Guidance on how variations to Marketing Authorisations (MAs) will be handled after exit day if there is no-deal

The approach the MHRA intends to take to the processing of variations to marketing authorisations after exit day in a no-deal scenario.

Published 18 March 2019

From:

Medicines and Healthcare products Regulatory Agency

Contents

The guidance describes the approach the MHRA intends to take to the processing of variations to marketing authorisations after exit day in a no-deal Brexit.

1. Variations Procedures

The secondary legislation revokes the Variations Regulation (EC) No 1234/2008, as amended, which was immediately binding in the EU and applied immediately before exit day and incorporates in the Human Medicines Regulations 2012 (“HMRs”) the elements of that Regulation that remain applicable in a no-deal Brexit.

The procedures detailed under Chapter IIa of that Regulation, which specifically applied to variations to purely national Marketing Authorisations, will continue to apply to both pending and new variations to UK Marketing Authorisations, all of which will be purely national, after

exit day and can be found in new regulation 65C and Schedule 10A to the HMRs.

In addition, unless specifically highlighted under section 3, the current variations classification guidelines, which explains the type of variation (Type IA, Type IAIN, Type IB, Type II or Extension) to submit and, where relevant, the conditions to be met and any required supporting documentation, will continue to apply.
Any extension application should be submitted in accordance with the procedures for new Marketing Authorisations. The variations classification guidelines will continue to apply until the MHRA issues any revised guidance in the future.

The UK will recognise any Article 5 recommendation published by the Co-ordination group for Mutual recognition and Decentralised procedures – human (CMDh) before exit day. Any specific request from a Marketing Authorisation Holder (MAH), concerning the classification of a variation, which is still pending (no recommendation) on exit date or is submitted after exit day will need to be submitted directly to the MHRA, who will issue its own recommendation.

2. Variation of a UK marketing authorisation

If not the case before exit day, all Marketing Authorisations authorised in the UK by the MHRA will become purely national. Any pending and new variations will therefore only be processed to conclusion after exit as national variations, where the relevant national procedures will be followed.

Any centrally authorised products (CAPs) which are grandfathered will also be national Marketing Authorisations. Transitional provisions make special arrangements to handle these variations and these are explained in separate guidance on converting CAPs in the event of a no-deal scenario.

2.1. Pending variations (no decision)

How variations that are pending (‘no final decision) on the day we leave the EU would be finalised:

Purely national Marketing Authorisations (not part of any worksharing procedure)

These will be processed to conclusion under the transitional provisions, using the same purely national procedures that were in place prior to Brexit.

UK Marketing Authorisation covered under Chapter II of Regulation (EC) No 1234/2008 (variations to marketing authorisations granted in accordance with Chapter 4 of the 2001 Directive i.e. mutual recognition/decentralised variations (Type IA, Type IB or Type II)

and

Purely National Marketing Authorisations before exit day, but part of a Worksharing Procedure under Article 20 of Regulation (EC) No. 1234/2008 (Type IB or Type II)

For variations falling under either of these two scenarios, whether or not the UK was the Reference Member State/Reference Authority (lead) for the procedure, the variation will be processed to its conclusion as a purely national variation. Every effort will be made to ensure that relevant procedural time periods are observed. The ongoing assessment will take into account where in the overall procedure the application has got to on exit day. Therefore, any information previously obtained, and any assessment reported on before exit day will be taken into consideration as part of the UK assessment process.

2.2. Pending variations (decision made)

In the event that the UK is not the Reference Member State or Reference Authority for a variation procedure and a final decision has

already been taken by the lead authority, but not finally processed in the UK before exit day, the MHRA will implement the agreed outcome of the procedure.

2.3. New variations submitted post exit day

All new variations submitted after exit day will be processed as purely national variations, according to the same transposed procedures, as were in place prior to Brexit. There will be no provision for worksharing.

3. Points to note for specific changes submitted post Brexit

3.1. Change to finished product manufacturer

A change in finished product manufacturing site, including as appropriate primary and/or secondary packaging site should be submitted under the relevant sub-change code under B.II.b.1 and be suitably supported. This includes the submission of a copy of the relevant Manufacturing Authorisation or as appropriate a valid good manufacturing practice (GMP) certificate issued by the UK, or a GMP certificate (or equivalent document) from the competent authority of a country on the approved country for batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, Switzerland and the USA).

More information about batch testing including a list of approved countries for authorised human medicines in a no-deal scenario.

Where relevant reference to the EudraGMP database will suffice.

3.2. Change to importer/batch release site/quality control site

A change in importer/batch release site and/or quality control site should be submitted under the relevant change code under B.II.b.2 and be suitably supported.

3.2.1. Importer/batch release

The change should be supported by including a copy of the relevant Manufacturing Authorisation or a valid GMP certificate issued within the last 3 years (as issued by the UK or a country included on the approved country for import list (currently EU/EEA Member States).

Where relevant reference to the EudraGMP database will suffice.

3.2.2. Quality control site

The change should be supported by including a copy of the relevant Manufacturing Authorisation or a valid GMP certificate (as issued by the UK or a country included on the approved country for batch testing list (currently EEA Member States, Australia, Canada, Israel, Japan, New Zealand, and Switzerland. However, see separate guidance considering any specific exclusions.

Where relevant reference to the EudraGMP database will suffice.

3.3. Change of Marketing Authorisation Holder (MAH)

A change of MAH, such as from a company outside the UK to one established in the UK, cannot be done as a variation. That change requires the submission of a Change of Ownership application. It should be noted that after Brexit the MAH must be established in the UK within 21 months beginning on exit day.

However, in the interim, the MHRA will require a contact in the UK. The MHRA will contact EU or EEA MAHs to ask for details of a UK contact.

A change to the name/address of the MAH can be submitted as a Type IA IN under change code A.1, provided that it is not a change to the legal entity.

3.4. Change to the location of the Pharmacovigilance Systems Master File (PSMF) or the Qualified Person for Pharmacovigilance (QPPV)

As the MHRA will no longer have access to the Article 57 database, any change to the QPPV or location of the PSMF should be submitted under change code C.I.8.a (Type IA IN), provided the conditions and documentation requirements can be fully met.

The QPPV should be established in the UK on day one, although those without a current UK presence will have 21 months beginning on exit day to do so. This temporary exemption will allow an EU QPPV to assume responsibility for UK MAs until a QPPV who resides and operates in the UK can be established.

3.5. Implementation of the outcome of referrals and procedures concerning PSUR or PASS

Where the procedure has been finalised before exit day, the outcomes in relation to any required variations will be processed based on the decision already taken. Depending on the nature of the required changes, the variations should be submitted under the relevant main change codes of C.I.3 or B.V.b (usually type IA). The actual submission category will depend on the specific nature of the required changes, taking into consideration if further assessment is required and its level.

Following exit, the MHRA will be carrying out our own assessments, the outcomes of these assessments will be published together with advice on implementation. Where a variation is required will usually be a Type IA.

3.6. Submission of protocols and study reports for post authorisation safety studies (PASS)

Although not actually variations, whether or not carried out in relation to a condition of the MA or voluntarily, the protocol and final study reports from safety studies should be submitted to the MHRA within 12 months of the end of data collection.

It has been decided that the most effective way of processing these is according to the Type II variations procedure, and they should be submitted under change code C.I.13. The submission should be accompanied by the appropriate fee, which is the same as that of a Type II complex variation. See also separate guidance on our approach to pharmacovigilance procedures in the event of a no-deal Brexit.

3.7. Submission of paediatric study reports for assessment

After exit day, holders of a UK marketing authorisation who sponsor a paediatric study (which involves the use in the paediatric population of a medicinal product to which that authorisation relates), must submit the results of this study to the MHRA within the period of six months from the end of the study. MHRA has issued separate guidance setting out the submission requirements and procedures for assessment of completed paediatric studies. In cases where an initial appraisal indicates that an assessment is required, the MAH will be asked to submit the paediatric data as a Type II complex variation to MHRA under change code C.I.13.

If the results of a paediatric study have been submitted for assessment to EMA or CMDh under Article 46 of Reg.1901/2006/EC prior to exit day MHRAwill request MAHs to submit a Type IB variation to update the product information (PI) if there are proposed changes to the PI that can be directly implemented to relevant UK products following the completion of the EUprocedure.

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