

**BEST PRACTICE GUIDE**  
**ARTICLE 46 – PAEDIATRIC REGULATION**  
**(EU WORK SHARING PROCEDURE)**

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## **INTRODUCTION**

This document was produced by the CMDh in order to facilitate the assessment of information about nationally authorised medicinal products (including MRP and DCP) in a harmonised and practical way according to Article 46 of the Paediatric Regulation. Another similar guidance on Article 45 was published by the CMDh on September 2008 for paediatric studies already completed by 26 January 2007.

### **Legal background**

*Article 46 of Reg. 1901/2006*

1. Any other marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation, whether or not they are conducted in compliance with an agreed paediatric investigation plan, shall be submitted to the competent authority within six months of completion of the studies concerned.
2. Paragraph 1 shall apply independent of whether or not the marketing authorisation holder intends to apply for a marketing authorisation of a paediatric indication.
3. The competent authority may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly.
4. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.
5. The European Medicines Agency (EMA) shall coordinate the exchange of information.

### **Scope**

This best practice guide applies to all MAH-sponsored paediatric studies conducted with a medicinal product covered by a marketing authorisation granted through a purely national, mutual recognition or decentralised procedure, and completed after 26 January 2007. Separate guidance is developed by the EMA for centrally authorised medicinal products.

## **EU WORKSHARING PROCEDURE**

In order to evaluate paediatric studies submitted by the marketing authorisation holders (MAHs) in accordance with Art 46 of Reg. 1901/2006, Member States adopted the principle of a European worksharing procedure. To coordinate the work between the Member States and EMA, a Paediatric Subgroup CMDh/EMA has been established.

The worksharing procedure between the Member States in the assessment of paediatric data according to Art 46 of Reg. 1901/2006 is very similar as for Art 45. As mentioned in the Scope, Art 46 worksharing procedure is applicable only to paediatric studies completed after **26 January 2007**, which corresponds to the date of entry into force of the Paediatric Regulation.

Completion of a trial is defined in the Commission guideline on Paediatric Investigation Plan as the last visit of the last patient, as foreseen in the latest version of the protocol (as submitted to competent authorities).

### **Submission of information**

Information on paediatric studies should be submitted by the MAHs on an ongoing basis. The MAH should indicate in the cover letter whether the studies are linked to other paediatric studies which have been or will be the subject of other Article 46 submissions, and whether a variation/extension or any other application including paediatric data has been or will be submitted.

For nationally authorised medicinal products (including MRP and DCP), the MAH is required to submit a cover letter and the line-listing within six months of completion of the concerned paediatric studies to the Member States where the product is authorised in electronic format only, with a copy to the EMA (for information only), using the dedicated mailbox or e-mail addresses. Only information on newly completed studies must be indicated in each submission of the cover letter and line-listing. In order to facilitate the management of the submitted data, only the excel format of the complete line-listing (with no merged cells) will be accepted.

In the case there are several MAHs within the same company, it is recommended to combine all national MAHs in one line listing indicating in which MS the product is authorised (one line per MS). The combined line listing has to be submitted to all concerned NCAs and the EMA along with one cover letter only.

A single company contact point per INN/combination of INN is very much encouraged.

The paediatric data needs to be available upon request.

The list of contact addresses for the Submission of Paediatric information for each Member State and the EMA is published on the CMDh website: <http://www.hma.eu/69.html>

### **Specific situation in case of paediatric studies submitted as part of a Paediatric Investigation Plan**

In the case where the study was part of a Paediatric Investigation Plan (PIP) agreed by the Paediatric Committee of the EMA (PDCO), this information has to be included in the line-

listing including the PIP procedure number, the EMA decision date and number on the PIP and the date when the PIP should be completed.

It is reminded that even if the MAH-sponsored study according article 46 is part of a PIP agreed by the PDCO, information on this study (cover letter + line-listing) must be submitted to the Member States where the product is authorised, and to the EMA, within 6 months of completion of the study.

### **Organisation of the Worksharing**

Further to the receipt of the cover letter and the line-listing, the EMA will prepare each month an overview of products with paediatric studies for assessment according to Article 46. The worksharing procedure should start immediately after the submission of the cover letter and the line-listing unless there is an agreement from the Member States to delay the start of the evaluation of the paediatric data in specific situations such as the paediatric study submitted according to Art 46 is also included in a PIP, or linked to additional ongoing paediatric studies, or will be part of a future variation etc. The MAH will be informed by the EMA accordingly.

The worksharing procedure will follow the same principles as the previous scheme, set up by HMA, outlined below with the participation of all Member States as Rapporteurs in the evaluation of paediatric data.

The template of the paediatric assessment report should be followed by the Rapporteurs (<http://www.hma.eu/193.html>).

Rapporteurs will be appointed in the meeting of the Paediatric Subgroup CMDh/EMA in the month following submission of the cover letter and line-listing. A Co-Rapporteur will normally not be appointed.

The appointed Rapporteurs will inform the EMA within one month after appointment if the MAHs should be requested to submit the paediatric data or if one of the above mentioned exemptions apply.

The EMA will inform the MAH of the decision taken and, if needed, request them to submit the paediatric studies conducted with an approved medicinal product in accordance with Art 46 of Reg. 1901/2006 to the Rapporteur, in electronic format only and within one month of request.

The Rapporteur will be the main contact point for the MAH during the procedure. For the correspondence, a single company contact point per INN/combination of INN for different affiliates within one company should be indicated at submission of the cover letter and line listing.

The timetable for the assessment of new paediatric data is identical to the one in the previous worksharing procedures which is based on a 90 day Type II variation procedure. The Rapporteur will conclude the assessment with a proposal for a text for inclusion in the SmPC and PL, if appropriate. Recommendations for the text to be included in the SmPC and PL will be published on CMDh website, if appropriate.

## **Update of the product information (if appropriate)**

### - Update of the product information for the MAH concerned by the worksharing procedure

A Type IB procedure shall be submitted within 30 days by the concerned MAH after the end of the procedure in order to update the product information in accordance with Section C.I.3 a) of the Classification Guideline, if appropriate.

In cases where the MAH has not submitted the requested variation the RMS takes responsibility on behalf of CMS to request the variation from the MAH and initiate the procedure

### - Update of the product information for other MAHs

If considered necessary to guarantee safe use in the paediatric population of the medicinal products with the same active substance, submission of type IB variations will be requested from other MAHs, in order to add text agreed during the paediatric assessment procedure and published on the CMDh website (e.g. safety information), to the SmPC/PL of products with the same active substance and pharmaceutical form within 60 days of publication of the public assessment report.

Individual NCAs may also send requests for updates to SmPCs and PLs as a result of the agreed worksharing assessment report at their discretion. The application should include a confirmation that the texts as proposed in the variation are identical to those published in the Article 46 procedure and that no further changes are applied for.

MAHs are advised to check also websites of NCAs for further information on the implementation of the outcome of the paediatric worksharing.

Fees are a national decision.

## **PUBLIC PAEDIATRIC ASSESSMENT REPORT**

A public paediatric assessment report will be drafted by the Rapporteur, unless otherwise justified, and published on the CMDh website 60 days (<http://www.hma.eu/291.html>) after the finalisation of the procedure, if appropriate. A draft copy of the PAR will be provided to the MAH to comment (particularly on what is considered to be commercially sensitive information).

It is recommended to follow the format and procedure that has been agreed in CMDh for the preparation of public assessment reports in the framework of the EU Work sharing procedure in the assessment of paediatric data (<http://www.hma.eu/99.html>).

## **INTERNAL COMMUNICATION**

It has been agreed to use a dedicated Paediatric mailbox for circulation of timetables, assessment reports and comments. A new independent sequential numbering system for these procedures should be used together with the *name of the active substance*, in order for the worksharing procedure to be easily recognised by all Member States. The same numbering system will be applied to procedures following submission of paediatric data under Art 45 and 46 of the Paediatric Regulation. The Rapporteur will assign a procedure number based on the active substance or combination of active substances:

**CC/W/nnnn/pdWS/vvv**

(Example: **UK/W/0123/pdWS/001**)

With :

CC a two letter code representing the Rapporteur

W a new domain for Work sharing procedures

nnnn a counter. Each number equals one active substance (e.g: /1234/ = propofol)

pdWS qualifies a paediatric work sharing under Art 46

vvv is a sequence number for follow-up issues/assessments

Marketing Authorisation Holders are advised to contact the Rapporteur for details of the electronic submission. All electronic submissions should be sent to the national contact addresses (See list of contact addresses for the submission of Paediatric information in Member States published on CMDh website: <http://www.hma.eu/69.html>).

## **APPOINTMENT OF RAPPORTEURS**

The CMDh will appoint the Rapporteurs, after discussion in the Paediatric Subgroup CMDh/EMA.

The following principles will be considered in the assignment of Rapporteurs:

- Products from the same therapeutic class can be assessed by the same rapporteur
- Experience as Rap/Co-Rapporteur in previous work sharing procedure
- The P-RMS from the PSUR worksharing
- Specific expertise or knowledge available in a MS
- Number of products per MSs
- If a product is approved via MRP or DCP the rapporteur could be the RMS, but not necessarily
- PIP Rapporteur
- Rapporteur for Art. 45 paediatric worksharing procedure
- Member States where the product is authorised

## **CONTENT OF APPLICATIONS**

Marketing Authorisation Holders are expected to submit the following documentation to the Rapporteur and upon request for other Member States:

- A short critical expert overview should be added clarifying the context of the data, and relevance for EU situation,
- Final clinical study report(s) should preferably follow the CTD format and be submitted either as word or PDF documents,
- A SmPC/PL proposal or justification that changes are not necessary.

For studies not available in English, an English extended synopsis will be acceptable, to accompany the report in its original language.

All Member States have agreed to receive the data in electronic format only.

For further information visit the Q&A document published on the CMDh website: <http://www.hma.eu/216.html>

## **FLOW-CHART PAEDIATRIC ASSESSMENT PROCEDURE**

- 14 Calendar days      Validate the application and indicate start date procedure. This validation includes a check whether the documentation is complete to start the assessment.  
Rapporteur creates file in CTS.
- Day 0      Rapporteur informs the MAH and MSs of start date and timetable.  
(Circulate timetable via paediatric mailbox).
- By Day 70      Rapporteur circulates preliminary paediatric assessment report (PPdAR) to MSs via paediatric mailbox.
- By Day 85      Receive contribution from other MSs for inclusion in final PdAR or supplementary information request; rapporteur prepares consolidated list of questions.
- By Day 89      Rapporteur sends one request for supplementary information as appropriate (clock stop) together with the draft PdAR to those companies which submitted data with a copy to MSs and the MAH.  
Rapporteur informs MSs of request to the MAH  
MAH replies to request for information.  
  
Consider response from the MAH. Rapporteur assesses the response to the issues raised.  
Rapporteur takes the lead in the discussion with MSs and considers whether a break out may be needed. Timetable set (as before) for a breakout to be possible at Day 105. Rapporteur contacts EMA (CMDh-secretariat) if needed to book a room.

- By Day 90 (Clock on) Rapporteur circulates finalised PdAR to MSs with draft decision and give the MSs a set timeframe to respond for deciding whether a breakout has to take place.
- Around Day 105 Hold break-out meeting (when needed), in case discussion is required between Member States to come to harmonised decision.
- By Day 115 Receive confirmation from MSs of acceptance/non-acceptance of PdAR decision.
- By Day 120 Rapporteur finalises the procedure and provides a formal position and the final PdAR to the MAH with a copy to MSs. This formal position is then used as supporting documentation in the Type IB variation, if required. Rapporteur requests the MAH to submit a Type IB variation (or extension of application) within 30 days, if appropriate to implement the proposal and amend the marketing authorisation, as necessary.
- By Day 180 Rapporteur prepares a public paediatric assessment report, unless otherwise justified, in accordance with standard procedure agreed in CMDh, if appropriate. The public assessment report will be published on CMDh website.
- By Day 240 If considered necessary to guarantee safe use in the paediatric population of the medicinal products with the same active substance, submission of Type IB variation will be requested from other MAHs, in order to add text agreed during the paediatric assessment procedure and published on the CMDh website (e.g. safety information), to the SmPC/PL of products with the same active substance and pharmaceutical form within 60 days of publication of the public assessment report.
- In the exceptional situation where no agreement can be achieved between the Member States following discussions in this procedure, the Rapporteur can forward the matter for discussion in the CMDh with the aim to achieve consensus.