Procedures for UK Paediatric Investigation Plan (PIPs) in the event the UK leaves the EU without a deal

The process for applicants applying for a Paediatric Investigation Plan (PIP), waiver in a no deal scenario.

Published 20 March 2019

From:

Medicines and Healthcare products Regulatory Agency

Contents

The guidance also covers information for applicants or companies with an agreed EU-PIP opinion conferred prior to Brexit.

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

General approach to UK Paediatric Investigation Plans

The UK aims to simplify the PIP application process for applicants by offering an expedited assessment where possible, and by mirroring the submission format and terminology of the EU-PIP system. Therefore, the

scientific content and assessment required will be kept in line with European Medicines Agency (EMA) guidance documents.

The UK will be following the principles established in "The Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies", from the European Commission.
The format and submission procedure for UK-PIP applications will be published separately. Applicants should include information relevant specifically to the UK, particularly with respect to any areas of unmet therapeutic need that this product intends to cover in the UK [Section 6 of this document].

This guidance addresses the common scenarios that may occur when a UKpaediatric procedure is submitted to the Medicines and Healthcare products Regulatory Agency (MHRA) after exit day.

A case by case discussion should always be considered for any UK paediatric submissions that do not fall into any of the prespecified criteria listed below.

Further step by step information on the process of submitting PIPs via the new MHRA submissions portal will be available in a user reference guide which will be published separately.

Section 1: PIP submissions

1.1. EU-PIP or modifications to PIPs submitted before the UK leaves the EU

EU-PIPs and modifications agreed by the EMA prior to the UK leaving the EU, will be adopted as UK-PIPs on or after exit day:

- These PIPs will not require re-submission to the MHRA.

Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but no decision has been given before exit day, the EU-PIP will be adopted as a UK-PIP if the EMA Paediatric Committee (PDCO) has given a positive opinion with which the UK has concurred.

- These PIPs will not require re-submission to the MHRA.

Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but the PDCO has issued a negative opinion:

- In this case, the MHRA will treat the application as refused. However, applicants can submit an updated PIP to the MHRA which addresses the reasons for refusal.

Where a valid request for an EU-PIP or modification or waiver has been made to the EMA, but the PDCO has not yet given any opinion, or where the UKdisagreed with the PDCO opinion:

- These PIPs should be resubmitted to the MHRA unless the applicant notifies MHRA that they do not wish the application to proceed.

EU-PIPs which become UK-PIPs under these transitional provisions will be referred to as adopted UK-PIPs in this guidance. New UK-PIP submissions after exit day that have been assessed and agreed by the MHRA, will be referred to as agreed UK-PIPs.

1.2. UK-PIP submissions after the UK leaves the EU

When a UK-PIP is submitted, information should be provided on whether there is:

- an agreed EU-PIP and the opinion and supporting documentation is included
- an ongoing EU-PIP assessment, its timeline in the PDCO assessment cycle (i.e. day 30, 60, clock stop, day 90 or 120)
- any scientific divergence between the submitted UK-PIP and the EU-PIP

This information will be used to establish the MHRA assessment process as described in Sections 1.3 to 1.4.

The assessment pathways for UK-PIP submissions, if the UK leaves the UKwithout a deal, are outlined in Annexes I and II (PDF, 77.1KB, 2 pages) .

1.3. UK-PIP with agreed EMA opinion after the UK leaves the EU or ongoing assessment at EMA after the UK leaves the EU

In principle, the MHRA will aim to accept a positive PDCO opinion. A focused assessment may be needed considering (but not restricted to) the following:

- unmet UK paediatric needs [Section 6 of this guidance];
- paediatric only development particularly for an innovative product (such as a new drug class, mechanism of action)
- the incidence of the disease in the UK population
- the relevance of the scientific arguments by EMA / PDCO in the summary report (SR) to the UK paediatric population
- any additional safety or efficacy concerns for the UK population
- the nature and number of licensed products already available for the intended paediatric indication
- the feasibility of performing the proposed paediatric studies in the UK only
- PIP is to support a UK Paediatric Use Marketing Authorisation (PUMA)

A full assessment may be requested by the applicant.

If the PDCO opinion is negative, the applicant has the option to withdraw the UK PIP or continue with the MHRA assessment.

If the applicant chooses to continue with the MHRA assessment despite PDCO negative opinion, the applicant should consider incorporating changes to the UK-PIP during clock-stop, for the elements that received a negative PDCO assessment.

If a UK-PIP has been withdrawn and a new UK-PIP submitted, the new PIP will undergo review using the same assessment criteria as noted in Section 1 of this guidance.

1.4. UK-PIP with no EU-PIP after the UK leaves the EU

Full assessment of the UK-PIP is required.

The applicant should additionally clarify if:

- there has been a previous negative EMA / PDCO PIP opinion
- there was a withdrawn EU-PIP prior to the adoption of an EMA/PDCOopinion
- the current UK submission has been updated since the previous negative or withdrawn EU-PIP
- the applicant has included the previously withdrawn or negative EMA / PDCO PIP SR as part of the supporting documents in the MHRAsubmission
- during assessment, consideration will be given to the scientific discussions of the EMA / PDCO which led to the negative opinion or the withdrawal of the EU-PIP

Section 2: PIP Modifications

2.1. Modification of an adopted or agreed UK-PIP

For both adopted and agreed UK-PIPs:

When a PIP modification is submitted, it should be confirmed if there is:

- an agreed EU-PIP modification
- an EU-PIP modification assessment ongoing
- the modification submitted is for an adopted or agreed UK-PIP

- a significant scientific divergence between the current agreed EU-PIP and the agreed UK-PIP

Modifications submitted for UK-PIPs where there is an EU-PIP should include the most recent PDCO opinion and PIP SR.

For Agreed UK-PIPs, there will be either a focused assessment in cases where the EU opinion for the initial UK-PIP was accepted by the MHRA or a full modification assessment in cases where the initial UK-PIP underwent full assessment.

The applicant may request a full assessment.

2.2. UK-PIP modification of an agreed EMA opinion or ongoing assessment at EMA

In principle, the MHRA will aim to accept a positive PDCO opinion on modifications in cases where the initial UK-PIP was agreed on the basis of an agreed EU-PIP. A focused assessment may be needed if the criteria in Section 1.3 are met.

If the PDCO opinion is negative whilst the UK assessment is ongoing:

- The applicant has the option to withdraw the UK-PIP modification request or continue with the MHRA assessment
- Once a PIP has been withdrawn, a new UK-PIP modification can be submitted and will undergo review using the same assessment criteria discussed in Section 1.3 of this guidance
- If continuing with the MHRA assessment, the applicant can discuss amendments to the proposals before the final MHRA opinion on the proposed Modification is agreed

2.3. UK-PIP modification with no agreed EU PIP modification

If there is no agreed EMA modification opinion a full assessment of modification will be required.

Section 3: Class Waivers

3.1. Submission of Paediatric Class Waiver

The current EMA class waivers list will be adopted by the UK after exit day.

In principle, the MHRA will aim to accept a positive EMA opinion on a class waiver request. Where there is no EMA opinion, a MHRA assessment will be undertaken.

For a negative EMA opinion on whether a Class Waiver applies:

- The applicant should submit a full product specific waiver request for MHRA assessment which should include EMA opinion on the class waiver
- If there is an EMA opinion on the applicant's subsequent product specific waiver request, then this should be made available to determine if a focused or full assessment is required

Section 4: Compliance Check

4.1. Adopted UK-PIP Compliance check (CC)

A positive PDCO CC or interim CC will be adopted as the UK CC outcome unless subsequent modifications have led to divergence between the UK- and EU-PIPs.

However, the applicant must pay particular attention to the agreed timelines of those measures which would need to be completed after the PDCO CC to ensure compliance on the date of the UK Marketing Authorisation (MA) submission.

The PDCO compliance outcome documents should be submitted ahead of, or at the time of MA application. The format and submission procedure for UK-PIP applications will be published separately.

4.2. Agreed UK-PIP CC

A UK assessment is required for full or interim CC if:

- there is any scientific divergence between the agreed UK-PIP and the EU-PIP
- there is no PDCO CC

The MHRA will adopt the PDCO CC outcome if:

- there is a positive PDCO CC
- the UK-PIP is equivalent to the EU-PIP

Applicants are encouraged to request a CC ahead of submission of an MAapplication where one is required for validation. At completion of the CCprocedure, the MHRA will issue compliance outcome documents similar to those noted in Section 4.1 above.

4.3. Non-Compliance

- For non-compliance due to (minor) administrative issues, or discrepancies that do not affect the scientific conduct of the study, a streamlined assessment will be proposed at the time the applicant is informed of the noncompliance outcome
- This streamlined assessment will combine a shortened modification procedure with a rapid CC
- If the above is not applicable, the applicant will be required to submit a modification for a full assessment to align the non-compliant key elements of the opinion with those of the completed study report
- A rapid CC will be offered at the end of a positive modification agreement

4.4. Statements of compliance

An MHRA statement of compliance when all of the agreed PIP measures have been completed, will be issued, if appropriate, when an MA application (initial, extension or variation) is granted:

The development of this product has complied with all measures in the agreed paediatric investigation plan < reference number >.

The Summary of Product Characteristics and, where applicable, the package leaflet will include the results of the studies referred to in the UK-PIP.

Section 5: Paediatric Study Plans (PSP)

5.1. Paediatric study plans (PSP)

Regarding the applicant’s paediatric study plans (PSP) agreed by the US Food and Drug Administration (FDA):

- Applicants should provide the agreed PSP as part of their UK-PIPsubmission
- However, the inclusion of an agreed PSP does not influence the criteria for assessment of UK-PIP submissions by the MHRA

Section 6: Unmet needs in the UK paediatric population

The unmet needs for the UK paediatric population will be defined by:

- therapeutic areas identified by UK health bodies as high priority public health concerns
- product development in conditions identified after consultations with UKexperts and patient groups, including those for rare diseases

identified under the auspices of the Department of Health and Social Care (DHSC) policy paper - UK strategy for rare diseases
- product development in conditions (or paediatric groups) identified as critically important in the Paediatric Regulation 10 year report
- products which are intended to be authorised as orphan medicines.

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

The legal requirements for UK-PIPs are set out in the Human Medicines Regulations 2012, as amended by the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019 (HMRs), including transitional provisions.