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Short papers

Short communication

The EMA perspective: Case studies from the PDCO formulations group (chemicals & biologicals)

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Since the Paediatric Regulation (EC) No. 1901/2006 came into force in January 2007, it is mandatory to submit an early development plan for medicines which is targeted to the paediatric population, where necessary (i.e. not required for Generics).

More than fifty per cent of medicines used in the European Union for children have never been studied in the paediatric population and are used off-label or off-licence. Hence, the objective of the Regulation is to ensure that children can benefit from better and safer medicines.

A Paediatric Investigation Plan (PIP) is a development plan aimed at ensuring that the necessary data to support the authorisation of the medicine for children are obtained through studies in children which demonstrate Quality, Safety and Efficacy for the Paediatric population. The plan should be submitted by pharmaceutical companies to the Paediatric Committee (PDCO), which is responsible for agreement or refusal of the plan and follows the time line as per Fig. 1. The safety of a PIP is carefully assessed in each individual case.

The PIP should include a description of the studies and the measures taken to adapt the formulation to make its use more acceptable for children. It covers the needs of all age groups of children, from birth to adolescence.

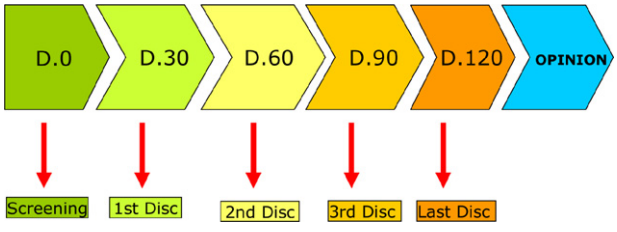

Fig. 1. PIP life cycle (disc = discussion).

In order to assess the appropriateness of a PIP, the Quality of Medicines Sector (Chemicals and Biologicals) and the PDCO Formulation Working Group (composed of experts from PDCO, Hospitals, Pharmacists and Academia) review monthly the acceptability of the formulation, excipients used and their potential safety risks for the paediatric population. Currently, all PIPs received are screened at early stage in order to identify potential formulation issues. Waivers and deferrals are excluded. Until now, approximately 35% of the PIPs received have been reviewed as per Fig. 2.

European commission Directives (European commission 1995, 2003, 2009, 2010), European guidelines on excipients, reflection paper on paediatric formulations and the on-going guideline on pharmaceutical development for paediatric formulations, opinions for the European Food Safety Agency (EFSA) and literature (e.g. Costello et al., 2007; Davies and Tuleu, 2008; Whittaker et al., 2009) are consulted during the assessment.

The objective of this presentation was to highlight principles to consider when reviewing a PIP and some relevant references for use in their preparation. Seven case studies were presented (4 cases for chemical products and 3 for biological products).

The examples were focused on the main issues encountered during their evaluation by the PDCO FWG, i.e. excipients selected, acceptability and palatability, appropriateness of the strengths, size of oral dosage forms, suitability of administration device including wastage and dose accuracy and justification of preservatives use.

As a conclusion of the case studies, the EMA would like to emphasise the importance of the risk based approach while developing and assessing paediatric formulation.

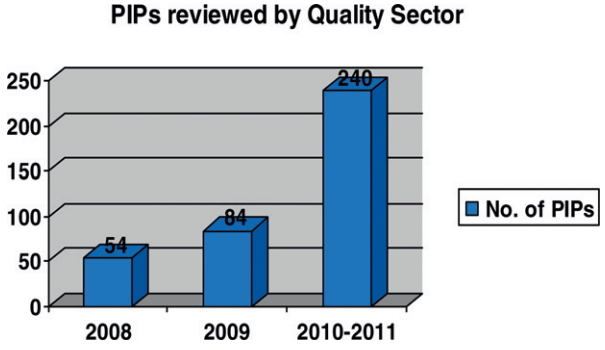

Fig. 2. PIPs applications reviewed by quality sector.

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The EMA quality guideline on the pharmaceutical development of medicines for paediatric use

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In the 1960s, the teratogenic effect of thalidomide strengthened the awareness at the European authorities that the responsibility to protect public health against the harmful effects of medicines could not be left to industry only. As a result, several pieces of national legislation were installed which are now harmonized through European Directives and Regulations, the most important being Directive 2001/83 as amended (i.e. the Medicines Directive). This Directive describes the clinical, pre-clinical and quality documentation that industry has to send to the national competent authorities (NCAs) or the European Medicines Agency (EMA) for assessment. A marketing authorization is issued in case of a positive benefit to risk ratio and adequate and consistent product quality (European Union, 2001). The Directive is supplemented by guidelines that further detail the information to be provided (EMA Committee for Medicinal Products for Human Use). The quality guidelines do generally not differentiate between medicines for children and adults (EMA Committee for Medicinal Products for Human Use).

As science is evolving, so is guidance, and the quality requirements at the time of marketing authorization of a medicinal product licensed, e.g. 15 years ago are different from a product licensed today. However, Article 23 of the Medicines Directive describes that marketing authorization holders have the responsibility to ensure that their products remain state of the art (European Union, 2001). Consequently, they may need to submit a variation in order to update the quality dossier (European Commission, 2008, 2010).

In the 1990s, general awareness increased that the medicines legislation was not working to its full benefit. The availability of licensed medicines and active substances for children was lagging behind those for adults, unlicensed and off-label prescription rates were high, there was a lack of suitable formulations for children especially the very young and, despite a positive benefit to risk profile, the suitability of some licensed paediatric medicines was questioned in literature (Cohen et al., 2009; European Medicines Agency, 2007; Van Riet-Nales et al., 2010). All this resulted in Regulation 1901/2006 or the Paediatric Regulation. This Regulation aims at better medicines for children by several incentives including stimulation of research in areas where knowledge is scarce and making more medicines available to children. The regulation therefore introduced the requirement to submit a Paediatric Investigation Plan (PIP) to the EMA at an early phase in the development of a new medicine or indication. The PIP describes the plan for the paediatric development of the medicinal product, including the formulation to be developed. The PIP is to be agreed by the EMA Paediatric Committee (PDCO) and the agreed terms are binding at the time of Marketing Authorization. A waiver or deferral may be granted (Breitkreutz, 2008; European Union, 2006a,b; Olski et al., 2011).

To facilitate the development of paediatric medicines, a draft guideline has been developed by the EMA Quality Working Party in close cooperation with members of the PDCO and the EMA secretariat. The aim of the guideline is to guide industry in the pharmaceutical development of medicines for paediatric use irrespective of the (foreseen) type of application (i.e. generic or innovator) and procedure (i.e. national, decentralized, mutual recognition or centralized). The guideline covers the quality aspects to be described in the PIP and/or marketing authorization dossier. The guideline will describe aspects that are specific to children only. The proposed guidance has been developed on basis of the concept paper of July 2008, the relevant legislative framework, experiences from the assessment of marketing authorization dossiers and PIPs, literature and stakeholders contributions. Following further agreement by the EMA Safety Working Party (SWP), the draft guideline was released for public consultation by the EMA Committee for Human Medicinal Products (CHMP) in May 2011 (European Medicines Agency Committee for medicinal product for human use, 2008, 2011).

The guideline starts with the usual three sections introduction, scope and legal basis. In chapter 1 (introduction), the need for this guideline is explained. In chapter 2 (scope), the principles of the guideline are pointed out including its applicability to PIPs for both applications for a new marketing authorization and applications to vary or extend an existing marketing authorization with a paediatric indication.

Children and carers may expect similar quality standards for commercially available medicines irrespective of the active substance included, e.g. with respect to excipients, tablet sizes for use in young children, breakability or dosing devices. They may also expect similar quality standards for products containing the same active substance in the same dose and dosage form, irrespective of the date of marketing authorization. Combining these expectations with signals on the questionable quality of some licensed paediatric medicines, a 5-year transition period is proposed for marketing authorizations holders to verify whether their paediatric medicinal products comply with the main aspects of the guideline, i.e. are sufficiently state of the art according Article 23 (European Union, 2001). This requirement is not meant to force marketing authorization holders to update their marketing authorization dossiers