preparation of baseline data for the grandfathering process. The process described is to allow for unforeseeable events and therefore we expect this to be exceptionally rare as there is already an option to submit a minimal baseline data set for most urgent cases with a second step then required to submit the full data set after the critical variation has been reviewed. Submission of a variation without any supporting base data at all will need close co-ordination with the MAH to

[2] *Section 6 table 1 here: https://www.gov.uk/guidance/converting-centrally-authorised-products-caps-to-uk-marketing-authorisations-mas-in-a-no-deal-scenario-grandfathering-and-managing-lifecycle-ch#general-approach-to-variations-to-converted-eu-mas-after-exit-day*

avoid assessment delays arising counter-intentionally and so if a MAH thinks their circumstance apply, they must first contact RIS to discuss and get agreement. If necessary and by MHRA request only, a follow up TC may be required before such agreement can be confirmed.

6. With reference to section 15 on the legal presence requirement of the CAP conversion guidance, will any of the deadlines stated in the guidance shift if a no-deal Brexit is confirmed on 31 January 2020? For example, as regards the Change of Ownership application which should be submitted "before the end of 2020" in accordance with the current guidance.

   The legislation does not use fixed dates, but instead uses formulae calculated from exit day. The guidance included fixed dates to help users, but these have now necessarily shifted as exit day has been delayed.). The submission deadline will be 21 months from exit day.

7. What will be the deadline for submitting the baseline / consolidated files for conversion of CPs to National Procedures?

   For CAP conversion the baseline must be submitted within 1 year from exit day.

8. Will the MHRA be providing any guidance on when MAHs can submit baselines (i.e. does the system have capacity for large volumes of submissions at the same time?)

   We will only accept baselines from exit day. MHRA have prepared as far as possible to deal with large volumes and our portal should be comparable in capacity to CESP.

9. Do we need to submit a baseline for a CP product before we can submit a new PSUR to MHRA after exit day?

   No, MHRA has a specific system for submission of PSURs - so they will not be linked to the lifecycle.

10. I have not seen any written guidance regarding CAP conversion into the UK legal entity when the current MAH is based in EU. We have been issued with PL numbers (for the EU MAH), but we would want to receive PL numbers for our UK legal entity. What will be the process for this?

    Our guidance provides an answer to this[3]*. However, MAHs using option 2 must ask for PL numbers to be issued for the UK MAH by requesting them from capconversions@mhra.gov.uk and use them in the eAF and the initiating sequence. The initiating sequence must contain the current granted EU patient information and, additionally, mock-ups of the UK patient information should be included for text-only versions.*

11. Approximately how long will it take to get the baselines processed and new MA issued to then allow companies to make subsequent submissions?

    MHRA have a contingency team of 19 to be assigned to dealing with several hundred baselines per month whilst also dealing with other Brexit submissions. While we therefore cannot give a specific time commitment, we can guarantee significant resources will be devoted to this.

12. Can a Certificate of Pharmaceutical Product (CPP) be submitted on a Minimal Initiating Sequence or does it have to be a complete baseline submission before a CPP can be issued?

[3] https://www.gov.uk/guidance/converting-centrally-authorised-products-caps-to-uk-marketing-authorisations-mas-in-a-no-deal-scenario-grandfathering-and-managing-lifecycle-ch#legal-presence-requirement

We know they require the baseline, but can it be a step 1 (minimal baseline - no dossier) or do they need the full thing?

A CPP can be generated with just the MIS.

13. Should we include CoA change details in the same cover letter as grandfathered CAP application or do we need two separate cover letters?

Two separate cover letters would not be required. The submission package for the initiating sequence for the grandfathered CAP application must contain a cover letter and declaration that only approved documentation is included in this sequence. The cover letter should clearly identify the submission as a "CAP Grandfathering Submission Incorporating Change of Ownership (CoA)" in the title and state in the body that a CoA from company A to company B has been included.

14. If the PSUR has been submitted before exit day but review not concluded, it is not clear whether companies have to make a submission because MHRA say "they will assess the PSUR". PSURs are not being included in the UK baseline so can MHRA confirm that no re-submission is required?

New submissions will need to be made onto our new PSUR system under the new MHRA submissions. In general, we will not expect PSURs submitted to the repository prior to exit day to be re-submitted but there may be some circumstances where we will need to ask the MAH for a copy.

15. Registering the QPPV on EU Exit with respect to the format of module 2 in the baseline - do we need to submit a consolidated module 2 or is the original document + addendums for any changes made acceptable?

Please note that UK QPPV details and the UK PSMF number/location cannot be submitted with a baseline submission for a converted CAP. The company will have one year starting on Exit day to submit the initiating sequence data and related information in eCTD format for the EU MAs. Following submission of the initiating eCTD sequence and receipt of the approval letter from the MHRA, Type IAIN C.1.8 a) variations should be submitted to update the QPPV details and UK PSMF number/location (please note, the timing of these variation submissions should follow the guidance published on the MHRA's website.[4]

16. If a PSUR assessment which includes proposed safety changes has received its final PRAC recommendation, but the opinion has not yet been issued, is it possible to include the safety changes in the baseline, or will the safety update need to be submitted as a type II variation in the UK?

Yes, this can be included in the baseline.

17. Can a variation submission use the existing EU PSMFL number on the UK Summary of Pharmacovigilance System (SPS) if variation submissions are required before a UK PSMF is established?

[4] https://www.gov.uk/guidance/guidance-on-qualified-person-responsible-for-pharmacovigilance-qppv-including-pharmacovigilance-system-master-files-psmf-if-the-uk-leaves-the-eu-w

There is a temporary exemption in place in relation to the PSMF covering UK authorised products ('UK PSMF'). Consequently, UK MAHs must implement a UK PSMF at the point when the UK-resident QPPV is established (within 21 months of exit day).

The UK PSMF number is unique and assigned by the MHRA; it is therefore different to the PSMFL number assigned by the EU.

If a variation to update the SPS is required to be submitted prior to when the UK PSMF is established, the submission can include the EU PSMF number. Once the UK-resident QPPV and UK PSMF are established, an updated SPS must be submitted to the MHRA and should include the UK PSMF number. Within 21 months of exit day, every pharmacovigilance system covering UK authorised products must be registered with the MHRA directly and be identifiable by this unique number.

A UK PSMF number can be requested via the MHRA Submissions portal after exit day in a no-deal Brexit scenario. You should follow the online instructions for requesting a UK PSMF number and you should receive the number by email immediately upon completion of the online form. You are encouraged not to request the UK PSMF number until the UK-resident QPPV and the UK PSMF have been established.

Pharmacovigilance

1. QPPV exemption was initially stated as 21 months from the end of March, will this exemption, if required in October, still be 21 months or reduced to 15 months?

   It will be 21 months from exit day, irrespective of when exit day is. This is set out in the Human Medicines Regulations, Schedule 33A paragraph 57(3), as amended by the EU Exit Regulations.

2. Will companies be required to resubmit PSURs, or will the MHRA ensure all information is downloaded from the central repository?

   The MHRA has developed its own PSUR submission portal and this will be available from exit day. Where a PSUR has been submitted before exit day but the EU single-assessment procedure has not been concluded, the MHRA will assess the PSUR considering any relevant information, including any EU decision and may request further information, where appropriate, in order to conclude the assessment. In general, we will not expect PSURs submitted to the repository prior to exit day to be re-submitted but there may be some circumstances where we will need to ask the MAH for a copy.

3. As the EU and UK PSMF are likely to be identical (apart from the detail of the UK QPPV and location) is it possible to use a single PSMF with a UK-specific annex, or is a separate PSMF required?

   The requirements for the PSMF covering UK authorised products are described in Schedule 12A Part 1 of the HMRs (introduced by the EU Exit Regulations). Assuming that the PV system for UK and EU authorised products is the same, the UK PSMF main body is likely to be very similar to the EU PSMF in content (apart from the UK QPPV details and potentially some other minor differences depending on the PV system, e.g. computerised systems may differ in the UK versus rest of EU, lists of relevant PV system deviations and audit findings may differ slightly, etc.). The UK PSMF annex information should be specific to UK authorised products but should represent the global availability of safety data (i.e. global partners related to UK authorised products, etc.). Consequently, a separate UK PSMF is required.

4. The MHRA submission webinar covered e-cigarettes, human medicines, PSURs and PIPs but did not appear to cover how AEs will be submitted in the event of a no-deal, please can this be clarified.

   There are webinars available on the MHRA website which cover how to submit adverse events, please check online[5]*. Guidance for the submission of ICSRs to MHRA can be found online*[6]*.*

5. For Post Approval Measures (PAM) submission of a protocol has been made with multiple rounds of questions; should all sequences relating to the PAM be resubmitted post Brexit?

[5] https://www.gov.uk/government/publications/how-to-make-regulatory-medicines-submissions-to-the-mhra-if-the-uk-leaves-the-eu-with-no-deal
[6] https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario#registering-to-use-the-vigilance-systems-mhra-gateway-and-icsr-submissions

Only the most recent version of Post-Authorisation Safety Study (PASS) protocols need to be resubmitted, as long as all previous rounds of questions and responses have been seen by the MHRA.

6. When there is a requirement for a PIP modification post-Brexit, how will this be handled by the MHRA if the EU-PIP does not require re-submission to the MHRA?

   EU-PIPs agreed by the EMA before exit day will be adopted as UK-PIPs ('adopted UK-PIPs') and will not require resubmission to the MHRA. When a modification is required for an adopted UK-PIP, the applicant will need to submit the proposed modification to the MHRA, via the MHRA submissions portal. In the submission, the applicant should provide information in relation to the proposed modification, as outlined in Section 2 of the guidance 'Procedures for UK Pediatric Investigation Plan (PIPs) in a no-deal Brexit'. The MHRA will subsequently complete the modification assessment based on the information provided.

   Note: Information on how to register to make submissions to the MHRA post-Brexit, including PIP-related submissions, can be found online[7].

7. My understanding is that if we have PSUR submissions due in November we would need to submit the PSUR with the baseline in order for the PSUR to be assessed? We have 2 PSURs due early November. Will we still have to abide by the EU birth date for the PSUR submission for the UK submission even if we have left by then?

   The PSURs should be submitted according to the submission date on the EURD list and in a no-deal Brexit this will apply to the UK. We have developed a submission portal specifically for PSURs and the MAH will need to submit their PSURs via this portal in the event of a no-deal. You do not need to submit a baseline prior to submission of a PSUR. As stated in our guidance for converting centrally authorised products the UK will not require PSURs to be submitted as part of the lifecycle and they shouldn't be included in the initiating sequence.

8. For PASS Protocols where EU PRAC has endorsed a draft protocol or issued substantial amendments before exit day – MHRA will accept the draft or amended protocol. Will this also apply to protocols post-exit day? What happens if we submit an amended PASS protocol to both EMA and MHRA and each agency has different comments on the same protocol?

   In most circumstances we anticipate that the EMA and MHRA will be aligned. Protocols will need to be assessed separately in the UK, but we will take into account any information available to us regarding the EU procedure

9. Regarding nullification/downgrade of ICSRs to MHRA that are required for cases previously sent to EMA, we are experiencing challenges as described in the MHRA response to this question. What are the potential options for those companies at risk of non-compliance due to our system/vendor product?

   All ICSRs that meet the report requirements in UK legislation (including downgrades) should be reported to the MHRA from exit day. We are aware of a limitation in one vendor system that would prevent submission of downgrade ICSRs in certain circumstances and understand that a software patch is being developed. Companies that are at risk of non-compliance as a result of this issue should contact ICSRTesting@mhra.gov.uk in order that we can agree a resolution pathway. Will consider pragmatic work arounds depending on the situation.

[7] https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario

10. As there is are no specificities should MAH assume that the other criteria for reporting remained unchanged?

    Reporting timelines will remain unchanged. Literature cases should be included in submissions to MHRA and will be acknowledged, however, only a single version of the ICSR will be loaded to the MHRA database to avoid duplication. MLM cases will be excluded from MHRA outbound submission.

Variations

1. Will there be any practical implications for the completion of running procedures where the UK is CMS (e.g., variations and renewals)?

   Procedures where UK is CMS will continue to be processed in line with guidance for in-flight variations. If variations have not reached the key EU milestone defined in guidance at exit day, they will be progressed as national variations to the now national licence. MRDC variations applications submitted to the MHRA before exit day will not require resubmission.

2. Will companies be required to resubmit MA Applications or Variations submitted prior to Brexit that have not yet been validated?

   Assuming the centralised application is subsequently validated by the EMA - or an invalid application is resubmitted to the EMA before exit day and the submission is subsequently validated - the following applies:

   - *Type IA and IB variations submitted to the EMA but not granted prior to exit day which are subsequently granted by the EMA, will not be required to be resubmitted to the MHRA. These variations can be implemented in the UK at the same time they are implemented in the EU and must be included in the initiating sequence.*
   - *Type II variations submitted to the EMA but not granted prior to exit day but with a positive CHMP opinion before exit day will not be required to be resubmitted to the MHRA. The variations can be implemented in the UK at the same time they are implemented in the EU and must be included in the initiating sequence.*
   - *Type II variations submitted to the EMA prior to exit day but not granted prior to exit day which are in or before clock stop on exit day, will require resubmission to the MHRA. These variations should be submitted in a separate sequence along with the initiating sequence.* If the variation has received numerous rounds of questions, *for efficiency of processing, the MHRA strongly recommends submitting a consolidated sequence*
   - *Most variations submitted to EMA prior to exit and at this stage of progress can be submitted in the identical format as were submitted in EU but some adaptation of the eCTD may be required so that they are technically valid. The approach taken to achieve a technically valid sequence remains a matter for the companies to resolve. In some base data submission scenarios, it may be preferable/acceptable to amend some or all of these variation documents, but any such changes must fall in line with published guidance for the submission of the base sequence itself.*

   Please refer to section 7 and 8 and table 1 in the MHRA CAP Grandfathering guidance[8]. For details CAP new MA applications in-flight on exit day will require re-submission of the application and data to the MHRA.

[8] https://www.gov.uk/guidance/converting-centrally-authorised-products-caps-to-uk-marketing-authorisations-mas-in-a-no-deal-scenario-grandfathering-and-managing-lifecycle-ch#approach-to-variations-submitted-to-the-ema-but-not-granted-before-exit-day

eCTD, eAF & Submission Processes

1. Will the MHRA send acknowledgement of baseline receipt and acceptance? If not, how long after baseline submission can companies begin submitting variations?

   CAPs will legally convert to UK national licences on exit day and can continue to be marketed. Additionally, a licence grant letter will be issued at the end of the CAP conversion process (and/or next MRP/DCP sequence or baseline).

   Variations can either be submitted along with the initiating sequences or anytime afterwards but will always be processed after the initiating sequence has been processed.

2. Which application forms should be used when submitting via the new submission portal? Will there be E-application forms?

   Continue to use the latest version of eAF until we release any further guidance.

3. For pending MAA initially submitted as UK National via CESP, will it be possible to switch to the MHRA National portal before the MAA is approved?

   Yes, any regulatory submissions required post day 1 can be submitted via the UK national portals, including those in flight. It is recommended that you register for the new MHRA Submission portal prior to day 1. Details on how to register can be found online[9]*.*

4. A new version of the eAF has just been released for use in EU submissions after 11th Nov 2019. As companies have already invested significant time in prepared baseline submissions in readiness for a no deal on Oct 31st using the then current eAF version, will MHRA be able to still accept these after 11th Nov? (Reworking existing eAFs to copy all data fields over to the new version of the eAF would impose a significant burden on companies with large CP portfolios.)

   We will accept the current version and any later versions of eAF for the foreseeable future.

5. If we have no way of avoiding validation errors in the forms (e.g. if information is truly unavailable) will this affect the baseline submission validation and cause issues with processing the baseline? We will of course avoid this wherever possible.

   The eCTD sequence itself must of course be technically valid i.e. all pass/fail criteria must pass, or we will be unable to load it into our system. We understand that best practice warnings may arise in certain areas of the validation report but this will not cause the eCTD to be technically invalid and we are not aware of any instances where technical validation would fail when supplying a grandfathering initiating sequence according to our guidance.

6. The guidance seems to indicate a need to submit a separate eAF for each PL. If that is the case, has the MHRA tested that this will not cause any eCTD validation issues, as this is not how the eAFs are used in the EU process today?

[9] https://www.gov.uk/guidance/making-submissions-to-the-mhra-in-a-no-deal-scenario

Yes, a separate eAF is needed for each PL. MHRA are trying to establish a licence in our own system and require all the documentation that relates to it. For maintenance applications after the initial round it may then revert to previous processes.

7. Does it still take 42 days to process applications done as part of grandfathering? How does this relate to CPP requests where we are due to put in an application shortly after grandfathering?

   Processing from the time when the initiating sequence is received by MHRA involves essential validation checks which includes a technical validation of the eCTD and a check for the presence of the critical documents defined in the guidance, including a statement from the MAH that the baseline submitted is an accurate reflection of the currently approved EU authorisation. For clarity, at the end of this process a letter acknowledging that the submission has been formally 'granted' will be sent but the license itself will be valid from day 1. We have not set a specific timescale for this process as it will depend on the volume and timing of data submissions sent but we have allocated and trained resources to cover a range of scenarios.

   A company can submit a CPP application as soon as the UK licence has been approved. We issue 2 different services.
   - *Urgent Service - £152. Companies would expect their documentation back within a week of submitting their applications*
   - *Standard Service - £68. Companies would expect their documentation back within 3 weeks of submitting their applications"*

8. Are the annexes for the eApplication Form required for product baselines?

   MHRA does require these annexes. We expect that CAP MAHs will provide each submission as if they were applying for the original new MAA but doing so with only the EU approved documentation that best reflects the current status of the licence together with any UK specific updates where relevant and acceptable in terms of any new UK specific regulations and guidance. If the content required by current annexes were not required/completed for the original there is no requirement to produce them specifically for the initiating sequence but if they have been produced since and are available they should be provided (making clear when content is not approved in the EU).

9. Further clarification would be welcomed on the timelines for "in-flight assessment" for those procedures at Day 120-180 at time of exit: Does "Start dates will be aligned with published CHM dates" mean the start dates will be the same as CHM date? If not, applicants will need to know the start dates for planning purposes. Are clock stops permitted during the 60-day timetable? If so, how does this affect the 60-day timetable (e.g. will there be another 60-day assessment)?

   The start dates and CHM dates will not be the same. We will publish CHM and procedure start dates. The 'in flight' applications will be dealt with on a case by case basis depending on the circumstances - there may be a clock stop. This is the purpose of the telecons with each applicant.

10. Line extension applications to CAPs will be following the same timetable as new applications. Will the option of targeted assessment also be available for line extension applications ongoing on exit day? The "Guidance note on new assessment routes in a no deal scenario" suggests line extensions would be out of scope for targeted assessment, but this would seem inconsistent with MHRA's proposed pragmatic handling of new applications and post-licensing submissions (including variations) that are ongoing on exit day.

Line extensions do not fall under the targeted assessment process but 'in flight' applications will be handled pragmatically.

11. Would the MHRA require a cover letter with the PSUR submission and, if so, is there a template of such a cover letter?

    A cover letter is not required but you will need to fill out the webform when submitting the PSUR.

12. How soon after a “no deal” Brexit will MAHs will be expected to submit licence variations?

    The timeframes for the submission of variation applications to update the summary of pharmacovigilance system (SPS) are described in the no-deal guidance published on the MHRA’s website[10]*.*

[10] *https://www.gov.uk/guidance/guidance-on-qualified-person-responsible-for-pharmacovigilance-qppv-including-pharmacovigilance-system-master-files-psmf-if-the-uk-leaves-the-eu-w*

Databases

1. When will national equivalent to EU databases be available (for example, Article 57) and what are the expectations regarding data population?

   The Agency has built IT contingency systems to ensure regulatory activity and submissions can continue from day one if the UK leaves without a deal. Post day 1 the Agency will explore options to enhance and build new technology as part of its transformation programme, but we continue to focus now on ensuring systems are ready for users on day 1.

2. Will a download from existing databases EU/EMA be taken prior to Brexit?

   Usage of data obtained from EU databases is currently under consideration by the MHRA.

3. Will MHRA develop a UK equivalent of the XEVMPD database?

   Yes; this has been developed and will be available from exit day.

Supply Chain

1. According to published guidance on the Conversion of Centrally Authorised Products, IB variations pending at the time of Brexit may be submitted in parallel to the baseline. Table 1 Summary of Approach to Variations (embedded in section 8 of the guidance) indicates that these pending IB variations will not be assessed by the MHRA. Please can this be confirmed, and if the MHRA are not assessing these IB variations may MAHs proceed with implementation of concerned changes upon EMA approval?

   Type IB variations submitted to EMA but not granted before exit day and subsequently accepted by the EMA may be implemented in the UK at the same time as in the EU. These variations should be included in the initiating sequence and will not be re-assessed by the MHRA.

2. According to section 2 of the Guidance on Importing Medicines on an Approved Country for Import list in a No-Deal Brexit, companies looking to import a medicine from a country on the list must hold a Wholesale Dealer's Licence that authorises import. The licence must also authorise wholesale distribution operations including: 2.5. Products imported from countries on a list; and 2.5a. Products certified under Article 51 of Directive 2001/83/EC. Do these requirements still apply if a company holds a Manufacturer's/Importer's Licence? If not, will products imported from a country on the approved list need to be listed in Annex 8 of the Manufacturer's/Importer's Licence.

   Importation of QP certified products from EEA will require a WDA(H) with RPI. This cannot be performed under an MIA.

3. Will the inclusion of IA IB variation in initiating sequence be possible even if a minimum sequence has already been submitted first?

   The same rules apply whether or not MIS has been done, the MIS merely gets basic information onto the database which may have to be updated as part of the process when the CAP baseline is submitted.

Product Information

1. Are there any possibilities for combined labelling in the future (for example, German-English packs to be marketed in UK, IE, DE, AT)?

   The UK will continue to accept joint packs, where information is presented both in English and the language(s) of the other member state(s), provided that the information in the UK SmPC and that of the other member state(s) remains aligned.

2. Will UK labelling requirements continue to be based on the EU QRD template?

   UK labelling requirements will continue to be based on the QRD template. Additional guidance and product warning statements will be available via the MHRA Best Practice Guidance in the Labelling and Packaging of Medicines and Warning Statements for Labels and Leaflets of Certain Medicines, as is the current situation[11]*.*

3. At present, MAHs are required to update any external websites (e.g. eMC) within 10 working days of approval of new SmPCs and PILs. Following Brexit, and where a divergence of the EU label from the UK label occurs, is the MAH obligated to update external websites with the most up to date EU product information or wait for a delayed assessment and approval by the MHRA?

   UK websites should not be updated until the UK particulars have been approved.

4. Can we keep with our current SmPC with the old non-UK MAH and MA number until the next labelling update (in the same way as allowed for the packaging) or will we be obliged to issue a new SmPC straight away? 'Straight away' would need defining if so.

   It will not be necessary to submit a revised SmPC straight away.

5. For SmPCs, as we are submitting the whole SmPC we are assuming that MHRA do not require us to submit fragments.

   This is correct.

6. Can we submit combined SmPCs as this is what we currently have available for the EU?

   Yes, combined SmPCs are acceptable.

7. How long will we have to update artwork and product packaging in line with the administrative changes associated with Brexit?

   Once you have been issued with your new Marketing Authorisation (MA), you have 21 months to establish and register a UK presence for your MA. This will include submitting amended artwork for approval to accommodate the following new administrative information:

   - *name and address of MAH or representative*
   - *UK MA number*
   - *name and address of product manufacturer for batch release*

[11] https://www.gov.uk/government/publications/best-practice-in-the-labelling-and-packaging-of-medicines, Also see - https://www.gov.uk/government/publications/warning-statements-for-labels-and-leaflets-of-certain-medicines

You will then have a further 12 months (33 months in total from exit day) to ensure all stock released to market is in compliant packaging. This additional time allows for assessment of your submission(s) and time for implementation in the production schedule.

8. How do you submit packaging texts – under which headings in the EU eCTD structure should the EU texts be submitted and which for the UK texts or UK mock-ups?

   We need to have what has been approved in the EU but the product information will also include a text version of the SmPC along with the labelling and the PIL. Currently these are in the annex.

9. If submitting a Change of Ownership with the baseline, is the current approved EU artwork (PIL and packaging) sufficient to include in the baseline or does it have to indicate new UK-specific MAH and PL details – even if these details are not being implemented into printed components immediately?

   Current artworks can be included with the submission but these will have to be varied within the transition period to the new mock-ups

10. The baseline guidance indicates that current EU labelling needs to be included but also references including SmPCs in the SmPC template. The way that presentations have been grouped/split in the current EU CP label annexes and associated SmPCs is not necessarily how the MHRA has grouped different presentations on the proposed UK PLs, for some products. For the initial baselines, can we simply mirror the current EU SmPCs or do we need to revise them to align with UK PL grouping (which will require extra work and extend timelines for baseline availability)? Do the baseline SmPCs need to additionally include the new, UK-specific MAH and PL numbers? Do we need to include artwork mock-ups of the current EU PIL and packaging in the baselines – and if so can we clarify that we do not also need to include PIL text?

    SmPC should be in the UK (Word) template which should be the same as the published EU version in most cases. If supplying a SmPC for a CAP grandfather + COA the section 7 & 8 should be updated with new MAH details. Current artworks can be used during the transition period and therefore these can be provided as the mock-ups until a variation is submitted with the new mock-ups which will include the new MAH & PL number details.