EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Experience with article 46 of the Paediatric Regulation

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Human Medicines Evaluation and Development, Safety and Efficacy of Medicines

Contents

Introduction

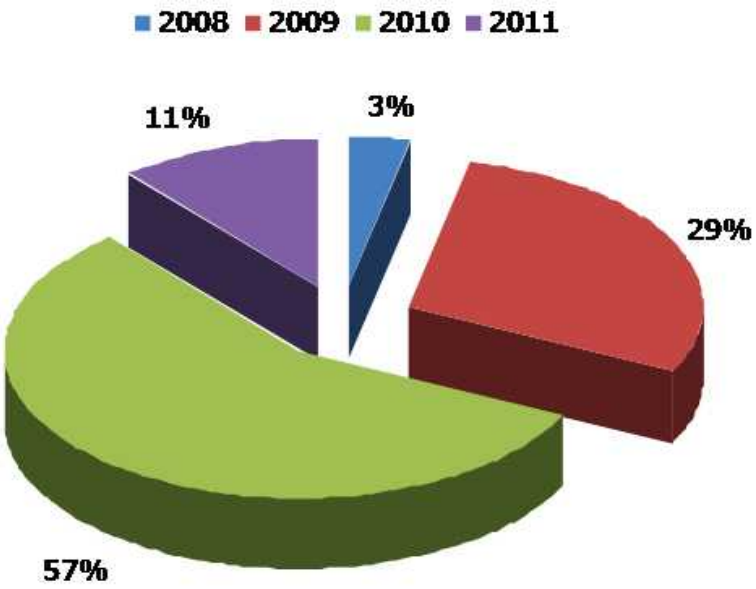
- **Legal basis**

1. Any other marketing authorisation holder-sponsored studies which **involve the use in the paediatric population** of a medicinal product covered by a marketing authorisation, **whether or not** they are conducted in compliance with an agreed **paediatric investigation plan**, shall be submitted to the competent authority **within six months of completion** of the studies concerned.
2. Paragraph 1 shall apply independent of **whether or not** the marketing authorisation holder intends to **apply for a marketing authorisation of a paediatric indication.**

Introduction

- **Analysis**
  - Retrospective
  - Relates to centrally authorised products
  - Covers 3.5 years (cut off date as of May 2011 submission)
  - Includes all submissions made under article 46 as stated by the Marketing Authorisation Holders (MAHs)
    - Cover letter or Application Form templates

Overview



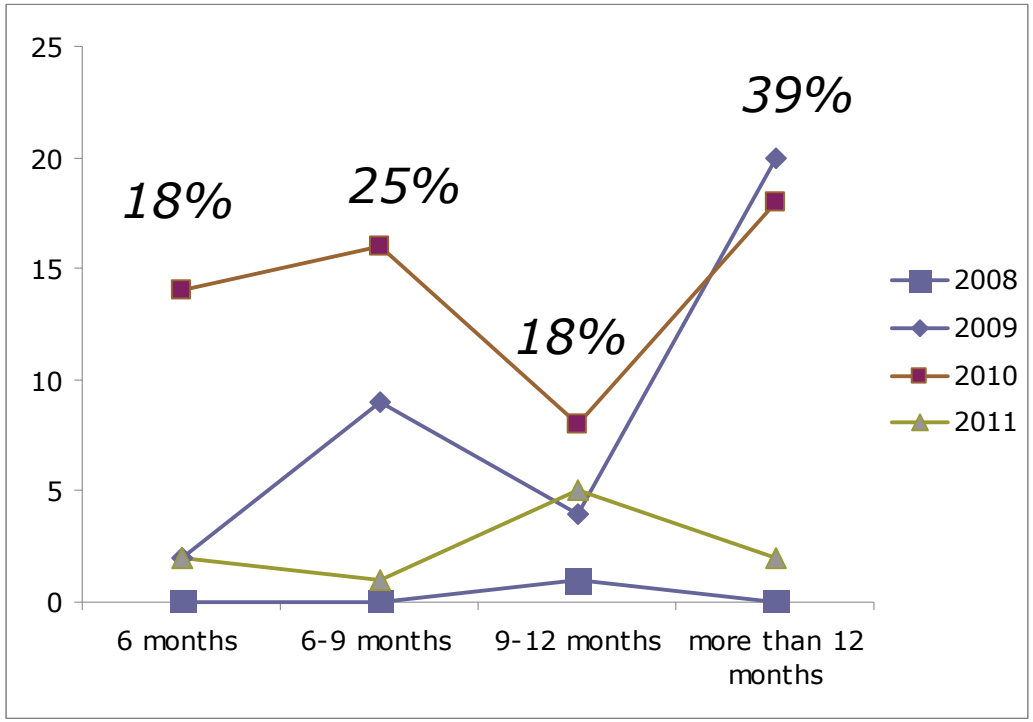
Article 46 submission is increasing steadily since the entry into force of the Paediatric Regulation on 26 January 2007

N=94

Content of the Dossier

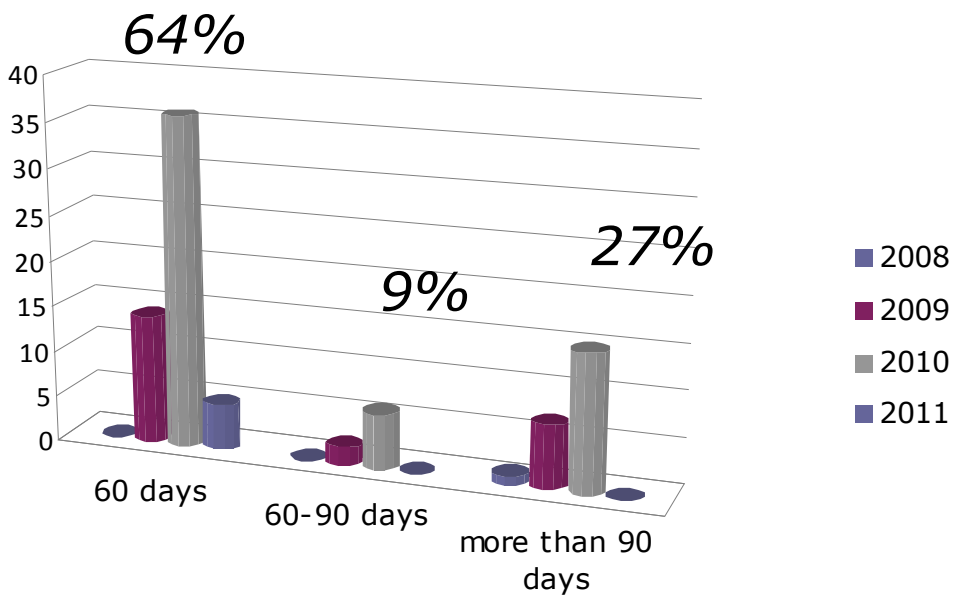
- **A large majority of dossiers (80%) relates to one clinical study submission**
- **"No regulatory action" stated by the MAH : 87%**
- **Around 85 % of the dossier included a short critical expert overview**
- **Information on whether or not studies are part of a forthcoming application intended for submission is not always provided**

Timelines for submission



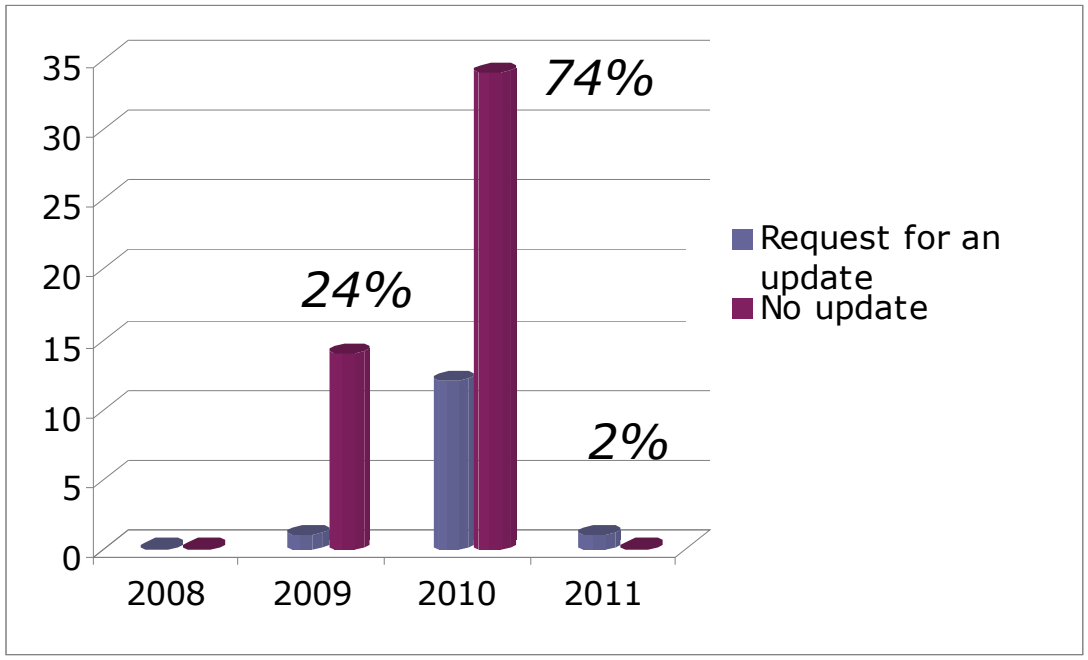
Nearly 40% of the studies were submitted beyond 12 months after their completion

Timelines for assessment



More than 70% of the CHMP assessment is performed within the 60-90 days timelines

Outcomes



Some updates of the Product Information are requested by the CHMP following assessment of studies not directly submitted via a variation/extension application

Outcomes

- **CHMP reasons for not Updating the Product Information included:**
  - Similar safety profile than already known in the paediatric population for authorised **or** non-authorised indications
  - Limited number of paediatric patients: early terminated study, adult study
  - Confirmed efficacy (e.g dosing recommendation) profile in the paediatric population for authorised indications
  - Limitations in study design or need for other supportive data
  - Upcoming variation/extension application

New aspects

- **SmPC Advisory Group consultation**
  - Advice on all matters related to SmPC guideline
  - Has been consulted several times in relation to paediatric information including variation resulting from article 46 procedure
- **Better transparency on outcomes of article 46**
  - Forthcoming EMA publication of article 46 final assessment report for centrally authorised products

New aspects

- **Example of updated SmPC for non-authorised paediatric indication by the CHMP following SmPC Advisory Group consultation**
  - **<u>Section 4.2</u>:** *<…>the safety and efficacy of X in children and adolescents below 18 years of age have not yet been established in irritability associated with autistic disorder. Currently available data are described in section 5.1 but no recommendation on a posology can be made.*
  - **<u>Section 5.1:</u>**
    - **Description of the study design**
    - **Results and Assessment:** *<…> X demonstrated statistically superior efficacy compared to placebo on the Aberrant Behaviour Checklist Irritability subscale.* ***However, the clinical relevance of this finding has not been established****. The safety profile included weight gain and changes in prolactin levels. <…>*

Conclusions

- **Higher volume of procedures is expected in the future**
- **A large majority of the dossiers complies with the EMA procedural guidance**
- **Compliance with deadline for submission to be followed up with justification for delay sent in advance to EMA**
- **Good results for CHMP review timelines**
- **A few CHMP request for updating the Product Information encouraging the submission of direct variation/extension**
- **Continuous monitoring of article 46 procedures**

Thank you