Guidance on pharmacovigilance procedures in the event of a no-deal Brexit

This guidance summarises our approach to pharmacovigilance in the event of no-deal Brexit.

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Documents

Further guidance on pharmacovigilance procedures in the event the UK leaves the EU without a deal

1. General Approach to the operation of pharmacovigilance

If there is a no-deal Brexit, the Medicines and Healthcare products Regulatory Agency (MHRA) will have primary responsibility for the conduct and oversight of all pharmacovigilance activities in relation to

UK Marketing Authorisations (MAs), certificates of registration and traditional herbal registrations.

Sharing of common systems, and formal exchange and recognition of data submitted for regulatory activities between the UK and EU countries will cease.

From exit day, for medicines sold in the UK, MA Holders (MAHs) will be required to submit pharmacovigilance data to the MHRA, including:

- UK and non-UK Individual Case Safety Reports (ICSRs)
- Periodic Safety Update Reports (PSURs)
- Risk Management Plans (RMPs)
- Post-Authorisation Safety Studies (PASS)

These will be assessed taking into account all relevant information and decisions will be made reflecting UK clinical practice to best support UK public health.

The Good Vigilance Practices (GVP) modules will remain in force but we may, in time, publish UK guidance on good pharmacovigilance practice. Further guidance on the conversion of Centrally Authorised Products (CAPs) to UK MAs in the event of a no-deal Brexit is available on our website. Any conditions or restrictions subject to which the CAP was granted immediately before exit day will apply to the converted MA, as will any post-authorisation obligations prior to exit day.

In general, submission of historical data will not be required but we may request this where it is needed for assessment purposes. Where a request is made, the data must be supplied to us within the specified time period. MHRA already holds its own database of ICSRs, so will not require historical information from MAHs.

More information on specific areas, including transitional measures is given below:

2. Actions for submitting and receiving ICSRs

We will require submission of all UK ICSRs (serious and non-serious) and serious ICSRsfrom third countries via the new gateway/ web tool which has been developed, and connectivity validated by MAHs.

MAHs can now register on the gateway.

This will enable MAHs to configure their systems for such a scenario during March.

3. Signal generation

In line with current requirements, MAH signal detection systems will need to enable them to meet their requirements for cumulative signal detection across all available data sources. We will not require MAHs to conduct signal detection against our own database, as we will make relevant UK data available for inclusion in MAH systems.

4. Risk Management Plans (RMPs)

The MHRA will continue to accept EU versions of the RMP, but where the UK has made a specific request for information to be included this may need to be provided in a UK specific annex. For CAPs the current approved version of the RMP should be included in the initiating sequence as part of conversion process. Further guidance on the conversion of Centrally Authorised Products (CAPs) to UK MAs in the event of a no deal scenario is available on our website.

5. Periodic Safety Update Reports (PSURs)

5.1 PSURs submitted after exit day

The MHRA will continue to accept EU versions of the PSUR but where the MHRA has made a specific request for information this may need to be included in a specific annex. We may develop our own submission requirements and develop a list of UK reference dates, but until this happens the EU reference date (EURD) list should be followed and PSURs, with submission dates after exit day, should be submitted to the UK at the same time as submission to the EU.

We will assess all UK PSURs for the same active/combination as part of the same procedure. The content and format will be the same as that required in the EU, and the expectation is that the same PSUR will be submitted to the UK as to the EU. PSURs for actives/combinations not currently on the EURD list should be submitted to us according to the usual frequency.

We are developing our own submission portal for PSURs which will be ready for use from exit day. More detailed requirements for submission will be issued shortly but submission to the portal will be via a delivery file with the PSUR as part of the eCTDstructure. A fee of £890 will be payable for the assessment of PSURs for actives/ combinations currently listed on the EURD (or future UK reference date list) but there will be a reduction to £445 for each PSUR where more than one PSUR is involved in the procedure. Following assessment, we will publish the outcome of PSUR assessment procedures. No further fee will be payable for the amendment of the product information as a result of the assessment which will generally be made by a Type IA variation.

5.2 PSURs submitted before exit day

Where a PSUR has been submitted before exit day but the EU single-assessment procedure has not been concluded, we 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.

Where the assessment has been concluded but the outcome not implemented on exit day, the MHRA will take the necessary steps to implement the outcome. Where this involves a variation to the MA, the application should be submitted taking into account the recent guidance on converting CAPs to UK MAs in the event of a no deal scenariowhere this applies.

6. Post Authorisation Safety Studies (PASS)

6.1 PASS protocols and results submitted after exit day

Where a study is a condition of the UK MA, the protocol and final study reports should be submitted to the MHRA and will be assessed in line with usual practices. We will continue to accept the EU format for PASS protocols and final study reports.

Where studies are conducted voluntarily by the MAH, the final study report should also be submitted to the MHRA.

For both studies that are a condition of the MA and those conducted voluntarily, the final study report should be submitted within 12 months of the end of data collection. The fee for assessment of PASS protocols or final study reports is £8,309. Both protocols and final study reports should be submitted to us using the Type II complex variation route (classification C.I.13) with the corresponding fee.

6.2 Ongoing issues regarding PASS protocols on exit day

For products authorised in the UK where the EU PRAC (Pharmacovigilance Risk Assessment Committee) has either endorsed a draft study protocol or a substantial amendment to a draft protocol before exit day, we will accept the draft or the amended draft study protocol but may request that further information is submitted to us within a specified time.

Where a non-interventional PASS has been proposed or imposed but the draft protocol has not been endorsed prior to exit day, any information required by the Pharmacovigilance Risk Assessment Committee (PRAC) together with any information required by the MHRA regarding the protocol must be submitted directly to the MHRA.

This must happen even if the information was submitted via the EU procedure prior to exit day. The MHRA will then assess the information in line with usual procedures.

6.3 Ongoing issues with PASS final study reports on exit day

For products authorised in the UK, where a final study report was submitted to the EMAbefore exit day but no recommendation was made before exit day, it may be required that the study report and abstract of the study report are submitted to the MHRAtogether with any further information relating to the study. In any event the MAHshould evaluate the impact of the results on the authorisation and submit a variation application as necessary.

Where PRAC made a recommendation prior to exit, the MHRA will implement the agreed measures in line with the agreed timetable. MAH should submit any variation to us (for CAPs please refer

to the recent guidance on our website and we will determine the application within the usual timeframes.

7. Safety Referrals

For procedures started but not concluded before exit day, the MHRA will complete the assessment and make a decision on the procedure based upon the information we have before exit day, including any decision made prior to exit day. We may request further information regarding the procedure on a case by case basis where deemed appropriate and take the necessary steps to implement the decision.

Where the referral has been concluded but the decision not implemented before exit day, the MHRA we will take the necessary steps to implement the final decision.

8. Major Safety Reviews

Following exit day, where there are significant concerns regarding the benefit-risk of a medicine or class of medicines, the MHRA may conduct a major safety review to resolve the issues. In these circumstances we will announce the initiation of the review, outlining the reasons for the review. MAHs will be requested to submit information as necessary. The outcome of the review will be published.

A major safety review will incur the following fees for assessment:

- £51,286 where one or two active ingredients or combinations of active ingredients are included
- £59,595, where three active ingredients, or combinations of active ingredients, are included
- £67,904, where four active ingredients, or combinations of active ingredients, are included
- £76,213, where five or more active ingredients, or combinations of active ingredients, are included

Where the review relates to 2 or more authorisations, the fee will be divided by the number of authorisations forming part of the review and each MAH will pay that reduced fee for each relevant authorisation it holds.

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