

## RECOMMENDATIONS ON PAEDIATRIC USE MARKETING AUTHORISATIONS

Doc. Ref.: CMDh/152/2009  
July 2009

### BACKGROUND

#### Paediatric Use Marketing Authorisations (PUMAs)

1. The recitals to Regulation (EC) No 1901/2006 (Paediatric Regulation) set out the purpose of Paediatric Use Marketing Authorisations (PUMAs). The relevant recitals (19-22) are attached at Annex 1. Such authorisations are intended to establish incentives for the paediatric development of authorised medicinal products which are no longer covered by intellectual property rights and are therefore ineligible for the rewards of extension of periods of patent protection provided elsewhere in the Regulation.
2. PUMAs are defined in Article 2(4) of the Paediatric Regulation as follows:  
*‘paediatric use marketing authorisation’ means a marketing authorisation granted in respect of a medicinal product for human use which is not protected by a supplementary protection certificate under Regulation (EEC) No 1768/92 or by a patent which qualifies for the granting of the supplementary protection certificate, covering exclusively therapeutic indications which are relevant for use in the paediatric population, or subsets thereof, including the appropriate strength, pharmaceutical form or route of administration for that product.*
3. Articles 30 and 31 set out the requirements for PUMAs (Annex 2).
4. The key points can be summarised as follows:
  - PUMAs apply to ‘off-patent’ drugs
  - Existing marketing authorisation procedures should be used
  - The product must be for *exclusive* use in the paediatric population
  - Applications for PUMAs must include documents to support quality, safety and efficacy in accordance with an agreed paediatric investigation plan (PIP)
  - Applications can cross-refer to data in the dossier of an existing product owned by a different MA holder, provided the appropriate data protection period has expired.

- The brand-name of the product used in adults may be used for the paediatric-use product, provided both are held by the same MAH.
- Data may be bibliographic or new pre-clinical or/and clinical data or a mixture
- A direct application for a PUMA can be eligible for the centralised procedure.

## LEGAL BASIS OF APPLICATIONS

5. Recital 19 indicates that PUMA applications may be made using existing procedures i.e. centralised, mutual recognition, decentralised or national procedures.
6. Recital 20 and Article 30(3) states that the application may cross-refer to dossiers for existing authorised products within the usual rules of data and market protection i.e. 6/10 yrs or 8+2(+1) yrs.
7. PUMA applications should be submitted according to the current legal basis of Directive 2001/83/EC. As a PUMA application will include new paediatric data in compliance with an PIP, it is expected that the legal basis and dossier requirements for submission of a PUMA application would normally be based on Article 8(3), 10(3), 10(4) or 10b of Directive 2001/83/EC as appropriate (see Q49 in the EMEA Pre-submission guidance <http://www.emea.europa.eu/htms/human/presub/q49.htm>).
8. Applications under Article 10a (well-established use) may be considered on a case-by-case basis but would also have to demonstrate compliance with an agreed PIP.
9. PUMA applications may also be submitted through the centralised procedure described in Regulation (EC) No 726/2004 according to Article 31 of the Paediatric Regulation (see Q1 in the EMEA pre-submission guidance <http://www.emea.europa.eu/htms/human/presub/q01.htm>).
10. Subsequent changes to a PUMA like new indications, pharmaceutical forms, routes of administration or strengths would need to be supported by data collected in compliance with either the initial PIP or a subsequent one as necessary.

## ACCOMPANYING DOCUMENTATION

11. A PUMA application should be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan as set out in Article 30(2). Recital 20 indicates that this data may be derived from literature or new studies. Thus it is expected that the same range of supporting information should be provided as for other MA applications through a combination of new data (as required by the PIP) and/or existing data, if necessary by cross-referral to another product and/or literature studies.

12. Cross-references to products already authorised should take into consideration any periods of data or market protection – Article 30(3).
13. PUMA applicants are required to detail the measures to ensure the follow-up of efficacy and of possible adverse reactions to the paediatric use of the medicinal product, as for other applications including a paediatric indication in accordance with Article 34 of the Paediatric Regulation. A risk-management plan should be submitted with an application for a PUMA in accordance with NTA vol 9A, chapter I.3, section 3.4 ‘situations requiring an EU-RMP’.
14. Thus the PUMA submission should comprise:
  - Application form (NtA)
  - Demonstration of compliance with a PIP (including by provision of a Paediatric Committee opinion on compliance)
  - Cross-references to existing data
  - Module 3 – quality: documents to support age-appropriate strength, form, route as designated in the approved PIP, with appropriate cross-referenced data
  - Module 4 – pre-clinical: documents to support safe use in paediatric population as designated in the approved PIP, with appropriate cross-referenced data
  - Module 5 – clinical safety and efficacy: studies as designated in the approved PIP with appropriate cross-referenced data
  - Details of measures to ensure follow-up of efficacy and safety (Risk management Plan)

## **REWARDS ASSOCIATED WITH PUMAs**

15. The reward for a PUMA offered by the Paediatric Regulation is the same periods of data and market protection as for medicinal products not previously authorised in the Community – Article 38. It follows that the MA would have to be granted for the reward to be obtained. It is not necessary for an application for authorisation to be made or granted in every MS for the reward to apply.
16. The periods of data and marketing protection are set out in Article 14(11) in the case of Community authorisations and Article 10(1) of Directive i.e. 8 years data protection, 10 years marketing protection which can be extended to a maximum of 11 years if an indication of significant clinical benefit is authorised in the first 8 years.

**EXTRACT FROM RECITALS TO REGULATION (EC) No 1901/2006 (PAEDIATRIC REGULATION) RELEVANT TO PUMA APPLICATIONS**

(19) In order to establish incentives for authorised products no longer covered by intellectual property rights, it is necessary to establish a new type of marketing authorisation, the Paediatric Use Marketing Authorisation. A Paediatric Use Marketing Authorisation should be granted through existing marketing authorisation procedures but should apply specifically for medicinal products developed exclusively for use in the paediatric population. It should be possible for the name of the medicinal product that has been granted a Paediatric Use Marketing Authorisation to retain the existing brand name of the corresponding product authorised for adults, in order to capitalise on existing brand recognition, while benefiting from the data exclusivity associated with a new marketing authorisation.

(20) An application for a Paediatric Use Marketing Authorisation should include the submission of data concerning use of the product in the paediatric population, collected in accordance with an agreed paediatric investigation plan. These data may be derived from the published literature or from new studies. An application for a Paediatric Use Marketing Authorisation should also be able to refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community. This is intended to provide an additional incentive to encourage small and medium-sized enterprises, including generic companies, to develop off-patent medicinal products for the paediatric population.

(21) This Regulation should include measures to maximise access by the Community population to new medicinal products tested and adapted for paediatric use, and to minimise the chance of Community-wide rewards and incentives being granted without sections of the Community paediatric population benefiting from the availability of a newly authorised medicine. An application for a marketing authorisation, including an application for a Paediatric Use Marketing Authorisation, which contains the results of studies conducted in compliance with an agreed paediatric investigation plan should be eligible for the Community centralised procedure set out in Articles 5 to 15 of Regulation (EC) No 726/2004.

(22) When an agreed paediatric investigation plan has led to the authorisation of a paediatric indication for a product already marketed for other indications, the marketing authorisation holder should be obliged to place the product on the market, taking into account the paediatric information, within two years of the date of approval of the indication. That requirement should relate only to products already authorised, but not to medicinal products authorised via a Paediatric Use Marketing Authorisation.

**ARTICLES OF REGULATION (EC) No 1901/2006 (PAEDIATRIC REGULATION) RELEVANT TO PUMA APPLICATIONS**

*Article 30*

1. Submission of an application for a paediatric use marketing authorisation shall in no way preclude the right to apply for a marketing authorisation for other indications.

2. An application for a paediatric use marketing authorisation shall be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration for the product, in accordance with an agreed paediatric investigation plan.

The application shall also include the decision of the Agency agreeing the paediatric investigation plan concerned.

3. Where a medicinal product is or has been authorised in a Member State or in the Community, data contained in the dossier on that product may, where appropriate, be referred to, in accordance with Article 14(11) of Regulation (EC) No 726/ 2004 or Article 10 of Directive 2001/83/EC, in an application for a paediatric use marketing authorisation.

4. The medicinal product in respect of which a paediatric use marketing authorisation is granted may retain the name of any medicinal product which contains the same active substance and in respect of which the same holder has been granted authorisation for use in adults.

*Article 31*

Without prejudice to Article 3(2) of Regulation (EC) No 726/ 2004, an application for a paediatric use marketing authorisation may be made in accordance with the procedure laid down in Articles 5 to 15 of Regulation (EC) No 726/2004.