

**RECOMMENDATIONS FOR IMPLEMENTING COMMISSION DECISIONS
FOLLOWING AN ARTICLE 29 APPLICATION
UNDER THE PAEDIATRIC REGULATION**

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BACKGROUND

Article 29 procedure (Paediatric Regulation)

1. Article 29 of the Paediatric Regulation (Commission Regulation (EC) No 1901/2006/EC as amended) allows submission of an application referred to in Article 8 using the referral procedures set out in Articles 32, 33 and 34 of Directive 2001/83/EC (referred to as ‘the Directive’ hereinafter). The text is reproduced below:

In the case of medicinal products authorised under Directive 2001/83/EC, an application as referred to in Article 8 of this Regulation may be submitted, in accordance with the procedure laid down in Articles 32, 33 and 34 of Directive 2001/83/EC, for authorisation of a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration.

That application shall comply with the requirement laid down in point (a) of Article 7(1).

The procedure shall be limited to the assessment of the specific sections of the summary of product characteristics to be varied.

2. To be eligible for this procedure the medicinal product must be
 - authorised in the Community through national, mutual recognition or decentralised procedure, and
 - protected by either a Supplementary Protection Certificate (SPC) or by a patent which qualifies for an SPC
3. Such an application must concern the authorisation of
 - new indications, including paediatric indications or
 - a new pharmaceutical form or
 - a new route of administration
4. The application must be accompanied by results of studies and information in compliance with an agreed paediatric investigation plan (PIP). The procedure is limited to the evaluation of the paediatric data including, if relevant, supportive adult data.

5. Therefore applications could be either extensions to existing authorisations leading to the grant of a new marketing authorisation (MA) or a variation to an existing MA in the case of new indications.
6. The Article 29 application is submitted to the EMA and all CHMP members allowing all Member States to have access to the data package.
7. The Commission Decision on the Article 29 is applicable to all Member States and must be implemented in all Member States where the medicinal product is authorised (no opt-out).
8. The reward can only be obtained when the MA has been 'varied' in accordance with the Commission Decision in all Member States of the EU.
9. Applicants may not use the Article 29 procedure as a route into obtaining a new Directive Article 8(3) marketing authorisation (MA) where one does not already exist in a Member State. Applicants may therefore wish to consider options such as the MRP repeat use procedure to obtain any additional MAs necessary to be eligible for the reward.
10. The reward can only be obtained in those Member States where the Supplementary Protection Certificate can be extended.

CHMP referral procedure

11. The Article 29 application is submitted directly to the EMA and the CHMP members in accordance with procedural guidance detailed by the EMA. This includes an initial eligibility request and the application is subject to a validation phase to ensure that the requirements of Article 29 are met. The application shall be accompanied by either the variation or extension application form as appropriate and the necessary supporting data for the new paediatric use. A supporting quality dossier will be included for a new pharmaceutical form.
12. The CHMP opinion will be issued within 60 days following the receipt of a valid application. This time period is not extendable but there is the possibility of a clock-stop. It will be followed by a Commission Decision. The timescale for Member States to implement the Commission Decision, whether it requires grant of an authorisation, or amendment of the current MA, is within 30 days of the notification.

Existing national procedures Procedures for implementing Commission Decisions

13. Section 6 of Chapter 7 of NtA sets out the ~~existing~~ procedures adopted by individual MS. ~~They mostly assume an update (variation) of an MA is required rather than grant of a new MA~~ These are applicable to purely national authorised products.
14. The document on CMDh recommendation for MR procedures after finalisation of a referral procedure is also relevant to the outcome of a paediatric Art 29 application particularly with respect to the appointment of an RMS. One of the aims of the Paediatric regulation is to make medicines for children equally available in all MS and therefore appointment of an RMS is desirable to maintain harmonisation of the SmPC with respect

to paediatric use. It is noted that purely national MAs are not brought into MRP by the issuance of a Commission Decision resulting from an Art 29 paediatric application.

15. The guideline on the categorisation of extension applications vs variation applications (NtA Volume 2C – under current revision) will apply as the basis for the Article 29 application, ~~but although~~ it is noted that individual MS will apply national practice (as stated in point 13 above) when it comes to implementation of purely national MAs. Recommendations should therefore facilitate either amendment of a current MA or grant of a new MA.
16. It is desirable that MS reach a common agreement on procedures for implementing Commission Decisions following an Article 29 (Paediatric Regulation) application, in keeping with the philosophy of equal access for the population across the EU. ~~The usual timescales for line extensions (210 days) to authorise new pharmaceutical forms and routes of administration or for variations to add indications (120 days) are not compatible with the need to implement the Commission Decision within 30 days.~~
17. The following recommendations are based on ~~current-existing~~ procedures for implementing Commission Decisions and address the requirements for the different categories of Article 8 applications bulleted in paragraph 3 above. ~~New pharmaceutical forms and routes of administration usually will require line extension applications whereas new indications are usually achieved by variation. Regulation (EC) No 1234/2008 concerning variations (the ‘Variations Regulation’) came into effect on 1 January 2010 for ‘mutual recognition’ variations. Applications for new indications, pharmaceutical forms and routes of administration are all considered to be variations (to the global marketing authorisation). Applications for new pharmaceutical forms and routes of administration are defined as extension applications according to Article 2.4 and Annex I of the Variations Regulation. Such extensions are normally evaluated and granted in accordance with the same procedure as the related initial marketing authorisation and or included in that initial authorisation (Article 19 of the Variations Regulation). However there is a need to implement the Commission Decision within 30 days. Where the grant of an extension application to an existing MR or DCP approved product results in the issuance of a new MA, this will be subject to MRP to maintain the harmonisation achieved through the Article 29 paediatric procedure.~~

Recommendations

18. ~~Line extensions~~Extension applications *for new pharmaceutical forms and routes of administration (where relevant)* It is recommended that the following principles are adopted for Commission decisions which result in the grant of a new MA: ~~Reference should also be made to the CMDh guidance on ‘Recommendation for MRP after finalisation of a referral procedure with a positive decision by the EC’.~~ Other more detailed aspects of the procedure can also reflect this guidance by analogy.
 - (i) For products not already subject to MR or DC procedures, the MA holder chooses an RMS – it is strongly recommended that an existing RMS is chosen, if there is one, for products in the same range with authorisations held by the same MA holder. By analogy with the finalisation of other referral procedures, “The choice of the RMS shall be made after the CHMP opinion is adopted and before the

Commission decision is forwarded to the MS concerned.” The MS of the Rapporteur will have the responsibility to oversee the transfer of national MAs into mutual recognition following completion of the referral. The MS will liaise directly with the MAH. If the MAH does not use his right to choose the RMS, the Rapporteur will refer the matter to the CMDh. ~~The wording in italics is the same as that used in the recommendation for MRP after finalisation of a referral procedure. Other more detailed aspects of the procedure can also reflect this guidance by analogy which will contact the MAH and appoint the RMS. It is the responsibility of the RMS to assign a procedure number for the product in CTS.~~

- (ii) The MA holder submits an application for ~~line~~ extension with the supporting information to all relevant MS. This consists of:
- A cover letter
 - Copy of the application form sent to EMA
 - Commission Decision and the national translations of the SmPC, PL and labelling
 - Mock-ups of the PL and labelling in the national language
 - If required by MS, the data which accompanied the original application to CHMP
 - Relevant fee.

There is no need for further assessment, other than checking the submitted national translated SmPC, PL and labelling (if relevant). The quality dossier, if required to support the Article 29 paediatric application, will have been assessed as part of the CHMP procedure. Provided the supporting information package is complete, national competent authorities will grant the application within 30 days.

- (iii) Fees are a matter for national decision

~~19. *Variations to add new indications (where relevant)* Regulation (EC) No 1234/2008 concerning variations (the ‘Variations Regulation’) came into effect on 1 January 2010 for ‘mutual recognition’ variations. *Other variations (where relevant, for example to add a new indication)* The Variations Regulation provides for implementation of Commission Decisions through Type IA immediate notifications (Category C.I.1a) in cases where the medicinal product is covered by the defined scope of a referral procedure. This category allows MS to comply with the Commission Decision within 30 days of notification of the Commission Decision. Implementation of Commission Decisions following Article 29 paediatric procedures may be considered an ‘unforeseen’ variation. Following consideration of a request for a recommendation of will also fall into this category. *unforeseen variation under Article 5 of the Variations Regulation, CMDh has agreed that variations to implement Article 29 Commission Decisions should be classified as Type IB default variations. A classification of C.I.1 z) has been published on the CMDh at <http://www.hma.eu/293.html>.* Member States will implement variations for nationally authorised products in accordance with their own procedures.~~

Other considerations

20. MA holders should consider maintaining harmonisation of purely national MAs with respect to paediatric use by agreement of a single RMS.

21. MA holders should liaise with the RMS at an early stage to discuss the implementation plan so that procedures can be finalised within 30 days of the notification of the Commission Decision. MA holders should send the complete SmPC to the RMS and

national translations should be discussed as soon as possible so that the final version can be agreed between the CHMP opinion and EC decision. Likewise, this time period can be used to establish requirements for any national follow-up measures or risk management plans recommended by CHMP.

22. ~~When~~The Commission Decision will state whether or not the application includes the results of all studies and details of all information collected in compliance with an agreed PIP. However, when implementing Article 29 procedures ~~where the CHMP opinion and Commission Decision include a compliance statement, Member States should~~ it is the responsibility of national competent authorities to ensure that the statementa 'Compliance Statement' as per Article 28(3) of Regulation (EC) No 1901/2006 and Commission Guideline 2008/C 243/01 is included in national marketing authorisations according to the where appropriate. The RMS takes the lead and CMDh guidance 'Recommendation for implementation of compliance statement for the agreed completed PIP' <http://www.hma.eu/216.html> should be followed. A template is also available.
23. Finally, Member States should consider the impact of the Commission Decision on the Article 29 paediatric application on other products on their markets including purely national authorisations and request updates from the MA holder if relevant and legitimate (subject to patent issues).