# Article 45 and 46 – Paediatric Regulation - EU Worksharing Procedure

Best Practice Guide

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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 Articles 45 and 46 of the Paediatric Regulation. The CMDh is the forum where paediatric studies of nationally authorised products, submitted under Articles 45 and 46, are discussed and where work sharing was agreed.

In order to evaluate existing and new paediatric studies submitted by the marketing authorisation holders (MAHs) in accordance with Art 45 and 46 of Reg. 1901/2006, Member States (MSs) adopted the principle of a European worksharing procedure. To coordinate the work between the MSs and EMA, a CMDh/EMA Working Party on Paediatric Regulation has been established.

This document should also be read in conjunction with the following documents published:

- On the CMDh website, Q&A on Paediatric Regulation;
- On the EMA website, Paediatric medicines regulation and related scientific guidances
  - Paediatrics medicines: Overview
  - Submitting results of paediatric studies
  - Paediatrics: Regulatory and procedural guidance

Legal background

In accordance with Regulation 1901/2006:

<table>
<thead>
<tr>
<th>Art 45</th>
<th>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.</th>
</tr>
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<tbody>
<tr>
<td>Art 46</td>
<td>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. The above paragraph shall apply independent of whether or not the MAH intends to apply for a marketing authorisation of a paediatric indication.</td>
</tr>
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</table>

The competent authority may update the Summary of Product Characteristics (SmPC) 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 European Medicines Agency (EMA) shall coordinate the exchange of information.

Scope

This best practice guide applies to all completed paediatric studies conducted with medicinal products covered by a marketing authorisation granted through a purely national, mutual recognition or decentralised procedure.
Completion of a study is defined in the Commission guideline on Paediatric Investigation Plans\(^1\) as the last visit of the last subject in the study or at a later point in time as defined in the protocol.

Furthermore, with respect to Art 46, this best practice guide applies to all MAH-sponsored paediatric studies completed after 26 January 2007 which corresponds to the date of entry into force of the Paediatric Regulation. Separate guidance is available for centrally authorised medicinal products on the EMA website\(^2\).

1. Communication

1.1. Communication between NCAs

It has been agreed to use a dedicated Paediatric mailbox for circulation of timetables, assessment reports and comments.

1.2. Procedure number allocation

A new independent sequential numbering system for these procedures should be used together with the INN and/or combination of INN for Art. 45 & invented name for Art. 46, 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:

\[
\text{CC/W/nnnn/pdWS/vvv}
\]

(Example: MT/W/0123/pdWS/001)

With:

- CC: a two letter code representing the Rapporteur’s Member State
- 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 or Art 46
- vvv: is a sequence number for follow-up issues/assessments

1.3. NCA contact point

The main contact point for the MAHs will be the appointed Rapporteur (see section 3.1). The MAHs are advised to contact the Rapporteur for details of the electronic submission. All electronic submissions should be sent to the national contact addresses.

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](http://www.hma.eu/69.html).

1.4. MAH contact point

When authorisations for a product or product range are held by subsidiaries or under licence agreements by different companies in different member states (MS), a single submission of studies by a single contact point is encouraged to facilitate communication with the Rapporteur. When a single contact point is used for a number of different companies, it should be made clear exactly which companies are being represented. The contact point will be used by the Rapporteur during the procedure and therefore any change in contact point should be notified.

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\(^1\) 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 (OJ 2014/C 338/01)

\(^2\) EMEA-H-19984. Rev. 77. EMA post-authorisation procedural advice for users of the centralised procedure (August 2018). Article 46 paediatric study submission (page 249)
immediately to the Rapporteur. Companies not linked by any agreements may also wish to consider joint responses to the Rapporteur, for example in connection with providing overviews of literature data (see below).

Likewise, any change in contact point due to transfer of licences should be notified to the Rapporteur.

For Art. 45, it would also be helpful for originators to identify a contact point even if they have not submitted studies and inform the Rapporteur when the list of active substances for each wave is published in CMDh website

| Art 45 | 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. |
|---|---|

| Art 46 | 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. |

2. Submission of information

2.1. Article 46: informing NCAs of new studies

| Art 46 | Information on new paediatric studies should be submitted by the MAHs on an ongoing basis to the competent authority within six months of completion of the studies concerned.

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.

Furthermore, MAH should indicate whether other paediatric studies for the same active substance falling under the scope of Article 45 of Regulation (EC) No 1901/2006 have not yet been assessed by a competent authority.

The MAH is required to submit a cover letter and the line-listing within six months of completion of the concerned newly completed paediatric studies to the Member States (MSs) where the product is authorised in eCTD format only, with a copy to the EMA using the dedicated mailbox or e-mail addresses. 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.

The paediatric data needs to be available upon request.

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. |
2.1.1. Paediatric Investigation Plan studies specific situation

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 the date when the PIP should be completed.

It is reminded that even if the MAH-sponsored study according to 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.

Please also refer to section 2.3 for specific submission requirements.

2.2. Initial submission

Companies should use MS contact information published on CMDh website. Note that the information given is not necessarily the personal contact details for Rapporteur but the relevant section of the national competent authority (NCA) dealing with worksharing procedures. In this case, studies and any correspondence relating to the submission should not be sent to the Rapporteur or CMDh Member personally.

Concerning Art. 45, companies should recognise that Rapporteurs may be dealing with a number of MAHs for each procedure, as assessment is active substance based. Prompt delivery and submission of all paediatric data in the line-listings is essential for timely start and smooth running of procedures. Any delays should be notified and agreed by the Rapporteur.

Key timelings of WS procedures set out in this Best Practice Guide should be noted. Key actions by MAHs are set out in the table below:

<table>
<thead>
<tr>
<th>Action by NCAs</th>
<th>Action by MAH</th>
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<tr>
<td>• Letter of Request from European Medicines Agency including the information on the appointed Rapporteur and Procedure number</td>
<td>• Acknowledge receipt by e-mail to Rapporteur</td>
</tr>
<tr>
<td>• Circulation of timetable by Rapporteur</td>
<td>• Prepare documentation and submit within one month of date of letter</td>
</tr>
<tr>
<td>• Circulation of preliminary paediatric assessment report (Day 70) and request for supplementary information by Rapporteur (Day 89)</td>
<td>• Submit responses by deadline given by Rapporteur</td>
</tr>
<tr>
<td>• Circulation of draft final assessment report with timetable for completion of procedure by Rapporteur</td>
<td>• Prepare updated product information ahead of variation submission</td>
</tr>
<tr>
<td>• Circulation of Public Paediatric Assessment Report</td>
<td>• Check Public Paediatric Assessment Report for confidential data</td>
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2.3. Content of submissions

All studies in the line listing should be submitted. If published data have been listed, electronic copies of the full article must be provided.

Art 45 In general, MAHs are expected to submit the following documentation:

- A short critical expert overview should be added clarifying the context of the data, and relevance for EU situation,
- A SmPC/PL proposal to update the paediatric information, or when none is considered required, justification that changes are not necessary.
• all data, including published information, quality, non-clinical and clinical relevant for the paediatric assessment;
• 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.

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

**Art 46**

MAHs are expected to submit the following documentation to the Rapporteur and, upon request, to other Member States, following the eCTD format:

• A short critical expert overview should be added clarifying the context of the data, and relevance for EU situation,
• A SmPC/PL proposal to update the paediatric information, or when none is considered required, justification that changes are not necessary.
• Final clinical study report(s),
• Any other paediatric studies of the same active substance falling under the scope of Article 45 of Regulation (EC) No 1901/2006 that have not yet been assessed by a competent authority, if requested.

If the study was part of a PIP, the following should also be submitted:

• the latest PIP decision with annexes (opinion and summary report). When the latest decision corresponds to a modification of the agreed PIP the MAH should also submit the initial PIP Decision with annexes.

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

**A good overview of the data** is strongly recommended and its importance for a satisfactory conclusion of the assessment cannot be overstated. The overview places the data into context, supports the proposals for updates to the SmPC made by the MAH and greatly facilitates assessment. An overview is likely to be requested at the clock stop stage if it is not provided with the submission, thus prolonging procedures. It is recommended that the overview contains the following information:

• Analysis of the studies
• Analysis of the literature including information on the search parameters used to obtain the list of publication
• Brief licensing history of product with respect to paediatric indications and studies already submitted. In cases where there has been a change in MAH during the lifecycle of the product, it is helpful if the summary could clarify which studies were conducted be the previous MAH and which by the current holder.
• Licensing position in different Member States including a list of all products authorised which contain the relevant active substance
• Any available information on off-label paediatric use
• Recommendations for updating the product information based on the information provided.

The overview is a valuable opportunity for the MAH to state how and why they believe their product information should be updated to reflect appropriate use in the paediatric population.

For further information visit the Q&A document published on the CMDh website: [http://www.hma.eu/20.html](http://www.hma.eu/20.html)
In case of initial eCTD submission the responses should be submitted as stated in the CMDh Best Practice Guide on the use of eCTD in MRP and DCP: [http://www.hma.eu/277.html](http://www.hma.eu/277.html).

### 2.4. Submission of responses

Companies should comply with the timeline stated in the request for supplementary information (RSI) and notify the Rapporteur as soon as it is known that there may be difficulties, giving the reason for any delay. Procedures will not be restarted until complete responses are obtained, including situations where the Rapporteur needs to raise further questions due to information lacking in the original submission.

Requests for supplementary information may include analyses of the information provided or summaries of the licensing position when these did not form part of the original submission (see 3.5.2.3).

### 3. Organisation of the Worksharing

#### 3.1. Appointment of the Rapporteur

The CMDh Secretariat will appoint the Rapporteur for Art. 46. A co-rapporteur will normally not be appointed.

<table>
<thead>
<tr>
<th>Art 45</th>
<th>A discussion in the CMDh/EMA Working Party on Paediatric Regulation <strong>will</strong> take place.</th>
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<tr>
<td>Art 46</td>
<td>A discussion in the CMDh/EMA Working Party on Paediatric Regulation <strong>can</strong> take place, if needed.</td>
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The following principles will be considered in the assignment of Rapporteur:

- Products from the same therapeutic class can be assessed by the same rapporteur;
- Experience as Rapp/Co-Rapporteur in previous work sharing procedures
- Specific expertise or knowledge available in a MS;
- Number of products per MSs;
- If a product is approved via MRP or DCP, whether the MS’s rapporteur was RMS;

<table>
<thead>
<tr>
<th>Art 46</th>
<th>The following principles could <strong>also</strong> be considered for Article 46 procedures in the assignment of Rapporteur:</th>
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<td></td>
<td>▪ Rapporteur for Art. 45 paediatric worksharing procedure;</td>
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<td></td>
<td>▪ MSs where the product is authorised;</td>
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<td></td>
<td>▪ MS of the PIP Rapporteur or Peer Reviewer;</td>
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In case the appointment is not accepted, a new Rapporteur will be appointed by the CMDh Secretariat.

#### 3.2. Initial communication with the Rapporteur

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<tr>
<th>Art 45</th>
<th>Based on line listings that MAHs have submitted in 2008 with information on the studies not yet submitted to NCAs, the EMA has prepared an overview of products for assessment of paediatric studies, considering the list of off-patented products EMEA/226983/2008 to decide on priority in assessment. At national level MSs will check unmet paediatric needs according to Article 45. The CMDh Secretariat will publish the list (&quot;Waves&quot;) at the CMDh website <a href="http://www.hma.eu/99.html">http://www.hma.eu/99.html</a> and EMA will inform the MAH about which MS will act as rapporteur, the procedure number and the timeframe and contact details for submission of</th>
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| Art 46 | |
|--------| |
the paediatric studies for assessment.

Art 46

The CMDh Secretariat will circulate the overview of products with paediatric studies for assessment according to Article 46 including the appointed Rapporteurs on a monthly basis.

The appointed Rapporteurs will inform the CMDh Secretariat at the latest one month after receipt of the overview if the appointment is accepted.

At the same time, the Rapporteur will inform the CMDh Secretariat if the MAHs should be requested to submit the paediatric data (and provides the worksharing procedure number) or if one of the exemptions mentioned under 3.4 apply.

When an Article 46 procedure addresses the results of a study conducted as part of a PIP, the PDCO Secretariat provides information on the submitted studies and the appointed Rapporteur to the PDCO members.

In case the MAH has indicated in the cover letter, that there are paediatric studies for the same active substance falling under the scope of Article 45 of Regulation (EC) No 1901/2006 not yet been assessed by a competent authority, the Rapporteur will consider whether a combined assessment of Art. 45 and Art 46 studies is feasible. The Rapporteur will inform CMDh Secretariat accordingly.

The EMA will inform the MAH of the decision taken, the appointed Rapporteur and procedure number and, if needed, the timeframe and contact details for submission and request them to submit the paediatric studies conducted with an approved medicinal product in accordance with Art 46 and possibly Art. 45 of Reg. 1901/2006 (see 3.3)

3.3. Submission of Art. 45 and/or Art. 46 paediatric studies

Following information of EMA on the appointed rapporteur and the request for submission of the paediatric studies, the paediatric studies should be submitted to the Rapporteur and the Netherlands.

The data package should be prepared in accordance with the recommended format for the submission of data according to Art 45 as described in section 2.3 (please also refer to No 15 Q&A on Paediatric Regulation).

All Member States have agreed to receive the data in electronic format only. For Art. 46 studies eCTD format is mandatory. For Art. 45 studies eCTD format should be used where available. Submission via CESP is preferred.

When sending an email in relation to a respective Art. 45 or Art. 46 paediatric worksharing, the following subject should be used: INN_<Art. 45> or <Art. 46> paediatric studies.

3.4. Start of the worksharing procedure

The Worksharing procedure will start following submission of the paediatric studies, normally within one month following request by EMA 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.

In these cases, it is recommended that the Rapporteur contact the MAH to establish their plans for upcoming submissions and agree a suitable timescale for the work-sharing procedure. The MAH will be informed by the EMA about the final decision taken at the CMDh working Party on Paediatric Regulation.

3.5. Conduct of the worksharing procedure

The worksharing procedure according to Art. 45 and Art. 46 will follow the principles outlined below with the participation of all Member States as Rapporteurs in the evaluation of paediatric data.
3.5.1. Timetable

See also 5. Flow-chart Paediatric Assessment Procedure at the end of this document.

The timetable for the assessment of new paediatric data 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.

However, in case the Rapporteur or one of the Member States identify a safety issue, which could have implications for clinical practice, it is recommended to forward and discuss this issue during a joint CMDh/EMA working party meeting, before the procedure is concluded (preferably around day 105).

3.5.2. Assessment guidance

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

When an Art. 46 procedure addresses the results of a study conducted as part of a PIP, consideration should also be given to the EMA scientific paediatric guidances, the PIP summary report(s) and PIP opinion adopted by the EMA Paediatric Committee (PDCO) provided in the dossier. In addition, the Rapporteur is encouraged to liaise with the PIP assessment team (EMA Paediatric coordinator, Rapporteur and Peer-reviewer3) or the PDCO expert, if one was assigned.

3.5.2.1. Combining Article 45 and 46 procedures

It is possible that MAHs have conducted a set of studies relevant to paediatric use of their product some of which were completed before the Paediatric Regulation came into force by 26th January 2007 and some of which finished after this date.

In case the MAH has indicated in the Art. 46 cover letter, that there are paediatric studies for the same active substance falling under the scope of Article 45 of Regulation (EC) No 1901/2006 not yet been assessed by a competent authority, the Rapporteur will consider whether a combined assessment of Art. 45 and Art. 46 studies is feasible. The Rapporteur will inform EMA accordingly.

Additionally, it is also possible to combine several Art. 46 procedures where there is successive submission of recently completed paediatric studies. In these cases, it is recommended that the Rapporteur contacts the MAH to establish their plans for upcoming submissions and agree a suitable timescale for the work-sharing procedure.

3.5.2.2. Differences in existing product information

Article 45 is not expected to be a full harmonisation process; where differences are identified in the paediatric aspects of product information, a recommendation can be made in the assessment report that the MAH achieve harmonisation through use of appropriate regulatory procedures. However, it should be possible to recommend consistent wording for existing indications and posology in the SmPC common to MSs. It is not the aim of Art. 45 or Art. 46 procedures to remove existing paediatric indications for products which are already in clinical use in particular Member States. Removal of indications, for example if there is new evidence regarding safety, should be considered by individual Member States unless there has been prior agreement by CMDh or through another regulatory procedure. If appropriate, Member States should consider referring the matter to CMDh or requesting a formal referral procedure to achieve harmonisation of the SmPC throughout the Community.

Much of the paediatric data submitted under Article 45 will relate to old studies conducted before current good clinical practices (GCP) guidance existed. Nonetheless, the information may be of value to prescribers and patients and it needs to be recognised that many products are already being used in clinical practice. A balance needs to be achieved in providing useful information whilst maintaining acceptable standards of assessment. Where some

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3 The names are mentioned in the Part A of the PIP summary report; if need be, the secretariat of the CMDh/EMA Working Party on Paediatric Regulation can assist with the contact details.
paediatric studies exist, which have been previously assessed, the overall benefit/risk balance should be evaluated, taking into account the previous studies and any earlier assessment reports. However, there is no need to reassess the original data.

3.5.2.3. Requests for additional information

If the licensing position in different Member States has not been provided by the MAH, it may be requested as part of the RSI during the WS procedure. The MAH cannot be requested to conduct further studies as part of an Article 45 or 46 work-sharing procedures. However, the assessment report may include a statement to encourage the MAH to carry out additional studies where these are desirable to clarify the use of a product in children. In case the PIP is not yet finalised (no final Compliance Check) most likely for Art. 46 work-sharing procedures the PDCO should be involved as this may be a subject to modify a PIP opinion, if the PIP is still ongoing.

The RSI may include a request for companies to submit additional information if assessors are aware of existing studies, for example in the literature, not otherwise submitted as part of the work-sharing or other regulatory procedures. Further analysis of the data submitted may be requested as part of the RSI and there will be occasions when a summary of previously reviewed data would be helpful to clarify use of a product in children. A Rapporteur may be aware that there are other MAHs such as the originator, who have not submitted studies as part of an Article 45 work-sharing procedure, but may be affected by the outcome. In this situation, they may wish to contact that MAH informally to invite them to join the procedure.

When assessing safety aspects of the submitted studies, assessors should take into account post-marketing safety data and may need to consider the involvement of pharmacovigilance assessors when new safety information is identified during assessment. Introduction of new Risk Management Plans or updates to existing ones and/or revision of Periodic Safety Update Reports (PSURs) reporting cycles may need to be considered.

3.5.2.4. Outcome of assessment

The outcome of assessment is expected to be, wherever possible, amendments to the product information for the benefit of prescribers and patients or their carers. Inclusion of paediatric information in section 5.1 of the SmPC should be considered, if the data is not considered sufficient for a paediatric indication and/or posology recommendation, unless the studies are seriously flawed. The table below sets out some possible outcomes and corresponding recommendations for text in the SmPC. Updates to the SmPC should follow the guidance in the EudraSmPC website. In addition, worksharing assessment reports should include recommendations for appropriate wording to be included in the package leaflet.

When an Article 46 procedure addresses the results of a study conducted as part of a PIP, the final outcome of assessment is communicated by the EMA to the PDCO members.
### Outcome of assessment | Recommendations for SmPC
---|---
**Existing paediatric use**  
No new efficacy information, no new safety information | No change or a recommendation to revise text in line with current SmPC guidance
New efficacy information not leading to a change in indication or posology/dose recommendations for paediatric population | Additional study information in section 5.1
New efficacy information leading to a change in indication or dose recommendations for paediatric population | Revision to indications and dose in sections 4.1 and posology recommendation in 4.2 and corresponding study information in 5.1
New safety information not affecting benefit-risk balance | Additional safety information as appropriate in sections 4.3-4.9
New safety information which affects benefit-risk balance | Appropriate changes to indications, dose and safety information in sections 4.1-4.9

**No existing paediatric use**  
Efficacy information insufficient, no adverse safety information | Recommendation not to use in section 4.2 and corresponding study information in section 5.1
Efficacy information shows lack of therapeutic benefit, adverse safety information | Recommendation not to use in section 4.2 and corresponding study information in section 5.1. Appropriate contraindications or warnings in sections 4.3 and 4.4.
New efficacy information leading to updated indication and dose recommendations for children | Revision to indications and dose in sections 4.1 and 4.2 and corresponding study information in 5.1

In some instances, the submitted data may indicate potential usefulness of an active substance but may not be sufficient to authorise paediatric use. In other cases there may be some outstanding questions, which could warrant further investigation. Although additional data cannot be requested as part of an Article 45 work-sharing procedure in these situations, a statement may be included in the assessment report that further studies would be valuable and that MAHs are recommended to conduct such studies. MAHs are strongly encouraged to consider these recommendations for the benefit of paediatric patients.

### 3.5.3. Update of the product information (if appropriate)

The aim of Article 45 and 46 procedures is to update authorisations with information on the use of the product in the paediatric population and to make the information on the use of medicines in the paediatric population available to health care professionals and patients (or parents), whatever the outcome of the studies. Companies should bear this in mind when responding to proposals from the Rapporteur and MSs on updating the product information.

Articles 45 and 46 of the Paediatric Regulation state that competent authorities 'may update the summary of product characteristics and package leaflet, and may vary the marketing authorisation accordingly’.

When an update of the SmPC and PL is requested by the competent authorities, such change can be submitted by the MAH within the regulatory timeframe in line with the recommendations of the worksharing procedure using a type IAIN C.1.3a procedure if no additional supporting data is submitted or further assessment is needed. In case translation is needed a type IB variation should be submitted as condition 1 of C.1.3a is not fulfilled. Grouped variations may be possible according to the Variations Regulation.
Where there are differences in the product information registered in different MSs, it is the responsibility of the MAH to consider how to address this situation, taking into account that it is an objective of the Paediatric Regulation to give children the same access to authorised medicinal products suitable for their use across the European Community. The MAH may consider a range of regulatory options, including submission of a series of variations or initiation of a referral procedure, in order to achieve a harmonised position. Reference can be made to the published statement on the CMDh website to support such applications. The MAH should note that the paediatric work-sharing procedure is not a basic harmonisation process.

**Art 45** Recommendations for the text to be included in the SmPC and PL will be published on CMDh website.

1. **MAH(s) concerned by the worksharing procedure**

   A type IAIN or type IB procedure shall be submitted within 60 days by the concerned MAH(s) to update the product information.

   It is reminded that MAH should submit variations without any delay when they receive information about paediatric populations, and should not wait for a future paediatric worksharing variation.

   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 (PAR) the RMS should request the variation from the MAH on behalf of all MSs and initiate the procedure.

2. **Other MAHs**

   All MAHs of the same active substance are expected to update their SmPC and PL in accordance with Art 45 of Regulation 1901/2006. 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 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 PAR.

   The applications do not require supporting information and will be accepted by Member States Competent Authorities without further assessment or amendment. The application should include a confirmation that the texts as proposed in the variation are identical to those published in the paediatric worksharing procedure and that no further changes are applied for.

**Art 46** Recommendations for the text to be included in the SmPC and PL will be published on CMDh website, if appropriate.

1. **MAH concerned by the worksharing procedure**

   A type IAIN or 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 should request the variation from the MAH on behalf of all MSs and initiate the procedure.

2. **Other MAHs**

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

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 paediatric worksharing 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.

4. Public Paediatric Assessment Report

A public paediatric assessment report will be drafted by the Rapporteur. The draft report will be provided to the MAH to comment (particularly on what is considered to be commercially sensitive information).

The public paediatric assessment will be available on the CMDh website 60 days after the finalisation of the procedure.

It is recommended to follow the format and procedure that has been agreed in CMDh for the preparation of PAR in the framework of the EU Work sharing procedure in the assessment of paediatric data.
### 5. Flow-chart Paediatric Assessment Procedure

<table>
<thead>
<tr>
<th>Timetable</th>
<th>Art 45</th>
<th>Art 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>- 14 Calendar days</td>
<td>Validate the application and indicate start date of procedure. This validation includes a check whether the documentation is complete to start the assessment. Rapporteur creates file in CTS.</td>
<td>Rapporteur creates file in CTS.</td>
</tr>
<tr>
<td>Day 0</td>
<td>Rapporteur informs the MAH and MSs of start date and timetable. (Circulate timetable via paediatric mailbox)</td>
<td>Rapporteur creates file in CTS.</td>
</tr>
<tr>
<td>By Day 70</td>
<td>Rapporteur circulates preliminary paediatric assessment report (PPdAR) to MSs via paediatric mailbox and to those companies which submitted data(^4).</td>
<td>Rapporteur circulates preliminary paediatric assessment report (PPdAR) to MSs and MAH via paediatric mailbox.</td>
</tr>
<tr>
<td>By Day 85</td>
<td>Receive contribution from other MSs for inclusion in final PdAR or request for supplementary information; rapporteur prepares consolidated list of questions.</td>
<td></td>
</tr>
<tr>
<td>By Day 89 (Clock stop)</td>
<td>Rapporteur sends one request for supplementary information, as appropriate, together with the draft PdAR to those companies which submitted data with a copy to MSs. MAH(s) replies to request for information. Rapporteur assesses the response to the issues raised. Rapporteur takes the lead in the discussion with MSs and considers whether a break-out session may be needed. Timetable set (as before) for a break-out session to be possible at Day 105.</td>
<td></td>
</tr>
<tr>
<td>By Day 90 (Clock on)</td>
<td>Rapporteur circulates finalised PdAR to MSs with draft decision and gives the MSs a set timeframe to respond for deciding whether a breakout session has to take place. Break-out sessions, involving Rapporteur, MSs and, if necessary, the MAH should be arranged to be held by teleconference, and should take place in advance of a CMDh plenary meeting so that further discussion (including identified safety issues with regard to clinical practice) can take place between MSs at the plenary meeting, if necessary</td>
<td></td>
</tr>
<tr>
<td>Around Day 105</td>
<td>Hold break-out session (when needed). The participation of the PIP assessment team can also be considered.</td>
<td></td>
</tr>
<tr>
<td>By Day 115</td>
<td>Receive confirmation from MSs of acceptance/non-acceptance of PdAR decision.</td>
<td></td>
</tr>
<tr>
<td>By Day 120</td>
<td>Rapporteur finalises the procedure and provides a formal position and the final PdAR to the MAH(s) with a copy to MSs. For PIP studies, the EMA informs PDCO members. This formal position is then used as supporting documentation in the Type IB variation, if required. Rapporteur requests the MAHs involved in the worksharing to submit a type IAIN or IB variation (or extension of application) within 60 days, if appropriate to implement the proposal and amend the marketing authorisation, as necessary.</td>
<td>Rapporteur requests the MAH to submit a type IAIN or IB variation (or extension of application) within 30 days, if appropriate to implement the proposal and amend the marketing authorisation, as necessary.</td>
</tr>
<tr>
<td>By Day 180</td>
<td>Rapporteur prepares public paediatric assessment report in accordance with standard procedure agreed in CMDh. The PAR will be published on CMDh website.</td>
<td></td>
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</tbody>
</table>

\(^4\) Under some circumstances it would not be possible to send it to MAHs if the PPdAR contains confidential data
<table>
<thead>
<tr>
<th>Timetable</th>
<th>Art 45</th>
<th>Art 46</th>
</tr>
</thead>
<tbody>
<tr>
<td>By...</td>
<td><strong>...Day 270</strong>&lt;br&gt;Submit type IAIN or 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 PAR.</td>
<td><strong>...Day 240</strong>&lt;br&gt;If considered necessary to guarantee safe use in the paediatric population of the medicinal products with the same active substance, submission of type IAIN or 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 PAR.</td>
</tr>
<tr>
<td></td>
<td>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.</td>
<td></td>
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</tbody>
</table>