

**RECOMMENDATIONS ON SUBMISSION AND ASSESSMENT
IN PAEDIATRIC WORKSHARING**

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1. INTRODUCTION

This guidance should be read in conjunction with the Best Practice Guides for Article 45 and 46 paediatric work-sharing procedures. It is intended to provide guidance for both MA holders to facilitate assessment of submitted studies, and for assessors to ensure a consistent approach to assessment and to making recommendations for updating product information. The submission guidance (Section 2) is primarily to assist MA holders and the assessment guidance (Section 3) is primarily to assist assessors and ensure consistency. These two sections are intended as complementary.

2. SUBMISSION GUIDANCE

2.1 MA holder contact point

Where 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. Where 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 immediately to the Rapporteur and CMDh secretariat.

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

2.2 Submission of studies – administrative aspects

Companies should use MS contact information published on CMDh website (<http://www.hma.eu/69.html>). Note that the information given is not necessarily the personal contact details for Rapporteur but the relevant section of the national competent authority dealing with work-sharing procedures. In this case, studies and any correspondence relating to the submission should not be sent to the Rapporteur or CMDh Member personally.

Companies should recognise that Rapporteurs may be dealing with a number of MA holders 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 timings of WS procedures set out in the Best Practice Guides should be noted. Key actions by MA Holders are set out in the table below:

	Action by MA holder
Letter of Request from CMDh Secretariat	<ul style="list-style-type: none"> • Acknowledge receipt by e-mail to Rapporteur and the European Medicines Agency • Prepare documentation and submit within one month of date of letter
Circulation of timetable by Rapporteur	<ul style="list-style-type: none"> • Plan future resources based on timetable
Circulation of preliminary paediatric assessment report and request for supplementary information by Rapporteur (Day 70)	<ul style="list-style-type: none"> • Submit responses by deadline given by Rapporteur
Circulation of draft final assessment report with timetable for completion of procedure by Rapporteur	<ul style="list-style-type: none"> • Prepare updated product information ahead of variation submission

2.3 Content of the dossier

The Best Practice Guidance sets out the documentation that should be submitted. All studies in the line listing should be submitted. If published data have been listed, electronic copies of the full article must be provided.

A good overview of the data is strongly encouraged to facilitate assessment and place the data into context. 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 by the previous MAH and which by the current holder.
- Licensing position in different member states
- Recommendations for updating the product information based on the information provided

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

2.4 Responses to requests for information

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.

Requests for supplementary information may include analyses of the information provided or summaries of the licensing position where these did not form part of the original submission.

2.5 Outcome of submission

The aim of Article 45 and 46 procedures is to update authorisations with information on the use of the product in the paediatric population, 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. Where there are differences in the SmPC registered in different MS, 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. The MAH should note that the paediatric work-sharing procedure is not a basic harmonisation process.

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. ASSESSMENT GUIDANCE

3.1 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. It is not the aim of Article 45 or 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.

Much of the paediatric data submitted under Article 45 will relate to old studies conducted before current 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 for whilst maintain acceptable standards of assessment.

3.2 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 that to encourage the MAH to carry out additional studies where these are desirable to clarify the use of a product in children.

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 procedure. 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.

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

3.3 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 information in section 5.1 of the SmPC should be considered if the data is not considered sufficient for a paediatric indication and/or dose recommendation, unless the studies are seriously flawed. The table below sets out some possible outcomes and corresponding recommendations for text in the SmPC. The latest SmPC guidance regarding information on use in the paediatric population should be followed (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-2/c/smpc_guideline_rev2.pdf). In addition, work-sharing assessment reports should include recommendations for appropriate wording to be included in the package leaflet.

Outcome of assessment	Recommendations for SmPC
<u>Existing paediatric use</u>	
No new efficacy information No new safety information	No change or recommendation to revise text in line with SmPC guidance
New efficacy information not leading to a change in indication or dose recommendations for children	Additional study information in section 5.1
New efficacy information leading to a change in indication or dose recommendations for children	Revision to indications and dose in sections 4.1 and 4.2 and corresponding study information in 5.1
New safety information not affecting risk:benefit	Additional safety information as appropriate in sections 4.3-4.9
New safety information which affects risk:benefit	Appropriate changes to indications, dose and safety information in sections 4.1-4.9
<u>No existing paediatric use</u>	
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 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

3.4 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 and some of which finished after 26th January 2007. They are thus eligible for a mixture of Article 45 and 46 work-sharing procedures. Where Rapporteurs become aware of this situation, they should consider combining the two groups of studies into one procedure.

4. UPDATING PRODUCT INFORMATION

Implementation of the recommendations for updates to product information following paediatric work-sharing procedures will be achieved through submission of variations which will be expedited to revise the SmPC and PL of all products containing the relevant active substance. Further information on this process is given in the Best practice Guide. 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'. By agreement at CMDh, MSs prefer to update SmPC and PL through cooperation with MAH using the expedited variation procedure described in the Best Practice Guide. Depending on the national approach, it may also be possible to combine paediatric updates with other regulatory procedures.