



## **The European paediatric initiative: History of the Paediatric Regulation**

### **Why there is a need to study medicines in children?**

The use of unlicensed and off-label medicines in children is widespread and has been an increasing concern over the last years. In the European Union (EU), fifty per cent or more of medicines used in children have never actually been studied in this population<sup>1</sup>, but only in adults, and not necessarily in the same indication (or the same disease).

The general lack of information and appropriate pharmaceutical formulations to support the administration of many medicines in children may expose them to unwanted side effects or underdosing without the expected efficacy. The need for more studies to obtain paediatric information for medicines used in children is now a matter of consensus on a global basis.

Based on this, it was clear that there was a need for a legal obligation for pharmaceutical companies to perform studies if they intended to develop medicines for use in the paediatric population.

### **What has been done in Europe?**

In 1997, the European Commission organised at the EMEA a round table of experts to discuss paediatric medicines. One of the conclusions at that time was that there was a need to strengthen the legislation, in particular by introducing a system of incentives<sup>2</sup>.

In 1998, the Commission supported the need for international discussion on the performance of clinical trials in children in the context of the International Conference on Harmonisation (ICH) – an organisation working on the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and the US. An ICH guideline was therefore agreed<sup>3</sup>. The goals were to encourage and facilitate timely paediatric medicinal product development internationally, and to provide an outline of critical issues in paediatric drug development and approaches to the safe, efficient and ethical study of medicinal products.

Subsequently, the ICH guideline became the European guideline ‘Note for guidance on clinical investigation of medicinal products in the paediatric population’ (ICH Topic E11), which has been in force since July 2002<sup>4</sup>.

The Directive (2001/20/EC) on Good Clinical Practice for Clinical Trials was adopted in April 2001, and came fully into force in May 2004. This Directive takes into account some specific concerns about performing clinical trials in children, and in particular it lays down criteria for their protection in clinical trials.

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<sup>1</sup> Conroy S et al. *Br Med J*. 2000;320:79-82

Chalumeau M et al., *Arch. Dis. Child*. 2000;83: 502-5.

<sup>2</sup> ‘Report on the Experts Round Table on the difficulties related to the use of new medicinal products in children’ ([EMEA/27164/98 Revision 1](http://www.emea.europa.eu/pdfs/human/ich/271199en.pdf)).

<sup>3</sup> For more information, visit the ICH website: <http://www.ich.org>

<sup>4</sup> Document available at: <http://www.emea.europa.eu/pdfs/human/ich/271199en.pdf>

In addition, in October 2006 the European Commission (DG Enterprise and Industry) released a draft document on 'Ethical considerations for clinical trials performed in children – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use'<sup>5</sup>.

This document aims to provide recommendations on various ethical aspects of clinical trials performed in children, intending to contribute to their protection as the subject of clinical trials as well as to facilitate a harmonised approach to clinical trials across the EU Member States, considering that the approval of clinical trials, including ethical approval, is primarily a national competence, thereby facilitating the conduct of clinical trials in the European Union.

### **Legislative process for a paediatric initiative in Europe**

Following a discussion on a memorandum presented under the French EU presidency, the Council of (Health) Ministers adopted a Resolution on 14 December 2000 asking the European Commission to draw up a legislative proposal (regulation) on this topic, which was considered a public health priority.

In February 2002 the European Commission published a consultation paper on 'Better medicines for children – proposed regulatory actions in paediatric medicinal products'. This paper represented one of the first steps of the Commission to address the problem. A reflection paper followed, incorporating the comments received in June 2002.

As a result of the Commission's Better Regulation Action Plan (com(2002)278), the proposed Regulation on medicinal products for paediatric use was subject to an extended impact assessment. This aimed at analysing all economical, social and environmental consequences of any major regulation. The legislative process could only start after this assessment.

In March 2004, the European Commission consulted on a draft Regulation on medicinal products for paediatric use.

On 29 September 2004, the European Commission released the first proposal for a Regulation on medicinal products for paediatric use, together with an explanatory memorandum, the extended impact assessment, and a question-and-answer document. Following the plenary vote of the European Parliament on the Commission's proposal on 7 September 2005, the Commission responded to the parliamentary amendments in the form of a modified proposal.

The Council of Health Ministers reached political agreement on 9 December 2005. The proposal for a Regulation on medicinal products for paediatric use went into a second reading in the European Parliament.

The Regulation was agreed on 1st June 2006 by the European Parliament.

On 27 December 2006 the Regulation was published in the Official Journal of the European Union. It entered into force on 26 January 2007. The new paediatric legislation comprises [Regulation \(EC\) No 1901/2006](#) and the [amending Regulation \(EC\) No 1902/2006](#).

### **CHMP Paediatric Working Party**

Aware of the unmet medical needs of the paediatric population, the Committee for Medicinal Products for Human Use (the CHMP, previously known as CPMP) took the initiative of creating an ad hoc Expert Group on Paediatrics (PEG). Dr Daniel Brasseur, chairman of the CHMP and a paediatrician himself, chaired this group. With the implementation of Title IV of Regulation (EC) No 726/2004 of the European Parliament and of the Council, the PEG was transformed into a temporary working party, which was constituted in 2005 under a new mandate.

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<sup>5</sup> Document available at:

[http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds\\_ethics\\_consultation20060929.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/paeds_ethics_consultation20060929.pdf)

The Paediatric Working Party comprised 14 experts representing the main areas of specific expertise (e.g. pharmaceutical formulations, pharmacokinetics, trials methodology, and several paediatric specialities such as neonatology, immunology, nephrology and adolescent medicine). In addition, several members ensured active links with other CHMP working parties (Safety, Efficacy, Pharmacovigilance, Quality) and with the Committee for Orphan Medicinal Products (COMP).

The mandate of the PEG was to coordinate the necessary actions and advise the EMEA and its scientific committees, the CHMP, the COMP and the Mutual Recognition Facilitation Group (MRFG) on all questions relating to the development and use of medicinal products in children. This concerned products already authorised, whether through the centralised or national mutual-recognition procedures, and those in development.

The PEG has now ceased its activities<sup>6</sup>, and has been replaced, in accordance with the Paediatric Regulation, by a new scientific committee within the EMEA – the Paediatric Committee – which held its inaugural meeting on 4-5 July 2007<sup>7</sup>.

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<sup>6</sup> A press release on the final meeting of the PEG is available [here](#).

<sup>7</sup> A press release on the first meeting of the Paediatric Committee is available [here](#).