The impact of the Paediatric Regulation on existing medicinal products

Author
Jill Challis, *NDA Regulatory Science Ltd, UK.*

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Abstract
Children are not simply young adults when it comes to medicines. Factors affecting growth, metabolism and development may result in adverse paediatric events even though the drug is safe for use in adults. The aim of the EU Paediatric Regulation was to better protect the health of children in the EU by increasing the availability of medicines intended for children, making information on those medicines widely available and stimulating high quality paediatric research. For currently authorised medicinal products, Articles 45 and 46 of the Regulation have resulted in the ongoing review of existing paediatric data, followed by updates to the product information for a number of medicines. The requirement for patent-protected products to have a paediatric investigation plan (PIP) in place has also resulted in an increase in research into innovative ways of delivering medicinal products to the different age groups from birth to <18 years in adaptable, age-appropriate dose forms. One aspect of the Regulation which combines both the provisions of an age-appropriate dosage form and paediatric updates to the product labelling is the introduction of the Paediatric-Use Marketing Authorisation (PUMA).

This article reviews the impact of the Regulation over the last five years on improving the likelihood for safer and more effective use of existing medicines in children. Specifically, it reviews the changes which have been introduced to product labelling in terms of paediatric dosing and safety information as a result of the Article 45 and Article 46 assessments, and discusses the increasing availability of licensed medicinal products in dosage forms suitable for use in the different paediatric age groups from birth through to adolescents.

Introduction

The implementation of the EU Paediatric Regulation (No 1901/2006 as amended) in January 2007 introduced sweeping changes into the regulatory environment for both new and existing medicinal products. Before implementation of the Regulation there was a scarcity of authorised medicines for children in many conditions despite the medical need. In the absence of paediatric information and inadequate dosage forms, prescribers and pharmacists had little option but to treat children with medicines licensed for adult use. This often resulted in unacceptable risks (eg, under- or over-dosing with inappropriate formulations). One of the main objectives of this Regulation is to increase the availability of medicines intended for use within the paediatric population from 0 to <18 years (including neonates, infants, toddlers, children and adolescents). This is a diverse group with changing physical, metabolic and psychological processes which influence both the efficacy and safety profile of a particular medicine. It is therefore critical that information relating to appropriate dose levels and safety issues, which have been identified as a result of studies conducted in this population, are communicated to the prescriber via SmPC and to the patient (or patient's carer/parent) in the product labelling.

Improvements in product labelling

To address the safety concerns related to the use of existing medicinal products in paediatric patients, Article 45 of the Regulation requires marketing authorisation holders (MAHs) to submit the results of all existing paediatric studies to the regulatory authorities. The objective is to assess these data with a view to including any relevant, useful paediatric information in the product labelling of each medicinal product (SmPC, and PIL). This can further assist a product's safe and effective use in children.

For centrally authorised medicinal products, the Committee for Medicinal Products for Human Use (CHMP) completed the Article 45 assessment of paediatric data on 60 medicinal products and recommended updates to be made to the SmPC for just six of these products.[1,2] In the few instances where information has been added (to sections 4.2 Posology and method of administration; 4.8 Undesirable effects; 5.1 Pharmacodynamics properties; and 5.2 Pharmacokinetic properties), not surprisingly it has tended to reflect the limited nature of the paediatric data available. Examples of updates to two centrally authorised products are described in Table 1.

For products authorised through national, decentralised or mutual recognition procedures, the extent of information received has been enormous (approximately 1,000 active substances). To cope with the workload, there is an ongoing worksharing exercise between EU member states and the assessment is being performed in waves.

In July 2011, the assessment of the data had been finalised for 63 active substances. In the majority of cases existing paediatric data were 'clarified' in the SmPC, particularly in section 4.2 Posology and method of administration.[3] There are a few products where the review of existing paediatric data has resulted in some important updates, particularly with regard to the harmonisation of paediatric information across Europe, and examples of some of these are summarised in Table 2.

In addition to the Article 45 assessment, marketing authorisation holders (MAH) are also required to submit any MAH-sponsored paediatric studies involving the use of an authorised medicinal product, within six months of completion (Article 46 of the Regulation) to the Regulatory Authorities. As would be expected, evaluation of studies submitted through this procedure has been similar to the Article 45 review. A number of SmPCs have been updated (9/60 centralised products and 7/19 nationally authorised products), primarily to sections 4.2, 5.1 and 5.2 as with the Article 45 assessment.[1,2,4] An example of the addition of new safety information to the SmPC of a medicinal product as a direct result of an Article 46 procedure is provided in Table 3.

Thus, the Article 45 and 46 reviews will go on for many years to come and will have a significant resource implication for EU member states.

As a result of the Paediatric Regulation, industry is now required to consider not only if the drug is safe and effective at a particular dose in each paediatric age group, but also what is the most appropriate dosage form for each age group.

Table 1: Outcome of Article 45 review of two centralised products	
Product and indication	**Labelling updates**
Perflutren (Optison) Contrast agent for use in patients with suspected or known cardiovascular disease	CHMP concluded that although demonstrating an effect that appears to be similar to that seen in adults, the submitted data (in the form of a study) did not allow any conclusions on posology in children and adolescents. However, safety data were available in 42 children, aged eight months to 19 years, which indicated that the safety profile of Optison is similar in this age group when compared with adults. As this information could be of use to the prescriber, the CHMP recommended that sections 4.2 and 5.1 of the SmPC were amended to reflect these observations.[5]
Interferon beta-1a (Avonex) Multiple sclerosis	CHMP recommended an update of the product information (sections 4.2, 4.8 and 5.1) to reflect results from one completed paediatric study; a trial treating 16 multiple sclerosis patients under the age of 16, with 15 micrograms IM Avonex once per week. The updates included the statement in section 4.8: 'Limited published data suggest that the safety profile in adolescents from 12 to 16 years of age receiving AVONEX 30 micrograms IM once per week is similar to that seen in adults'.[6]

Table 2: Outcome of Article 45 review of three nationally approved products	
Product and indication	**Labelling updates**
Amoxicillin Moderate-spectrum, β-lactam antibiotic used to treat bacterial infections. In clinical use in Europe and globally for almost 20 years; it has been extensively used in paediatric patients of all ages.	As a result of the Article 45 procedure it was recommended that the paediatric posology and other information relevant for paediatric use of amoxicillin should be harmonised. Specific wording relating to paediatric use has been introduced into sections 4.2 Posology, 4.4 Precautions & warnings and 5.2 Pharmacokinetic properties, of the SmPC. The indications still vary to some extent between member states, but this was not considered an issue for the Article 45 procedure.[7]
Baclofen Centrally acting skeletal muscle relaxant commonly used for the symptomatic relief of severe chronic spasticity associated with a variety of neurological conditions, (eg, spinal cord injury, cerebral palsy, multiple sclerosis, amyotrophic lateral sclerosis).	The Article 45 assessment identified inconsistencies between member states in relation to the indications and the dosage in paediatric patients. The assessment concluded that the data justified the use of oral formulations of Baclofen (tablets and syrup) in the entire paediatric population for symptomatic treatment of spasticity. The dosing regimes in the SmPCs/PILs were standardised across the EU to reflect the current clinical evidence of optimal treatment with Baclofen. The assessment also resulted in extension of the use of the intrathecal dosage form to patients older than four years of age. For children younger than four years of age, intrathecal use was not recommended due to insufficient data on safety and efficacy. Sections 4.1, 4.2 and 4.4 were updated.[8]
Gentamicin sulphate Broad spectrum aminoglycoside antibiotic, used to treat many types of bacterial infections, particularly those caused by Gram-negative organisms. In clinical use for almost 40 years with most indications approved for adults, children and neonates.	As a result of the Article 45 procedure it was recommended that updates were made to the SmPC including sections 4.1, 4.2, 4.3, 4.4 and 5.2. Safety updates included harmonisation of statements relating to once-daily dosing in newborns, infants and children; monitoring advice in relation to serum concentrations of gentamicin in newborns; and warning statements in relation to ototoxic and nephrotoxic potential.[9]

Table 3: Outcome of Article 46 review of a nationally approved product	
Product and indication	**Labelling updates**
Kytril (granisetron) For the prevention or treatment of nausea and vomiting induced by cytostatic therapy.	The MAH submitted a study report of a trial in the prophylaxis of postoperative nausea and vomiting in children aged two to 16 years and a Drug Safety Report on QT interval prolongation. Unfortunately, because of trial design issues, the submitted efficacy data did not warrant inclusion in the product information. However the Article 46 assessment recommended that the findings regarding QTc-interval prolongation should be reflected in the product information (SmPC, PL) in sections 4.4, 4.5 and 4.8.[10]

Table 4: Examples of solid oral dosage forms for use in the paediatric population[11]

Solid oral dosage form	Medicinal product	Indication	Target paediatric age group
Dispersible tablet	Coartem Dispersible (Novartis). Artemisinin-based combination treatment	Uncomplicated *P. falciparum* malaria	Infants (from 5kg), children and adolescents/adults (35kg and above)
Multiparticulates (small particles diameter <2mm, eg, granules or pellets)	Artequin Paediatric (Mepha). Artesunate and mefloquine pellets provided in stick packs; can be applied directly into the mouth	Treatment of acute, uncomplicated malaria in small children	Children with a body weight of 10-20kg
Mini-tablets (<3mm in diameter)	Lamisil Oral Granules, (Novartis). Predispensed in stick packs and capsules for sprinkling on soft food	Treatment of fungal infection of the scalp (tinea capitis)	Children and adolescents ≥4 years old
Chewable tablets	Singulair 4mg chewable tablets (Merck Sharp & Dohme)	Asthma	Children and adolescents from two to 14 years
Oral wafers or orodispersible strips (thin films of typically 2-8cm^2 area and 20-500µm thickness).	Setofilm (Ondansetron 4mg and 8mg) (Applied Pharma Research & Labtec & MonoSol Rx).	Prevention and treatment of chemotherapy, radiotherapy and post-operative induced nausea and vomiting.	Infants from six months, children and adolescents.

Table 5: Projects funded through the 4th call within FP7[2]

Study identifier	Study objective
HIP trial	Evaluates the efficacy, safety, pharmacokinetics (PK) and pharmacodynamics (PD) of adrenaline and dopamine in the management of neonatal hypotension in premature babies, and to develop and adapt a formulation of both, suitable for newborns, in order to apply for a PUMA.
DEEP	Aims to evaluate PK and PD of deferiprone in two- to ten-year old children in order to produce an approved PIP to be used for regulatory purposes. (Current statement in section 4.2 of SmPC: 'There are limited data available on the use of deferiprone in children between six and ten years of age, and no data on deferiprone use in children under six years of age'.)[12]
TINN2	Aims to evaluate PK and PD of azithromycin against *Ureaplasma* and in bronchopulmonary dysplasia (BPD) in neonates.

Provision of age-appropriate dose forms

The draft Guideline on Pharmaceutical Development of Medicines for Paediatric Use (EMA/CHMP/QWP/180157/2011),[13] which was recently released for consultation, provides useful advice to industry on the development of age-appropriate dose forms. The guideline is aimed not just at the pharmaceutical development of new medicinal products, but also the improvement of formulations of existing products which are currently being used either off-label or within licence in children. Importantly, the guideline states that pharmaceutical companies should re-evaluate all of their products on the market, to ensure that they are 'state-of-the-art' and meet the requirements. In fact, the guidance goes one step further by requesting that this evaluation should be done within a period of five years from the date the guideline comes into operation. In relation to existing formulations, there is a clear message that simple 'manipulation' of the adult formulation for use in children will not normally be acceptable for marketing authorisation. The EMA's Paediatric Committee (PDCO), which was set up to implement aspects of the Regulation, is looking for well thought out, justified pharmaceutical development plans. The suitability of each dosage form now needs to be fully justified in relation to the age of the patient, disease, duration of treatment, 'therapeutic window' of the medicine and risks associated with the dose form itself (eg, risk of choking on a tablet).

As a direct consequence of the regulatory requirement to have a paediatric investigation plan (PIP) in place for authorised medicinal products which are still patent-protected (or covered by a supplementary protection certificate), there are many more age-appropriate dose forms now in development for existing products. Industry and academia are putting a lot of thought and research into innovative ways of delivering medicinal products to all the different age groups in one adaptable, stable dosage form (eg, the use of mini-tablets and oral wafers which can be taken in young infants, children and adolescents).[11] This will take some time as formulation development is not a quick process, but it is inevitable that the number of medicinal formulations and dosage forms available to infants and children will increase over the forthcoming years. Table 4

provides examples of different solid oral dosage forms for children.

One aspect of the Regulation which combines both the provision of an age-appropriate dosage form and updates to the product labelling to support the safe use of a product in paediatric indications, is the introduction of the Paediatric-Use Marketing Authorisation (PUMA).

Paediatric-Use Marketing Authorisation (PUMA)

A PUMA may be requested for a medicine which is already authorised but no longer covered by intellectual property rights (ie, patent or supplementary protection certificate), and which has been exclusively developed for use in children. A prerequisite for a PUMA is a paediatric investigation plan (PIP) which must discuss the potential use of the product in all paediatric age groups.

Linked to the PUMA is the EU funding for studies into off-patent medicines. This funding, which has been made available since 2007, is provided through the EU Framework Programmes for Research and Technological Development (FP7), and covers the development of off-patent medicinal products with a view to the submission of an application for a PUMA. In order to ensure that funds are directed into research of medicinal products with the highest need in the paediatric population, the PDCO adopted a priority list of off-patent products for which studies are required.[14] In particular, the development of age-appropriate formulations and strengths and the generation of data in neonates are considered to be of high priority. As a result, in 2010 the three projects listed in Table 5 were selected to be funded for approximately €16 million.

In May 2011, the CHMP adopted its first positive opinion for a PUMA which was for Buccolam (midazolam), intended for the treatment of prolonged, acute, convulsive seizures in paediatric patients from the age of three months to 18 years.[15] The PIP for Buccolam was approved on 11 August 2009. Buccal midazolam has been used for some time as an unlicensed medicinal product by doctors and carers for the treatment of prolonged epileptic seizures, clusters of epileptic seizures and status epilepticus. Previously it was available only as a 'special order' from special manufacturers or importing companies.[16] The licensing of this product introduces evidence-based treatment guidelines via the SmPC, ensuring that doctors prescribe the correct dose for a specific paediatric indication and use the appropriate pharmaceutical form in these age groups. It is expected that these medicines will be preferentially prescribed to paediatric patients and the use of unapproved and untested medication will decrease.

Unfortunately, uptake of the PUMA by industry has been poor, with only 1% of PIP applications being related to PUMAs (at the end of June 2011, there had been 26 PUMA applications submitted and seven PDCO opinions adopted on related PIP applications.[17] In hindsight, the incentive of ten years of data protection afforded to PUMAs may have been overestimated, as the protection only relates to the new paediatric data and the product often remains open to generic competition. The EMA and EU Commission have openly expressed their disappointment and concern over the low number of PUMA applications being submitted. However the Commission does not intend to update the legislation to improve these aspects in the near future, so we are unlikely to see an increase in the number of these applications.

In conclusion, it is encouraging to note for all stakeholders including Regulators, the pharmaceutical industry, prescribers and importantly patients, that the implementation of the EU Paediatric Regulation has begun to have an impact on improving the labelling and availability of age-appropriate dose forms of existing medicines which can be used in the different age groups of the paediatric population. The number of paediatric clinical studies performed and planned in the EU has been increasing rapidly since 2007 and so has the accumulation of evidence regarding adequate dosing, efficacy and safety. Incorporation of this information into the product labelling represents an improvement in the communication of evidence-based treatment. The EU initiatives complement the existing US FDA paediatric legislation, which was established more than ten years ago, and also the World Health Organisation (WHO) initiatives, 'Better Medicines for Children' and 'Make Medicines Child Size'.[18,19]

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