

BEST PRACTICE GUIDE
ARTICLE 45 – 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) as requested by the Paediatric Regulation in a harmonised and coordinated way.

Legal background

Article 45 of Reg. 1901/2006

1. By 26 January 2008, any paediatric studies already completed, by the date of entry into force, in respect of products authorised in the Community shall be submitted by the marketing authorisation holder for assessment to the competent authority.

The competent authority may update the Summary of Product Characteristics and Package Leaflet, and may vary the marketing authorisation accordingly. Competent authorities shall exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisations concerned.

The EMA shall coordinate the exchange of information.

Organisation of the Worksharing

Further to the receipt of the line listings with information on the studies not yet submitted to NCAs, the EMA will prepare an overview of products for assessment of paediatric studies, according to Article 45.

The Worksharing procedure will start after an initial planning and prioritisation phase, following submission of the line-listings by MAH.

The work-sharing procedure will follow the same principles as the previous scheme, set up by HMA, outlined below.

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

Rapporteurs will be appointed by the joint subgroup CMDh/EMA. A co-rapporteur will normally not be appointed.

The paediatric studies not yet submitted to National Competent Authorities will have to be forwarded to the Rapporteur, once appointed, according to priorities as agreed in the EMA/CMDh sub-group on Paediatric Regulation. The paediatric studies should be sent to the Rapporteur in electronic format only within one month of request.

The EMA will inform the Marketing Authorisation Holder which Member State will act as rapporteur and the timeframe and contact details for submission of the paediatric studies for assessment. The data package should be prepared in accordance with the recommended format for the submission of data according to Art 45 (*please refer to Q&A 15*). The rapporteur will be the main contact point for the MAH during the procedure.

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 (http://www.hma.eu/uploads/media/BPG_WS_pediatric_01.pdf). The Rapporteur will conclude the assessment with a proposal for a text for inclusion in the SmPC and PL, if appropriate.

A Type IB procedure shall be submitted within 60 days by the concerned MAH(s) publication to update the product information in accordance with Section C.I.3 a) of the Classification Guideline.

It should be noted that the guidance reminds MA holders to submit variations forthwith to competent authorities once information becomes available which might entail variation of the MA, rather than awaiting assessment through a work-sharing procedure.

All MAHs of the same active substance are expected to update their SmPC and PL in accordance with Art 45 of Regulation 1901/2006. Reference can be made to the published statement on the CMDh website to support this variation.

Fees are a national decision.

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 MSs. 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 45
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>).

COMMUNICATION WITH MARKETING AUTHORISATION HOLDERS (MAHs)

It is possible that for some substances (especially those off-patent) more than one MAH will be concerned.

The rapporteur will usually communicate with the originator/owner of the data. If several MAHs have submitted studies with the same active substance the rapporteur will inform all concerned MAHs taking into account potential confidential data.

For MAHs with national subsidiaries it is strongly recommended to assign a single contact point for communication.

APPOINTMENT OF RAPPORTEURS

The CMDh will appoint the rapporteurs, after discussion in the joint 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 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

PRIORITISATION IN ASSESSMENT

The priority list of off-patented products EMEA/226983/2008 will be considered to decide on priority in assessment. At national level MSs will check unmet paediatric needs.

CONTENT OF APPLICATIONS

Reference is made to Q & A 14, published on CMDh website.

In general, marketing authorisation holders are expected to submit the following documentation:

- all data, including published information, quality, non-clinical and clinical relevant for the paediatric assessment
- A short critical expert overview should be added clarifying the context of the data, and relevance for EU situation
- A SmPC/PL proposal or justification that changes are not necessary
- Relevant PSUR data or reference to PSURs already submitted
- Study reports should preferably follow the CTD format and be submitted either as word or PDF documents

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.

There is no need to resubmit data submitted earlier, but in the overview all available information on the paediatric use should be briefly summarised.

Public assessment reports

A public assessment report will be drafted and published 60 days after the finalisation of the procedure. A draft copy of the report will be provided to the MAH to comment (particularly on what is considered to be commercially sensitive information)

The report will be published on CMDh website.

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>).

Information in SmPC and PL

The aim of Article 45 procedure is to make the information on the use of medicines in the paediatric population available for all health care professionals and patients (or parents).

After finalisation of the assessment of the data recommendations for the text to be included in the SmPC and PL will be published on CMDh website. This information should be included in all SmPC's/PLs of products with the same active substance and pharmaceutical form within 90 days of publication of public assessment report.

The applications do not require supporting information and will be accepted by Member States Competent Authorities without further assessment or amendment. The MAH is responsible for submitting the variations within the 90 day period after publication of the PAR. 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 45 procedure and that no further changes are applied for.

No PVAR/FVAR should be needed as the RMS should take responsibility for the assessment of the implementation of the final SPC and PL text.

In cases where the MAH has not submitted the requested variation for MRP/DCP products within 90 days after publication of the public assessment report the RMS takes responsibility on behalf of CMS to request the variation from the MAH and initiate the procedure.

For purely nationally authorised medicinal products a longer timetable might be needed (i.e. 30 days).

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

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 MAH(s) 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 to those companies which submitted data ¹
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 paediatric assessment report (PdAR) to those companies which submitted data with a copy to MSs. Rapporteur informs MSs of request to MAH(s). MAH(s) replies to request for information. Consider response from MAH(s). 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 EMEA (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) preferably to coincide with CMDh meeting, 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(s) with a copy to MSs. This formal position is then used as supporting documentation in Type IB variations as required.

¹ Under some circumstances it would not be possible to send it to MAHs if the PPdAR contains confidential data

Rapporteur requests the MAHs involved in the worksharing to submit a Type IB variation (or extension of application) within 60 days, if appropriate to implement the proposal and amend the marketing authorisation, as necessary.

By Day 180

Rapporteur prepares public paediatric assessment report in accordance with standard procedure agreed in CMDh.
The public assessment report will be published on CMDh website.

By Day 270

Submit Type IB variation to add text agreed during the paediatric assessment procedure for all SmPCs/PLs of products with the same active substance and pharmaceutical form within 90 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.