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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

on any minor aspect of a paediatric medicine that is not in full compliance with the guideline, but rather as an incentive to reconsider and improve the quality of paediatric medicines that are largely non compliant with the guideline. Such improvement may include a change in the pharmaceutical design of the medicine or an update of the SPC section 6 on quality aspects. Examples include very badly tasting antibiotics that are not taken by children, products for neonates containing benzyl alcohol, dosing instructions that cannot be achieved with the available formulations, etc.

In chapter 4 of the guideline, the general considerations in the pharmaceutical development of medicines for paediatric use are discussed. Aspects to be taken into consideration, e.g. include the minimum age of the target age group(s), the condition to be treated, the 'criticality' of the dose, the pharmaceutical properties of the drug substance and patient acceptability.

In chapters 5–11 the different aspects of the pharmaceutical design of a paediatric medicine are described along the process of pharmaceutical development by industry. The selection of the active substance is described in chapter 5, the choice of the route of administration and dosage form in chapter 6, the desired dosing frequency and necessary modifications to the product in chapters 7 and 8, the selection of the excipients in the formulation in chapter 9 and the selection of the container closure system, dosing and administration device in chapter 11. The issue of patient acceptability is specifically addressed in chapter 10. These chapters contain extensive information which cannot be summarized in this publication. The CHMP is however specifically asking for further feedback on the following three aspects.

## 1. Acceptability of tablets in young children

Acceptability is defined as the overall ability of the patient to use a medicine as intended. The guideline requires that the evaluation of patient acceptability should be an integral part of the pharmaceutical development studies and that it should be studied in children where possible and if not, demonstrated otherwise. The guideline strongly encourages applicants to confirm adequate patient acceptability post marketing by actual studies in children who are already under treatment or by a careful evaluation of voluntary patient feedback. Palatability is considered an essential aspect of patient acceptance.

The aforementioned guidance on patient acceptance is unlikely to realize a consistent approach by industry and assessors with respect to the acceptability of different tablet sizes in children. Although scientific evidence is scarce (8), the guideline therefore proposes clear criteria on basis of supportive information from health care professionals. Feedback is particularly requested on the proposal that, unless otherwise justified by appropriate studies or clinical evidence, small tablets (i.e. tablets from 3 to 5 mm diameters width or length whichever is the longest) will not be considered acceptable for children below the age of 2 years, medium sized tablets (i.e. tablets from 5 to 10 mm) not below the age of 6 years and large tablets (i.e. tablets from 10 to 15 mm) not below the age of 12 years.

It is noted that the guideline also states that tablets larger than 15 mm would not be acceptable in children at all and that powders, pellets and granules would be acceptable in children from the moment the infant is able to accept solid food.

Following stakeholders comments at the EUPFI conference, it is acknowledged that guidance on the acceptability of tablets smaller than 3 mm is missing. This is likely to be corrected in the final version of the guideline. It is expected that the same requirements will apply as for powders, granules and pellets.

## 2. Subdivision of tablets

The Ph. Eur. monograph on tablets contains a binding section on this aspect (Pharmacopoeia, 2011). It states that subdivision is to be tested as part of the development studies of a medicine if the posology allows the dosing of half a tablet. The test method is based on a determination of the uniformity of mass of halved tablets. In view of high off-label and unlicensed prescription rates in children requiring halved tablets, the draft guideline considers that the Ph. Eur. monograph should be employed beyond its scope i.e. to all tablets for use in children which contain a (score) line. Feed back is asked with respect to the current approach of the Ph. Eur. that subdivision of tablets for use in children with a low dose or where dosing is critical does not need to be confirmed by a test on content uniformity of the halved tablets.

## 3. Safety of excipients

Excipients that are considered safe when used in medicines for adults will not necessarily be safe when used in medicines for children e.g. propylene gycol (Medicines Evaluation Board in the Netherlands, 2005). Therefore industry should carefully justify the use of each excipient in a paediatric medicine, even if the composition of the paediatric medicine is identical to the adult medicine. Information on the safety of excipients in children is however fragmented or missing. Therefore the guideline includes a detailed description on the way industry could justify the choice of the excipients in the formulation. A decision tree is included.

It is emphasized that the content of this guideline is not to be interpreted as written in stone. Any alternative approaches may be considered acceptable if scientifically justified by industry.

Industry is now invited to improve the current draft guideline by providing relevant feedback. Such feedback preferably includes scientific information from the closed domain and positive and negative feedback on the current wording. The guideline is open for public consultation until 31 December 2011. Comments should be sent to qwp@ema.europa.eu using the appropriate template.

All stakeholders' comments will be summarized and carefully evaluated. On basis of the comments received, it may be decided that further stakeholder communication is warranted. Such consultation may include a special meeting or workshop.

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## WHO guideline development of paediatric medicines: Points to consider in pharmaceutical development

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World Health Organization (WHO) guidance on the pharmaceutical development of paediatric medicines is being developed in the form of a "points to consider" document by the WHO Expert Committee on Specifications for Pharmaceutical Products. The current draft (Working Document QAS/08.257/Rev.3) will be submitted for adoption to the Expert Committee at its meeting in October 2011 and, hopefully, for final endorsement by the WHO Governing Bodies early next year and, hence, recommendation to Member States and other parties for implementation.

WHO launched in December 2007 its initiative "Make Medicines Child Size" in order to raise awareness and accelerate action to the need for improved availability and access to child-specific medicines. The WHO Model Formulary for Children 2010 provides independent prescriber information on dosage and treatment guidance for medicines based on the WHO Model List of Essential Medicines for Children, first developed in 2007 and reviewed and updated every second year.

The current "points to consider" document is another result of the efforts. The scope of the document is to present information to manufacturers and regulatory authorities on issues that require special attention in the pharmaceutical development of paediatric medicines, including also for use in developing countries. Such information cannot be exhaustive and will need updating along with progresses in our knowledge about development and uses of paediatric medicines. In parallel with this guidance, the Expert Committee has also developed a guideline on the pharmaceutical development of multisource (generic) products (Working Document QAS/08.251/Rev.3).

**Table 1**
Some desirable features of paediatric dosage forms (WHO Report of the Informal Expert Meeting on Dosage Forms of Medicines for Children. December 2008).

| |
|---|
| ◯ Convenient, reliable administration |
| ◯ Preferably ready-to-use formulations |
| ◯ Minimal manipulation by health care professionals, parents or caregivers |
| ◯ Dose and dose volume/weight adjusted to the intended age group |
| ◯ Acceptable and palatable dosage form |
| ◯ Minimum dosing frequency |
| ◯ Minimal impact on life style |
| ◯ Minimum, non-toxic excipients |
| ◯ Transportable and low bulk/weight |
| ◯ Easy to produce and stable in as variety of climates |
| ◯ Affordable |
| ◯ Commercially viable |

Table 1 lists some of desirable features of paediatric dosage forms. Some of these are common to all paediatric medicines, while others address end-user needs in developing countries.

It is important to bear in mind supply chain considerations such as ease of transportation and storage requirements. For example, storage in a refrigerator is not always possible. Lack of access to clean water is an important issue to take into consideration in the development of medicines to be dissolved, diluted or dispersed prior to administration. Regional and cultural differences with regard to preferred taste need to be considered as well as cultural differences in the use of and expectations to a medicine.

Dosage forms that, in general, are likely to prove most suitable, including also for developing countries, and which should be prioritized, are flexible dosage forms such as sachets and tablets that are orodispersible and/or can be used for preparation of oral liquids suitable also for the younger age groups. It is believed that the flexible dosage form design may be used for various active ingredients (APIs) provided that they do not require a precise dose titration or not belonging to the poorly soluble BCS classes. If the medicine can be dispersed in breast milk from the mother, it could potentially be used in very young children (less than 6 months).

For medicines that require precise dose measurement or titration, suitable dosage forms could be based on a platform technology to produce multiparticulate solids such as minitablets and spherical granules/pellets that allow production of dosage forms of varying strength as well as different dosage forms like tablets and capsules, and also dosage forms to be dispersed to form a liquid dose or sprinkled onto food. Platform technology has a potential flexibility for constructing appropriate fixed dose combination products (FDCs).

The WHO recommendation of such solid forms should also be seen in the context of product stability (generally no need for stabilizing agents), production using standard equipment, ease of transportation and low bulk volume/weight.

The WHO guidance document recognizes of course that various routes of administration and dosage forms are considered for the paediatric population. It provides *pro et contra's* for their formulation and use in the paediatric population. Emphasis is given to formulations for oral use, rectal use, parenteral administration, dermal and transdermal administration and inhalation use.

The choice of excipients and their level in dosage forms is a major challenge for the formulation scientist. The use of excipients is driven by functional requirements and should be justified through a risk based assessment taking into account amongst others the factors listed in Table 2.

The added challenge for paediatric medicines compared to adult medicines is that excipients in children may lead to adverse reactions that are not experienced in adult medicines or not seen to the same extent. Reviews on adverse reactions attributed to excipients show however that currently available data of excipient safety are of limited quantity and variable quality. Thus, it is not possible to day to outline specific recommendations