Converting Centrally Authorised Products (CAPs) to UK Marketing Authorisations (MAs) in a no-deal Brexit, 'grandfathering' and managing lifecycle changes

This guidance covers ‘grandfathering’ and managing the lifecycle changes of medicinal products.

Published 18 March 2019

From:

Medicines and Healthcare products Regulatory Agency

Contents

This guidance will apply from exit day in line with the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019.

If the UK leaves the EU without a deal, the Medicines and Healthcare products Regulatory Agency (MHRA) will be the UK’s stand-alone medicines and medical devices regulator, taking any decisions and

carrying out any functions which are currently taken or carried out at EU-level. This includes decisions on Marketing Authorisation (MA) applications which are currently authorised through the centralised procedure, paediatric investigation plans and orphan status, as well as pharmacovigilance responsibilities.

This guidance follows on from the further guidance note published on 3 January 2019 and the letters sent in November 2018 and January 2019.

General approach to grandfathering of CAPs

All existing CAP MAs will automatically be converted into UK MAs and issued with a UK MA number on exit day. These UK MAs are referred to in this guidance as “converted EU MAs”.

MAHs can choose to opt-out of the conversion process for all or some of their CAPs by notifying the MHRA in writing following which those UK MAs will be revoked. The details of how to exercise that option can be found in the first letter in November 2018. You must let the MHRA know if you wish to opt-out be 21 days before exit day.

If the MAH chooses to opt-out, their product(s) will no longer be licensed and must not be marketed in the UK. The MHRA will publish a list of products that have and have not been converted as a result of this exercise.

To support the ongoing regulation of these converted EU MAs, the MHRA needs essential baseline data to be submitted in the form of an initiating electronic Common Technical Document (eCTD) sequence together with certain other related MA-specific information for each converted EU MA.

MAHs will have a period of one year starting on exit day to submit this data and related information in eCTD format. Until these initiating sequences are submitted and processed, it will not be possible to submit a variation for the converted EU MA unless there are exceptional

circumstances relating to public health. There is no fee for the grandfathering process.

As with all national MAs, an annual service fee will be due for converted EUMAs from 1 April 2020 unless the MAH opts out by the required date.

Actions that holders of converted EU MAs need to take

1. What to submit in the initiating sequence and other related information

Within the period of one year starting on exit day, the MAH must submit the following information to the MHRA for each converted EU MA. (This is the information which is specified in paragraph 9(3)(a) of new Schedule 33A to the Human Medicines Regulations 2012, as inserted by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019).

The data submission package must contain:

a) cover letter and declaration that only approved documentation is included in the initiating sequence. The cover letter should clearly identify the submission as a “CAP Grandfathering Submission” in the title.

b) a single eCTD initiating sequence for the converted EU MA representing the currently authorised and approved position. Where more than one dosage form or strength will be converted for the same product trade name, it is expected these will be handled as one eCTD dossier. If the product dossier refers to an Active Substance Master File, the MAH must ask the active substance supplier to submit that to MHRA if they have not already done so. We have published guidance on how to do this

c) a completed electronic application form (eAF) for each converted EU MA.

d) a summary list of all historical regulatory activity from the grant date of the original CAP until the data is submitted. This will include:

I. type of submission (such as initial new Marketing Authorisation Applications (MAA), Variation, Periodic Safety Update Report (PSUR), Renewal)

II. the date of submission to the European Medicines Agency (EMA) (optional if the outcome date is available)

III. summary of the submission (such as a short description of a variation)

IV. regulatory outcome (such as granted or not granted)

V. the date of the outcome

VI. eCTD sequence number of the submission (only for eCTD format submissions)

Alternatively, the historical document can mirror the format of the EUprocedural steps document if this makes it easier to create.

e) notification of whether or not the product referred to in the converted EUMA is on the UK market at the time the notification is given. If it is not, the MAH must tell us whether the product has been on the UK market at any time after exit day and, if so, the date it was withdrawn from the market (for the purposes of Article 23a and Article 24 (4-6) of Directive 2001/83EC – as implemented in regulations 67 and 73 of the Human Medicines Regulations 2012), the “Sunset Clause”). This information may be included in the cover letter.

f) the Summary of Product Characteristics (SmPC) currently approved by corresponding EU procedure both in pdf format and in the SPC template (MS Word Document, 17.7KB) .

g) the packaging labels and leaflets as currently approved by the corresponding EU procedure which are:

I. the outer packaging of the medicinal product;

II. the immediate packaging of the medicinal product; and

III. the package leaflet for the medicinal product.

2. Further advice on documentation

The summary of historical regulatory activity (section d above) must be included in the Working Documents folder of the eCTD and the notification of marketing status (section e above) must be included in the cover letter.

The cover letter, electronic Application Form (eAF) and currently approved SmPC, Packaging and Patient Information Leaflet (PIL) must be included in the appropriate folders in Module 1 of the eCTD sequence.

The submission must reflect only what is relevant to the product intended for the UK so that this can be used as the start of the lifecycle for the nationally registered product(s). Inclusion of non-UK specific information could, over time, lead to inaccurate information held within the database and may lead to difficulties with the technical validation of subsequent submissions.

The eCTD sequence must pass technical validation (sections 4 and 5 below). The MHRA will apply an abbreviated content validation and will not issue a validation report, the presence of a SmPC, PIL and packing information are mandatory.

The MHRA expects that all information representing the currently authorised and approved position that has previously been submitted in eCTD format will be included in the initiating sequence submission. However, it is acknowledged that some information may not be available

in electronic format, particularly for older products, and that it may not be possible for the initiating sequence to be entirely complete.

In these circumstances, the MAH should submit what is available and the MHRA will accept a partially completed sequence, provided:

- The MAH makes all reasonable endeavours to include any information available in an electronic format other than eCTD format, in the appropriate eCTD structure in accordance with eCTD technical validation criteria. Avoid placing documents in the Working Documents section of the eCTD structure and use it by exception only.

The holder of the converted EU MA responds to a request to provide any information related to the MA either before or after submission of the initiating sequence, including historical information, within the time period specified in the request.

3. How to submit the application

In the event of no deal, the MHRA does not expect to be able to receive submissions through the Common European Submission Portal (CESP). We are developing a new national portal to be ready by exit day and expect that submissions will be made via this portal. Information on the use of this portal will be published in advance of exit day.

4. Specific advice on preparing the initiating sequence

Background information on the latest version of the eCTD standard, including EU guidance on Module 1 information and the electronic application form can be found on the EMA e-submissions website.

The date on which the minimal or full initiating sequence is received is referred to as “the data submission date”. The MAH should construct a single, technically valid, eCTD sequence (the “Converted EU MA Initiating Sequence”) showing the current, approved

information (“current authorised view”) of the converted EU MA(s) on the data submission date.

Information that has been “replaced” or “deleted” during the life cycle of the CAP MA that the converted EU MA is derived from should not be included.

The sequence should be assigned as sequence number 0000, submission type “maa” and submission unit assigned as “initial”.

Points to consider:

a) Only include UK relevant information. Remove previous cover letters and application forms, and remove all product information except UK specific information.

b) Remove all PSUR information. The UK will not require the PSURs to be submitted in the eCTD lifecycle.

c) Historical EU information about the PV Master File, etc. in module 1.8. is not required. New information must be submitted as a later type IA variation.

d) Remove all responses to questions in module 1 - i.e. remove any discussion and only show the outcome in terms of the documents in the rest of modules 1-5.

e) The submission must include a full eAF) for each of the products in the application. The “Initial MAA” eAF should be used with the initiating sequence and only approved information should be included - any changes to the approved information must be submitted as a variation after the submission of the initiating sequence using the normal process for variations to national MAs (see information on variations in sections 6 - 8).

f) The summary of historical regulatory activity must begin with the original CAP MAA submission and continue up to the data submission date. This must be a list of the submission events in a table format, not the individual eCTDsequences that were submitted for each event

(noting that for some products these events will predate the eCTD). Please submit this in the same format as the tracking table in module 1.0.

g) The initiating sequence must be a valid eCTD submission, built to EUmodule 1 v3.0.2 and ICH v3.2.2 standards or, if these are superseded, by such standards that are applicable at the time of submission. Non-functioning hyperlinks are acceptable if they are unavoidable.

h) The initiating sequence should include multiple dosage forms and strengths in a single eCTD dossier lifecycle.

5. Submitting the initiating sequence in two steps

The MHRA strongly prefers MAHs submit the initiating sequence as a single event. However, it is recognised that some MAHs may need to submit variations, renewals or Article 61(3) notifications to the MA before they can produce the complete initiating sequence.

In these circumstances, the MAH can use a two-step process by first submitting a minimal initiating sequence containing at least the mandatory documents at an early point following exit day. The mandatory documents are:

- those described in section 1f) and 1g)
- an eAF containing at least the mandatory information (as defined in the eAF section 1c))
- a cover letter and declaration (see section 1a)).
- a statement in the cover letter that this is a minimal initiating sequence and commitment to send the complete initiating sequence within a period of one year starting on exit day.

The sequence must also be technically valid (see section 4g) above).

If MAHs take this approach, a further complete initiating sequence, containing all documents electronically and the specific other related information defined in section 2, must still be submitted within a period of one year starting on exit day. The sequence number of this submission should be sequential to the earlier minimal initiating sequence and any subsequent variations or other submissions.

If MAHs submit an early minimal initiating sequence we advise making every effort to include Module 3 (quality) documents. This module is frequently varied and, if the documents are not available, any subsequent variation to M3 is likely to be delayed by the need to request missing data.

6. General approach to variations to converted EUMAs after exit day

In general, the MHRA will not consider variations to converted EU MAsbefore at least a minimal initiating sequence (as defined in section 5) and related documentation (the “data submission package”) have been submitted. The date on which the minimal or full initiating sequence is received is referred to as the data submission date.

In exceptional circumstances, we may consider a variation before the data submission date. An example would be if, in the absence of a minimal or full initiating sequence, we are of the view that:

- the variation is necessary on urgent safety grounds
- the variation is necessary in order to maintain supplies of a particular medicinal product to patients in the UK
- there are other good reasons for considering the variation in advance of receipt of the baseline information

If the holder of a converted EU MA considers that these conditions may apply, they should contact the agency’s Regulatory Information Service to ask for agreement from MHRA and discuss how to proceed.

Variation applications may be included with the data submission package as separate eCTD sequences in line with the normal national MA variation process. However the variation will only be considered after the baseline is processed and will be treated as if it was submitted after the data submission date.

This table provides a summary of the approach to variations (PDF, 60.3KB, 1 page) that MHRA will take in the different scenarios which may arise.

7. Approach to variations submitted to the EMA but not granted before exit day

To simplify handling of variation submissions the MHRA has adopted a pragmatic approach to these submissions.

Type IA Variations

For minor variations of type IA, the variation must be included within the initiating sequence submission as if it had already been accepted in the UK. It may be implemented in relation to the converted EU MA at the same time as it is implemented in relation to the corresponding EU MA.

The MAH must inform the MHRA when submitting the sequence if the variation was rejected by the EMA after exit day but before the data submission date, and the variation must be removed from the initiating sequence. The IA variation will be deemed to be accepted unless the MHRA notifies the holder of the converted EU MA, within 30 days of the data submission date, that it has been rejected.

The details of the type IA variation must be included in the summary of historical regulatory activity submitted with the initiating sequence.

Type II Variations

For major variations of type II, if the variation had reached positive Committee for Medicinal products for Human Use (CHMP) opinion stage before exit day:

- the variation must be included within the initiating sequence submission as if it had already been accepted in the UK
- the variation may be implemented in relation to the converted EU MA at the same time as it is implemented in relation to the corresponding EU MA
- The details of the type II variation must be included in the summary of historical regulatory activity submitted with the initiating sequence
- No fee will apply for these variations

If the Type II variation had not reached CHMP opinion and at exit day was in clock-stop following a request for further information:

- a copy of the variation application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on)
- The variation will only be considered after the initiating sequence is processed.
- No fee will apply for these variations the UK will assess responses when they are submitted.

If the Type II variation had not reached CHMP opinion and at exit day was before clock-stop:

- a copy of the variation application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on).
- The variation will only be considered after the initiating sequence is processed.
- The usual fee will apply for these variations and the variation will be assessed in line with normal MHRA practice.

8. Approach to variations to converted EU MAsapplied for after exit day

This advice applies where the holder of a converted EU MA has notified the EMA of, or applied to the EMA for, a variation of the EU MA after exit day but before the data submission date and intends the variation to be made in relation to the converted EU MA.

Type IA Variations

For minor variations of Type IA, these may be implemented in relation to the converted EU MA at the same time as they are implemented in relation to the corresponding EU MA. The variation must be included in the initiating sequence submission as if it had already been accepted in the UK.

The MAH must inform the MHRA when submitting the sequence if the variation was rejected by the EMA after exit day but before the data submission date, and the variation must be removed from the initiating sequence.

The IA variation will be deemed to be accepted unless the holder of the converted EU MA is notified, within 30 days of the data submission date, that it has been rejected.

The details of the type IA variation must be included in the summary of historical regulatory activity submitted with the initiating sequence.

Type IB and Type II Variations

For minor variations of type IB, and major variations of type II, if the variation has not been rejected by the EMA before the data submission date, a copy of the variation application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on). The variation will only be considered after the baseline is processed.

Type IB/II variations will be assessed in line with normal MHRA practice and the usual fee will apply.
This table provides a summary of the approach to variations (PDF, 60.3KB, 1 page) that MHRA will take in the different scenarios which may arise.

9. General approach to renewals to converted EUMAs after exit day

For the purpose of renewals, converted EU MAs are treated as if they were granted on the date on which the corresponding EU MA was granted. The converted EU MA will therefore have the same renewal date in the UK as in the EU. In general, the MHRA will not consider renewals to converted EUMAs before at least a minimal initiating sequence (as defined in section 5) and related documentation (the “data submission package”) has been received. The date on which the minimal or full initiating sequence is received is referred to as “the data submission date”.

In exceptional circumstances, we may consider a renewal before the data submission date (in the absence of a minimal or fully initiating sequence) if we are of the view that:

- the renewal is necessary on urgent safety grounds
- the renewal is necessary in order to maintain supplies of a particular medicinal product to patients in the UK
- there are other good reasons for considering the renewal in advance of receipt of the baseline information

If the holder of a converted EU MA considers that these conditions may apply, they should contact the agency’s Regulatory Information Service to ask for agreement from MHRA and to discuss how to proceed.

Renewal applications may be included with the data submission package as separate eCTD sequences in line with the normal

national MA renewal process, but will only be considered after the baseline is processed.

After the data submission date, the normal renewal application process for national MAs and fees will apply.

10. Approach to Renewals submitted to the EMAbut not granted before exit day

Converted EU MAs

This section applies where the holder of a converted EU MA has made an application to the EMA for a renewal of the EU MA before exit day but no final decision was made by the EMA before exit day.

A copy of the renewal application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on). The renewal will only be considered after the baseline is processed

In considering the application:

Where before exit day, the CHMP has given a positive final opinion and the UK concurred, the renewal will be treated as accepted:

- the renewal must be included within the initiating sequence submission as if it had already been accepted in the UK.
- The details of the renewal must be included in the summary of historical regulatory activity submitted with the initiating sequence
- No fee will apply for these renewals. If, before exit day, the renewal had not reached CHMP opinion and was in clock-stop following a request for further information:
- a copy of the renewal application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on).

- The renewal will only be considered after the initiating sequence is processed.
- No fee will apply for these renewals

If before exit day the renewal had not reached CHMP opinion and was before clock stop:

- a copy of the renewal application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on).
- The renewal will only be considered after the initiating sequence is processed.
- The usual fee will apply for these renewals and the renewal will be assessed in line with normal MHRA practice.

Where, before exit day, the CHMP had given a negative final opinion or had given a positive final opinion but the UK had recorded a divergent opinion, the renewal will be considered in line with normal MHRA practice:

- a copy of the renewal application must be included in the data submission package as a separate eCTD sequence (sequence 0001 and so on).
- The renewal will only be considered after the initiating sequence is processed.
- The usual fee will apply for these renewals

Converted conditional EU MAs

This section applies where the holder of a converted EU MA which was granted as a conditional MA has made an application to the EMA for a Renewal of the EU MA before exit day but no final decision has been made by the EMA before exit day.

A copy of the renewal application must be included in the data submission package as a separate eCTD sequence (sequence 0001

and so on). The renewal will only be considered after the baseline is processed.

In considering the application:

- Where, before exit day, the CHMP had given a positive final opinion and the UK concurred, the renewal will be treated as accepted
- Where, before exit day, the CHMP had not given an opinion or had given a negative final opinion or had given a positive final opinion but the UK recorded a divergent opinion, the renewal will be considered in line with normal MHRA practice

11. Approach to applications for renewals made after exit day

Converted EU MAs

This section applies where the holder of a converted EU MA is due to make an application for a Renewal of a converted EU MA during the period of one year following exit day.

Where this applies, the MAH must submit an application for renewal in accordance with the usual time limits. The application should be submitted as a separate eCTD sequence (sequence 0001 and so on) along with the initiating sequence (minimal or complete) if this has not already been submitted. The renewal will only be considered after the baseline is processed.

The MHRA will consider the application, which should be accompanied by the appropriate fee.

The MA will remain in force until the MHRA notifies the MAH of its decision on the renewal application.

Converted conditional EU MAs

This section applies where the holder of a converted EU MA that was granted as a conditional MA is due to make an application for a Renewal of the MAduring the period of one year following exit day and ending on the data submission date.

Where this applies, the MAH must submit an application for renewal in accordance with the usual time limits, and the application should be submitted as a separate eCTD sequence (sequence 0001 and so on) along with the initiating sequence (minimal or complete) if this has not already been submitted. The renewal will only be considered after the baseline is processed.

The MHRA will consider the application in accordance with new regulation 66B. No fee is due.

The MA will remain in force until the MHRA notifies the MAH of its decision on the renewal application.

12. General approach to Article 61(3) notifications for converted EU MAs after exit day

In general, the MHRA will not consider Article 61(3) notifications for converted EU MAs before at least a minimal initiating sequence (as defined in section 5) and related documentation (the “data submission package”) has been received. In exceptional circumstances we may consider an Article 61(3) notification before the data submission date and in the absence of a minimal or full initiating sequence, if we are of the view that:

- the notification is necessary on urgent safety grounds
- the notification is necessary in order to maintain supplies of a particular medicinal product to patients in the UK or

- there are other good reasons for considering the variation in advance of receipt of the baseline information.

If the holder of a converted EU MA considers that these conditions may apply, they should contact the agency's Regulatory Information Service to ask for agreement from MHRA and discuss how to proceed.

Article 61(3) notifications may be included with the data submission package as separate eCTD sequences in line with the normal national MA notification process but will only be considered after the baseline is processed.

After the data submission date, the normal Article 61(3) process for national MAs and fees will apply.

13. Approach to Article 61(3) notifications submitted to the EMA but not granted before exit day

Where:

- the holder of a converted EU MA has made an Article 61(3) notification for the corresponding EU MA before exit day,
- the change is applicable to the product information intended for the UK market
- the 90 day period referred to in Article 61(3) has not elapsed,
- the EMA has not objected to the change,

the notification must be included within the initiating sequence submission as if it had already been accepted in the UK. The change may be put in effect at the same time as for the EU MA.

No fee will apply for these notifications.

The notification will be deemed to be accepted unless the holder of the converted EU MA is notified that it has been rejected within 30 days of the data submission date.

The details of the Article 61(3) notification must be included in the summary of historical regulatory activity submitted with the initiating sequence and the MAH must notify the MHRA if the EMA rejects the notification after exit day but before the data submission date.

14. Approach to Article 61(3) notifications made after exit day

Where the holder of a converted EU MA has made an Article 61(3) notification for the EU MA after exit day but before the data submission date, and the change is applicable to the product information intended for the UK market, the notification must be included within the initiating sequence submission as if it had already been accepted in the UK. The change may be put in effect at the same time as for the EU MA.

No fee will apply for these notifications.

The notification will be deemed to be accepted unless the holder of the converted EU MA is notified that it has been rejected within 30 days of the data submission date.

15. Legal presence requirement

For grandfathered CAP MAs with a non-UK MAH, there is a requirement to establish an MAH in the UK by the end of 2020. MAHs have two options:

1. Submit a Change of Ownership application (COA) after the submission of the baseline initiating sequence and before the end of 2020

2. Include the COA in the initiating sequence as if it had already been approved by the MHRA and state in the cover letter that this option had been adopted.

MAHs using option 2 must ask for PL numbers to be issued for the UK MAHby 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 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.

The MHRA would prefer that MAHs took the latter approach and included the change in the initiating sequence. There will be no fee in either case.

For MAHs who choose to submit a COA should see our information on change of ownership published on our website.