

**QUESTIONS AND ANSWERS ON THE PAEDIATRIC REGULATION  
(REGULATION OF THE EUROPEAN PARLIAMENT AND  
OF THE COUNCIL (EC) No 1901/2006, AS AMENDED)**

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January 2011*

**ARTICLE 45 & 46**

**Question 1**

*Do Articles 45 and 46 apply to medicinal products irrespective of the route of authorisation?*

Yes. Articles 45 and 46 apply to medicinal products irrespective of the route of authorisation, i.e. centralised procedure, mutual recognition procedure, decentralised procedure and purely national procedure.

**Question 2**

*Do the obligations laid down in Articles 45 and 46 apply also to generic and hybrid products, well-established use products, authorised homeopathic medicinal product, biosimilar products and traditional herbal products?*

The requirement laid down in Articles 45 and 46 relate to all authorised medicinal products without exception.

**Question 3** *(Update - November 2009)*

*Should all completed paediatric studies (regardless of their place of conduct) be submitted to each competent Authority or does it apply only to studies conducted in the territory of the MS concerned?*

The submission of all completed paediatric studies is regardless of their place of conduct of the trial. They should be submitted to each competent Authority where the product is authorised. The assessment however will be carried out through the work-sharing exercise for medicinal products authorised through mutual recognition/decentralised procedure and purely national procedure, and by the CHMP for centrally authorised products.

The Competent Authority which has authorised the product in question, is in the case of centrally authorised products the EMA, for MRP/DCP the RMS and CMS(s) and for purely national authorisations the National Competent Authority of the relevant MS.

For the content of Art. 46 submissions, please refer to **Questions 12-14**.

#### **Question 4**

*For the purpose of this Regulation, shall paediatric studies mean only studies conducted in the paediatric population (under Art. 2) or also studies conducted simultaneously in the paediatric and adult population (e.g. enrolment criteria for subjects 12 to 65 years of age)?*

Paediatric studies means any studies including patients aged < 18 years, including those with both adult and paediatric patients.

#### **Question 5**

*For the purpose of this requirement, shall paediatric studies mean also studies performed by other sponsors than MAH, e.g. scientific associations?*

Article 45 refers to any studies for an authorised product, whereas Article 46 refers to marketing authorisation holder-sponsored studies only.

#### **Question 6**

*How should Marketing Authorisation Holders comply with the requirements of Article 45 of the Paediatric Regulation?*

Please refer to the Best Practice Guide – Article 45, which can be found on the CMDh website.

Marketing Authorisation Holders should identify the potential regulatory consequences and include proposals to amend the product information with the submission of the paediatric studies, if appropriate.

A short critical expert overview should be added, clarifying the context of the data overall.

#### **Question 7** (December 2007)

*Do Marketing Authorisation Holders have to submit proposals to amend the product information together with the line listings by 26 January 2008?*

The process is divided in the following three steps:

- 1) Submission of the line listings for all authorised medicinal products by 26 January 2008;
- 2) For MRP/DCP and purely nationally authorised medicinal products, submission, upon request of the CMDh-EMA, of paediatric studies not yet submitted to the Rapporteur for assessment in the framework of the Worksharing procedure;
- 3) Formal variation procedure, if applicable.

The proposals to amend the product information should be submitted together with the paediatric studies (step 2) at time of work sharing and for the formal variation procedure.

**Questions 8-11 were considered to be obsolete and have been deleted.**

**Question 12** (Update – November 2008)

***How should Marketing Authorisation Holders comply with the requirements of Article 46 of the Paediatric Regulation?***

- Within 6 months of completion of the study, any marketing authorisation holder-sponsored trial involving the use in the paediatric population of a medicinal product covered by a marketing authorisation, should be submitted to the Competent Authority(ies), i.e. NCA(s) or EMA. 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).
- Marketing Authorisation Holders do not need to resubmit safety data (as opposed to studies), submitted as part of Periodic Safety Update Reports (PSURs) in the context of article 46.
- The procedure described in the CMDh Best Practice Guide - Article 46 will be followed with regard to timelines for the assessment of the paediatric studies submitted according to Article 46 of the Paediatric Regulation. In this procedure it is foreseen to work with a single rapporteur.
- For nationally authorised medicinal products (including MRP/DCP) Marketing Authorisation Holders should submit information on the finalised studies only in the cover letter and line listing published on the CMDh website as described in the Best Practice Guide - Article 46 of the Paediatric Regulation. However, the paediatric data has to be available upon request.

**Question 13** (Update – November 2009)

***According to Article 46, marketing authorisation holder-sponsored studies involving the use in the paediatric population of a medicinal product covered by a marketing authorisation should be submitted to the competent authority within 6 months of completion of the study.***

***In case a variation is intended to be submitted, e.g. to extend the indication of the product based on the results of the study, is it still necessary to submit the study according to Article 46?***

***If yes, will the assessment of the study be done at the time of the submission of the variation?***

Marketing authorisation holder-sponsored studies which involve the use in the paediatric population of a medicinal product covered by a marketing authorisation have to be submitted to the competent authority within 6 months of completion of the study, regardless of the intention to submit a variation.

However, in the situation described above, Marketing Authorisation Holders are advised to clearly indicate their intention to submit a variation and whether it covers exactly the same set of data as the one being submitted.

Marketing Authorisation Holders should identify the potential regulatory consequences and include proposals to amend the product information with the submission of the paediatric studies, if appropriate.

For nationally authorised medicinal products (including medicinal products authorised via MRP/DCP), a cover letter and line listing (templates published on the CMDh website - <http://www.hma.eu/216.html>) need to be submitted to the competent authorities within 6 months of completion of the study. However, the study report has to be available for submission upon request.

For further guidance, please refer to the Best Practice Guide on Art. 46 (<http://www.hma.eu/216.html>).

For further guidance regarding centrally authorised products, please refer to the EMA Post-Authorisation Procedural Advice - Article 46 paediatric study submission. (<http://www.ema.europa.eu/htms/human/postguidance/list.htm>).

**Question 14** (*Update – November 2008*)

***Which data are to be submitted?***

Studies or trials mean here those not yet submitted to Competent Authorities, involving the paediatric use of medicinal products authorised in the Community. Article 45 refers to any studies for an authorised product, whereas Article 46 refers to marketing authorisation holder-sponsored studies only (Please refer to Q&A 5).

- Clinical studies and trials (phase I to IV)
- Non clinical studies (e.g. juvenile toxicology studies) not previously submitted, and relevant to the benefit/risk assessment of the paediatric studies submitted (not applicable for Article 46).
- Completed or discontinued studies;
- Published or not;
- Trials should be submitted regardless of the region where they were performed, the aim, outcome, population studied and indication.
- For paediatric trials, information on the pharmaceutical formulation(s) used in the trials, the existence of a formulation suitable for paediatric use, or on conditions for extemporaneous preparations should be submitted, if available.

**Question 15**

***Which format should the Marketing Authorisation Holders use?***

Study reports should preferably follow the CTD format and be submitted either as Word or PDF documents.

Electronic submission of information via CD-ROM is acceptable. In the case of older studies it may be necessary to submit an extended synopsis instead of a clinical study report when this is not available. For studies not in English, an English extended synopsis will be acceptable, to accompany the report in its original language.

**Question 16**

***When is a medicinal product considered authorised for paediatric use in the context of Article 45/46?***

A **medicinal product** is authorised for **paediatric use in the context of Article 45/46** if there is either an indication in children (0 to 17 years inclusive) in 4.1, *OR* dosing information in children in 4.2 of the SmPC.

**Question 17** (*October 2009*)

***How will the outcome of Art. 45/46 worksharing procedure be implemented?***

As outcome of the Art. 45/46 worksharing procedure a public assessment report will be published on the CMDh website.

In case the assessment under Art. 45 leads to changes in the SmPC/PL, the submission of a type IB variation is requested within 60 days after finalisation of the procedure for medicinal products included in the worksharing.

For medicinal products with the same active substance and pharmaceutical form, the submission of a type IB variation is requested within 90 days of publication of the public assessment report.

In case the assessment under Art. 46 leads to changes in the SmPC/PL, the MAH is requested to submit a type IB variation within 30 days after finalisation of the procedure.

In case the assessment under Art. 46 leads to changes in the SmPC/PL that are 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 also be requested from other MAHs within 60 days of publication of the public assessment report. The purpose of the type IB variation is to add the wording 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.

These applications do not require supporting information and will be accepted by Member States Competent Authorities without further assessment or amendment. A type IB variation is only applicable if no new additional data are submitted by the MAH (see section C.I.3 of Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products).

The MAH is responsible for submitting the variations within 90 days (Art. 45) or 60 days (Art. 46) 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 45/46 procedure and that no further changes are applied for.

For further information, please refer to the Best Practice Guides on Art. 45 and Art. 46 published on the CMDh website under Paediatric Regulation > Guidance Documents.

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

## **ARTICLE 7 & 8**

According to Article 7 of the Paediatric Regulation an application for marketing authorisation of a medicinal product which is not authorised in the Community shall be regarded as valid only if it includes either the results of all studies performed and details of all information collected in compliance with an agreed paediatric investigation plan (PIP) OR a decision of the EMA granting a product-specific or a class waiver OR a decision of the EMA granting a deferral.

### **Question 18**

***When is my medicinal product considered “not authorised in the Community?”***

As of 26 July 2008, applications for a marketing authorisation in respect of a medicinal product for human use which is not authorised in the Community at the time of entry into force of Regulation (EC) No 1901/2006 shall comply with the requirements of Article 7 of Regulation (EC) No 1901/2006.

A medicinal product is considered not to be authorised in the Community, if there is no marketing authorisation granted in one of the Member States of the EU in the context of the Global Marketing Authorisation.

For the application of the Global Marketing Authorisation concept in this regard, please refer to Question 22.

**Question 19** (April 2008)

***Will Article 7 apply to a Mutual Recognition Procedure (MRP) or a repeat-use MRP submitted as of 26 July 2008, for a medicinal product approved in the RMS before 26 July 2008?***

No. Article 7 will only apply to medicinal products which have not been authorised in any Member State by 26 July 2008.

Therefore, in the situation of an MRP or repeat-use MRP, if the medicinal product has been authorised in the RMS before 26 July 2008, it will not fall under Article 7.

In case of a MRP or repeat-use MRP, where the initial marketing authorisation application for the medicinal product has been pending on 26 July 2008, Article 7 will not apply.

**Question 20** (April 2008)

***What are the consequences of the Paediatric Regulation for applications for new indications, including paediatric indications, new pharmaceutical forms and new routes of administration after 26 January 2009?***

According to Article 8, the documents referred to in Article 7 (see Q&A 18) shall be required for applications for new indications, new pharmaceutical forms and new routes of administration submitted as of 26 January 2009, regardless of the route or the date of authorisation of the medicinal product as long as it is protected either by a supplementary protection certificate or by a patent which qualified for the granting of the supplementary protection certificate.

From 26 January 2009, any of the above mentioned applications shall only be considered valid if it includes the results of a PIP or a decision of the EMA granting a product-specific or class waiver or granting a deferral.

A PIP (or a decision of the EMA granting a product-specific or class waiver or granting a deferral) is not required in the case of an application for a new strength of the medicinal product, unless such application also concerns a new indication, new pharmaceutical form or new route of administration. The PIP shall cover all existing and new indications, pharmaceutical forms and routes of administration of the medicinal product.

**Question 21** (April 2008)

***Are there any exemptions to the application of Articles 7 and 8?***

Yes. The requirements of articles 7 and 8 of the Paediatric Regulation do not apply to medicinal products authorised or applied for under the following Articles of Directive 2001/83/EC:

- Article 10 - Generics (10.1), Hybrids (10.3), Similar biologicals (10.4);
- Article 10a - Well-established use;
- Articles 13 to 16 – Homeopathic medicinal products;
- Articles 16a to 16i – Traditional herbal medicinal products.

**Question 22** (Update – November 2008)

***Does Article 7 or Article 8 of the Paediatric Regulation take into account the Global Marketing Authorisation concept?***

Yes, in the context of Article 7 and 8, the Global Marketing Authorisation concept, as defined in Article 6(1), 2<sup>nd</sup> subparagraph of Directive 2001/83/EC, as amended, applies to define whether a medicinal product is authorised or not.

The Global Marketing Authorisation contains the initial authorisation and all variations and extensions thereof, as well as any additional strengths, pharmaceutical forms, administration routes

or presentations authorised through separate procedures and under a different name, granted to the marketing authorisation holder of the initial authorisation. For further reference, see NTA, chapter 1, section 2.3.

Thus, the Global Marketing Authorisation concept applies to medicinal products belonging to the same marketing authorisation holder. According to the Commission Communication on the Community marketing authorisation procedures for medicinal products (98/C 229/03), applicants belonging to the same mother company or group of companies or which are “licencees” have to be taken as one.

If an applicant holds more than one marketing authorisation of the same substance or combination of substances (independently of the procedure of authorisation), the medicinal product subject of the application, will be considered as “already authorised” in keeping up with the Global Marketing Authorisation concept. Consequently Article 7 will not apply for new applications. If the medicinal product is protected by a Supplementary Protection Certificate (SPC, or a patent which qualifies for a SPC, Article 8 shall apply for that application. In this case, the PIP/Waiver decision shall cover the existing and any new indication, pharmaceutical form or route of administration of the medicinal product concerned by the Global Marketing Authorisation.

For instance:

- Company A holds a marketing authorisation in indication A for a medicinal product containing substance x (still patented).
- Company B (subsidiary of company A) intends to apply for a new stand-alone marketing authorisation for substance x in a new indication B.
  
- The medicinal product will be considered as ‘already authorised’ based on the GMA concept, and company B will be required to cover also indication A in its PIP (i.e. Article 8 applies).

The Global Marketing Authorisation approach applies to PIP or Waiver applications as well as to variations, extension and new marketing authorisation applications falling under the requirements of Article 7 and 8. Where relevant, applicants should also consider whether any modification to an agreed or ongoing PIP/Waiver decision may be required in case the GMA concept had not been applied, in order to avoid difficulties at validation of the subsequent regulatory submission.

**Question 23** (June 2009)

***Does Article 7 or Article 8 of the Paediatric Regulation apply to informed consent or duplicate applications which cross-refer to a medicinal product for which a marketing authorisation was issued or an application was submitted before 26 July 2008?***

Article 7 does not apply to ‘informed consent’ or ‘duplicate’(MA) applications submitted after 26 July 2008 and which cross-refer to a medicinal product for which a marketing authorisation was issued or an application was submitted before 26 July 2008.

After authorisation of a medicinal product according to the ‘informed consent’ legal basis or a ‘duplicate’ application, Article 8 will apply as of 26 January 2009 if the conditions set out in this article are met.

For exemptions to the application of Articles 7 and 8, please refer to Question 21.

**Question 24** (January 2011)

**What is a “new indication” in the context of Article 8?**

A “new indication” is not defined in the European Union legislation. However, both the “[Guideline on the elements required to support the significant clinical benefit in comparison to existing therapies of a new therapeutic indication in order to benefit from an extended \(11-years\) marketing protection](#)”, and the “[Guideline on a new therapeutic indication for a well-established substance](#)” provide guidance on what is normally considered a new indication, i.e.:

- a new target disease;
- different stages or severity of a disease;
- an extended target population for the same disease, e.g. based on a different age range or other intrinsic or extrinsic factors;
- change from the first line treatment to second line treatment (or second line to first line treatment), or from combination therapy to monotherapy, or from one combination therapy (e.g. in the area of cancer) to another combination;
- change from treatment to prevention or diagnosis of a disease;
- change from treatment to prevention of progression of a disease or to prevention of relapses of a disease;
- change from short-term treatment to long-term maintenance therapy in chronic disease.

For the purpose of the application of Article 8, the same guidance should be followed.

However, case-by-case assessment may be needed for particular situations to define whether a criterion of the “extended target population” is fulfilled. For example, a modification of the Product Information may not be considered as a new indication in the following cases:

- information on the use of the medicinal product in the authorised target disease(s) on patients with renal or hepatic impairment;
- information on the use of the medicinal product in the authorised target disease(s) on pregnant women;
- for vaccines, information on the concomitant administration with other vaccines.

Applicants are encouraged to contact the NCA in advance of a planned submission in order to clarify paediatric requirements and to anticipate any regulatory issues which could prevent the validation of the application.