Completed Paediatric Studies - submission, processing and assessment in a no-deal Brexit

Guidance on the submission, processing and assessment of all completed paediatric studies sponsored by Marketing Authorisation Holders (MAHs) if there is a no-deal Brexit.

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From:

Medicines and Healthcare products Regulatory Agency

Contents

This guidance follows on from the guidance published on 3 January 2019 and the letter communicated in November 2018 and January 2019.

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

Legal background and scope

Regulation 78A(13) and (14) of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019, requires that holders of a UK marketing authorisation who sponsor a study which involves use in the paediatric population in respect of the medicinal product to which that authorisation relates must submit to the Medicines and Healthcare products Regulatory Agency

(MHRA) results of the study within the period of six months beginning with the day on which the trial ended.

This applies irrespective of whether or not:

- the studies are conducted in accordance with an agreed paediatric investigation plan (PIP); or
- the MAH intends to apply for a marketing authorisation for a paediatric indication in relation to the product.

These provisions replace Article 46 of Regulation (EC) No 1901/2006 (the 'Paediatric Regulation').

MHRA will also consider the outcome of CMDh paediatric work-sharing procedures (PdWS) reviewed under Article 45 of Regulation (EC) No 1901/2006 (as amended). If required, MHRA will request updates to the product information (PI) for UK Marketing Authorisations.

1. Submission of information

The MAH needs to submit a cover letter (suggested cover letter template) (MS Word Document, 29.3KB) within 6 months of completion (i.e. date of last visit of last subject undergoing the trial, unless otherwise justified in the protocol) of the concerned paediatric studies to the MHRA in eCTD format to this mailbox: paediatricstudies@mhra.gov.uk.

The MAH should indicate in the cover letter whether the study(ies):

1.1. are linked to other paediatric studies which have been or will be the subject of other submissions under Regulation 78A of the Human Medicines Regulations 2012, as amended by the Human Medicines (Amendment etc.) (EU Exit) Regulations 2019.

If this is the case, the MAH should provide the study title(s) with approximate date of completion. If the study(ies) relate to a UK PIP, the MAH should provide the PIP number.

1.2. have been or will be submitted in the UK as part of a variation/extension or any other application including this paediatric study. If this is the case, the MAH should:

- specify the UK procedure number, if available or the type of application this will be submitted under
- confirm that the application will be submitted within the next 6 months
- confirm that, based on the results of the study, no urgent safety update of the product information is required

MAH should provide any relevant information about any related Article 46 of Regulation (EC) No 1901/2006 procedure(s) or EU agreed PIP(s).

The MAHs should also state whether as a result of the paediatric study there is a need to update the product information.

2. Initial appraisal

On receipt of the cover letter, MHRA will carry out an initial appraisal of whether an assessment procedure is required at this stage. One of the following may apply:

2.1. If assessment of the data is not required at this stage, MHRA will maintain records including justification for the decision, e.g. that a regulatory submission to vary the Marketing Authorisation is planned in the next 6 months, or any other agreed reason(s) to defer the procedure.

2.2. If review of the data is required, MHRA will notify the MAH to submit the paediatric data within 60 days as a type II variation application (change code C.I.13 - complex type II variations fees will be applicable). The MAH should submit the following:

- Final clinical study report
- A short clinical overview clarifying the context of the data, including information on the pharmaceutical formulation used in the study, the existence of a suitable paediatric formulation and if relevant, conditions for an extemporaneous formulation.

- A summary of Product Characteristics/ Patient Leaflet (SmPC/PL) proposal to update the paediatric information, or when none is considered required, justification that changes are not necessary.
- For a paediatric study that is part of a development program including a PIP, a line listing of all relevant studies.
- If the MAH holds other paediatric studies for the same active substance falling under the scope of EU Article 45 of Regulation (EC) No 1901/2006 which have not yet been assessed by a competent authority, these should be submitted along with a clinical overview clarifying the context of the data.

If the MAH is unable to submit the type II variation within the 60-day timeframe, they must justify the delay and propose a new submission date.

3. Transitional provisions

If the results of a paediatric study have been submitted to EMA or CMDh under Article 46 of Regulation (EC) 1901/2006 prior to exit day, the process will remain within the EU assessment framework and no UK equivalent procedure will be initiated unless the MAH indicates that an urgent safety update of the product information (PI) is required.

Upon finalisation of the EU procedure and availability of the final assessment report, MAHs should submit this to paediatricstudies@mhra.gov.uk.

MHRA will check the applicability of the outcome of the EUprocedure for UK products. If there are proposed changes to the PI which can be directly implemented to relevant UK products, if not already submitted, MHRA will request MAHsto submit a Type IB variation to update the PI within 60 days.

Workflow steps for submission and assessment of MAH sponsored paediatric studies

Steps	Day	Action
1	0	Receipt of letter notifying MHRA of completed study from MAH (see suggested template) via paediatricstudies@mhra.gov.uk
2	7	Allocate procedure to medical assessor
3	14	Inform MAH whether assessment of the data is required: A). If required, a variation is requested within 60 days, details of a submission package is described in section 2.2 of Submission of information, go to step 4, B). If an EMA P46 or CMDh PdWS under Article 46 of Reg.1901/2006 has been completed prior exit day and PI changes is a direct implementation to relevant UK products, step 11, C). If not required, MAH will be informed that no further action is needed
4	-14	MAH submits data as variation type II, followed by Validation process (up to 14 calendar days)
5	Clock starts: 0	Provide MAH with start date of procedure
6	Standard: 59/60 (in exceptional circumstances for Extended: 89/90)	Preliminary AR followed by clock-stop period if there is a need for RFI or Preliminary/Final AR, where changes to the PI could be implemented at the end of the procedure if applicable
7	Clock-stop	Clock-stop period should not be longer than 60 days for responses + 60 days for assessment of the responses (extension of clock-stop period could be considered upon request)
8	Standard: 60 (Extended: 90)	Final AR sent to MAH, where changes to the PI could be implemented at the end of procedure if applicable

Steps	Day	Action
9	Standard: 75 (Extended: 105)	Draft Public paediatric AR sent to MAH to comment on any confidential/commercial sensitive information within 15 days
10	Standard: 90 (Extended: 120)	Publish Public paediatric AR on MHRA website
11	60	If step <3b> is applicable, request will be sent to MAHs for type IB variations submission, to update the PI within 60 days

Processing and assessment of outcome of EUArticle 45 work sharing procedures

MAHs are not required to submit to the MHRA information on paediatric studies completed by 26 January 2007 and which fall under the remit of Article 45 of Regulation (EC) No 1901/2006 work sharing procedure.

MHRA will monitor the published Public Assessment Reports (PAR) of Article 45 PdWS procedures. Once a new PAR is identified, any proposed (PI) changes and their applicability for UK products with the same active substance will be reviewed.

1. If products with the same active substance are not available in the UK or the PI changes proposed are not applicable to UK products, no further action will be taken.
2. If the proposed PI changes are directly applicable to UK products, if not already submitted, the MHRA will send a request to the UK MAHs to submit a type IB variation within 60 days.
3. If proposed PI changes are not directly applicable to the UK products, the MHRA may adapt the recommendations and subsequently send requests to UK MAHs for type IB variation, where the UK adapted recommendations will be provided, within 60 days.

4. If MHRA considers that the MAHs should provide supplementary data in order to conclude on potential PI changes for the UK products and further UK assessment is deemed necessary, a type II variation could be requested within 60 days.

Contact MHRA

Please direct any queries to specialpopulationsunit@mhra.gov.uk.