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Human Medicines Development and Evaluation

Publication of results-related information on paediatric studies submitted under Article 45 of the Regulation (EC) No 1901/2006 ('Paediatric Regulation')

In accordance with Article 41(2) of the Paediatric Regulation, the European Medicines Agency (the Agency) is required to publish the results of all the paediatric studies submitted to competent authorities in compliance with Articles 45 and 46 of the Paediatric Regulation.

As a consequence, all result-related information for nationally and centrally authorised active substances will become available to the general public via the European Clinical Trials Register (EU CTR).

According to European Commission's Implementing Technical Guidance For the Article 45 studies the submission of results-related data to the Agency for the purpose of publication may be done as a PDF file, for example of an authorised copy of a medical journal article, or in the format of a synopsis in accordance with the ICH Topic E 3 guidance. (http://ec.europa.eu/health/files/clinicaltrials/technical_guidance_en.pdf) MAHs are also referred to the CONSORT statement for the type of information of usefulness[1] (http://www.consort-statement.org)

For the purpose of the publication, a reduced set of fields has been established to identify the trials involved, to facilitate searching and to allow attachment of the PDF file containing the results.

This publication will encompass the results for all active substances or medicinal products with paediatric studies under Article 45 already submitted in line-listings, regardless of whether work sharing or CHMP assessment has been completed or not.

Based on the line-listings submitted by MAHs in January 2008, the figures below are the numbers of Article 45 studies the Agency is expecting for publication:

- 167 studies for centrally authorised products
- Over 18,000 studies for nationally authorised chemicals
- 609 studies for nationally authorised vaccines

1 Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. Ann Int Med 2010;152. Epub 24 March

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- 625 studies for herbal and homeopathic medicinal products

Please note that the numbers stated above do not take into account duplication or repetition of studies listed in line-listings.

Options for submissions:

Option 1

- Completion of a spreadsheet containing trial result information, in fields (columns) as specified in the European Commission's Communication on the EUDRACT fields to be made public in accordance with Article 57(2) of Regulation (EC) No 726/2004 also outlined in paragraph 3.2, "results related information", of Commission Communication 2009/C 28/01 dated 04.02.09. In addition, for the case of studies that are referenced in Medline the PMID or DOI should be provided (as a direct PubMed link in the appropriate column of the spreadsheet).

Option 2

- Submission of full clinical study reports / complete published articles or synopses in accordance with the ICH Topic E 3 guidance in pdf format. If this option is chosen, it is the responsibility of the MAHs to ensure that the document(s) submitted to this effect do not contain personal data or confidential information that should be protected.

In case studies are referenced in articles published in scientific journals, or other material protected by copyright, submissions must be in line with the terms of the owner's copyright. MAHs submitting such material should complete the appropriate Declaration form.

If the data are available ONLY as a published, copyrighted article in a scientific journal, submitting a link to an appropriate website (PubMed, journal website, etc.) is indeed acceptable as an interim solution.

What is the purpose of the publication?

The purpose of this publication is to make this vast amount of paediatric information available to the public.

Healthcare professionals and investigators need to be aware of studies that were conducted in the past to avoid unnecessary duplication of trials in children and to raise awareness on efficacy and safety information coming from the past.

Which studies are MAH expected to submit?

The European Medicines Agency expects the submission of the results-related information of studies as submitted in the line-listings by MAHs in 2008.

Should MAHs submit paediatric studies falling under Article 46 of the Paediatric Regulation?

This exercise applies only to paediatric studies falling under the Article 45 of Paediatric Regulation; i.e. paediatric studies completed prior to January 2007, regardless of whether they were sponsored by MAHs or not.

When making a submission for a particular active substance, should we choose either Option 1 or Option 2? Is it possible to submit data both as a spreadsheet and as document files (i.e. a combination of Options 1 & 2)?

A combination of options 1 and 2, i.e. some studies submitted as document files some as completed spreadsheets, will be acceptable as long as one document or XL spreadsheet is submitted per study and is clearly labelled to identify the corresponding study.

Products that are in the middle of a work-sharing procedure: Submission for work-sharing procedures often includes studies that were not listed in the line-listings. Our company wants to submit those as well for the interim publication. Will that be acceptable?

The Agency is expecting at least the results of all studies as tabulated in the line-listings. If additional studies falling under Article 45 are identified and submitted as part of a work-sharing, these can also be submitted for publication.

It is often noted that additional studies are submitted for assessment on top of studies tabulated in the line-listings. Usually these additional studies are more recent and do not fall under Article 45, although the information facilitates the work-sharing assessment. Please note that studies falling under Article 46 are not part of this exercise.

The clinical study reports for some of our products are in an old, not ICH E3 compliant format. For paediatric work-sharing procedures, there has been flexibility in accepting such old format clinical study reports. Will the same apply for this submission?

The level of information should provide a proper description of the study. Therefore, it is preferable to fill in the spreadsheet of option 1 in these cases. The level of details in the spreadsheet should be the same as the level of detail provided in a synopsis in accordance with the ICH Topic E 3 guidance.

Are MAHs obliged to submit studies for products that have been withdrawn from the market since the line-listings were submitted in 2008?

Yes. Paediatric information must also be made available to the public for medicines that are no longer used. Healthcare professionals and investigators need to be aware of studies that were conducted in the past to avoid repeating studies in children with products that might be ineffective for their condition or potentially unsafe.

What is the level of detail the Agency is expecting in the spreadsheet (Option 1)?

The level of details in the spreadsheet of option 1 should be the same as the level of detail provided in a synopsis in accordance with the ICH Topic E 3 guidance. MAH's are also referred to the CONSORT statement 2010.

The spreadsheet in Option 1 states "Discussion and interpretation of study results by sponsor (if available) ". What will happen if no discussion and interpretation is provided? Will the Agency request the study report and add the discussion and interpretation, or will the public not get this information?

If the discussion and interpretation of the results are available, they must be provided. There is no intention to request expert reports in addition to that in work sharing or centralised procedure evaluation.

The assessment reports regarding Article 45 studies are published.

If any of the studies listed in the line listings submitted in 2008 have in the meantime been submitted as part of paediatric worksharing procedure, PIP application or other regulatory submissions do these need to be resubmitted?

Yes. The results-related information will have to be submitted for the purpose of publication, not assessment by competent authorities. The data submitted for assessment cannot be made public directly, as they might contain personal data.

In addition, many Article 45 studies have been published in journals. Submissions of studies in articles must be in line with the terms of the owner's copyright.

If the PDF files of the articles have already been sent to the Agency, MAHs need to provide the form declaring that the submission is in line with owner's copyright, and state that the Agency is allowed to use these files for the publication. There is no need to duplicate the submission.

If an interventional clinical trial falling in the scope of Article 45 is also part of an agreed paediatric investigation plan (PIP), protocol and result information has to be posted directly to the EudraCT database using the full EudraCT dataset.

It may be that some CSR/Synopsis/Publications are available only in foreign language. Is it acceptable to provide them in the original language?

Studies will be acceptable in their original language. However we need English content in all cases. If translations in English are available, they should also be submitted.

Is it sufficient to submit the data via the company's headquarters or does the Agency expect a response also by affiliates?

A co-ordinated approach is very much encouraged. To avoid repetition of submissions, MAHs should liaise with any associated companies.

In all cases, it should be clearly indicated which companies participate in the submission of the data . The Agency will follow-up on the submissions.

Will the name of the company that submitted the data be visible for the public?

Yes, it is possible that the names of MAHs submitting the data will be visible to the public, as well as being mentioned in the Article 50 Annual Report to the European Commission.