



EFGCP Children's Medicines Working Party 2nd Annual Conference on
How can the EU Paediatric Regulation meet Expectations from the Beginning?
Management Centre Europe, Brussels, Belgium – 5 October 2006

Minutes

Executive Summary

This event took place a few months before the European Paediatric Regulation is published in the EU Official Journal. Speakers representing EU commission, EMEA and FDA expressed their high expectations, emphasized the preparedness of the EMEA to deal with the expected high first wave of paediatric Scientific Advice & PIPs. They also expressed the will of FDA and EMEA to closely work together in their endeavour to include children into the global drug development process. Pharmaceutical industry speakers expressed their expectation that the necessary implementation guidelines will be available soon, as well as some concerns for the expected operational challenges. Patient organizations emphasized their expectations. Several national Academic paediatric research networks as well as the disease-specific PRINTO network described their level of preparedness. Presentations the two EU-wide coordination networks MediChildren and TEDDY were given. Compared to the first conference in 2005, there was a high level of understanding many delegates of the complexity of the US and the EU legislations that aim at facilitating paediatric pharmaceutical research. In the working groups, people relatively new to this area had the opportunity to ask, challenge, learn and contribute. The conference provided a forum where questions and expected hurdles were addressed with an openness that is rarely found. Discussion was vivid and lively especially in the interactive working groups. The conference concluded with a positive, optimistic, but also realistic attitude towards the future of European paediatric research.

EU Commission Expectations

The European Commission, as authors of the proposal for a paediatric regulation presented the main measures and the priorities for implementation over the first year. Based on the impact assessment¹ and analysis of the final text of the paediatric regulation, the European Commission expects a major strengthening of European Paediatric Research through the EU paediatric regulation. In measurable terms, it is anticipated that the regulation will lead to reduced hospitalisation of children, fewer deaths, an improved quality of life (QoL), as well as economic benefits to society.

EMEA Preparations for the Paediatric Regulation

The EMEA is well advanced in its internal preparation. Projects are dealt with according to legal deadlines. A further prioritization of projects is not planned, but available resources may be a limiting factor. The EMEA expectations regarding strengthening of European Paediatric Research and benefit to child health care are high.

¹http://ec.europa.eu/enterprise/pharmaceuticals/paediatrics/docs/extended_impact_assessment_final_3_september.pdf

A National Competent Authority's view: Finland as an example

In 2004, Finland's National Agency for Medicines (NAM) made a strategic decision to focus on medicinal products for pediatric use and on biological products. It was based on the assumption that efforts to centralize the regulatory work regarding new innovations will continue in EU, and that rational, high quality and resource saving co-operation requires sensible sharing of duties and expertise among authorities. Since 2003, the NAM staff has included 2 paediatricians and one paediatric anaesthesiologist. The work in NAM is facilitated by the fact that there is a lot of paediatric expertise in the country. For decades, health care professionals have actively been involved in paediatric research. For example, in 2004 alone over 35 000 children took part in vaccine trials and almost 30 000 children were included in other paediatric drug trials. There is a well established infrastructure with a net of 'well baby' clinics across the country, and Finnish Paediatric Clinical Trials network has just started its work. Training of paediatricians is well established, and the number of practising paediatricians is high in the country (590/ population of 5 million). The general public is well informed, and has trust and a positive attitude towards research.

There is a lot of preparatory work that needs to be done by all NCAs across Europe, as well as by academia and pharmaceutical industry. Awareness of the paediatric regulation has to be increased within each institute, and also among general public. It is very important to take all the obligations of the regulation into account when recruiting or training new staff members and when building strategies for work sharing.

National competent authorities (NCAs) will have to

- check compliance with agreed upon paediatric investigation plan (PIP) with or without agreement to defer
- assess efficacy, safety, and quality of medicines studied in children according to the PIP for marketing authorisations for medicines not going through the centralized procedure
- ensure that product information include paediatric information
- assess quality, efficacy and safety of PUMA applications
- demand the risk management plan, if needed
- request from Marketing Authorisation Holders (MAHs) additional reports on the effectiveness of risk minimisation systems and the results of such studies performed.

EU member states (MSs) have to

- give to the Commission information on measures they have enacted to support paediatric research within one year from the regulation's entry into force
- collect available data on paediatric use of medicinal products
- assess all existing paediatric studies of authorized products that have been submitted by the MAH
- require from MAHs to submit results of all MAH sponsored studies in children within six months after completion

A Pharmaceutical Industry's Perspective

Industry has supported the preparation of the EU paediatric regulation. Industry is aware that expectations from the public are high towards industry, and industry should therefore try hard not to fail them. Industry hopes that the EMEA Paediatric Committee will find a way to use the expertise in paediatric drug development that exists in pharmaceutical industry. Regarding the planned paediatric database, industry agrees about the public part, but is concerned about confidential information in relation to competitiveness. Several national European networks exist already. As an example, the UK MCRN (Medicines for Children Network) has received considerable funding from the UK government

Working Group 1: Paediatric Investigation Plan (PIP) Requirements and Structure

There were many participants, mainly from the pharmaceutical industry. At first there were some practical technical questions concerning submission, deadlines and transitional measures of the PIP. There was a consensus among industry participants that submission of the PIP after Phase 1 studies in adults is too early. At least dose-range data would be needed not only in healthy volunteers but also in adult *patients*. In addition before going to children, safety data in adults are required as well. There was a proposal that the PIP could be submitted as soon as therapeutic dose range data are established in adults or if there is at least a proof of concept. It was highlighted that the submission of a PIP is not equivalent to starting the paediatric studies. For products only aimed at children for example, early submission is needed. Anyway, the PIP should be the subject of a continuous process of dialogue with the Paediatric Committee.

With regard to the scope of the PIP, it was agreed that the PIP should cover all aspects of development including additional non clinical studies if appropriate and the formulation although at this early stage since only the properties of the substance would be known, the applicant would only have some idea of what type of formulation would be feasible. There was a discussion concerning the indications for medicines in children. There are examples of drugs in adults (sildenafil – erectile dysfunction) that can be used in children for other indications (pulmonary hypertension). What would be a waiver at the onset can become an indication in children after having studied the mode of action of the drug and developed it in a different indication in adults. One suggestion was that the request could include any potential paediatric indication(s) in view of the mechanism of action of the product, but if outside of the sought adult indication, these won't be part of the final opinion on PIP.

Finally there was a discussion on which type of studies could be considered "significant" for the reward.

Working Group 2: Role and Procedural Details of EMEA Scientific Advice Working Group & Paediatric Committee

A helpful overview of the new EMEA Scientific Advice (SA) procedure was provided. The standard procedure takes 70 days and the scope includes (but is not limited to) Quality, Safety and Efficacy issues. Unlike for adult indications, SA pertaining to paediatric development plans is free of charge (from the day the Paediatric Regulation comes into force). SA can be sought by both commercial- and academic sponsors but it should be noted that it is not binding on the Agency. Though it is expected that most SA requests will probably be submitted after the approval of a Paediatric Investigation Plan (PIP), i.e., in order to "fine-tune" study designs, a SA request can be submitted before a PIP request is finalised for submission to the Paediatric Committee (PDCO).

The Scientific Advice Working Party (SAWP) currently has no 'in-house' paediatric expertise. In order to ensure consistency, it is foreseen that scientific advice requests concerning paediatric studies will be referred to the PDCO (once this new committee has been set up). However, there will be a "gap" between the entry into force of the Paediatric Regulation and the point where the PDCO becomes operational. During the interim period, SA requests related to PIPs will be referred to the current Paediatric Expert Working Party (PEG). Using the SA route may be particularly relevant in case of "mixed" advice requests (concerning both paediatric and adult indications) and for academic investigator networks (if there is a possibility of a future marketing authorisation application). The importance of including patient representatives when soliciting external expertise was underlined.

The EMEA workload for processing proposed PIPs and paediatric SA requests is expected to be "more than very high". Based on companies' survey, some 300 PIPs or more may be submitted to Agency in 2007. In addition, a number of paediatric SA requests will have to be added to that. Regardless, there is no legal basis for prioritising PIPs or SA requests according to their nature or urgency. To use the 'parallel' SA procedure (EMEA and FDA) in order to seek convergence between EU and US development programs is an attractive possibility although it is probably not realistic to expect the programs to be absolutely identical in most cases. Last and given the complexity of the procedures, the working group suggested that a description of the respective roles of the responsibilities of the SAWP and PDCO (or perhaps a 'decision algorithm' designed for sponsors) available on the EMEA website would be useful.

Working Group 3: Challenge of Consistency between FDA and EU Paediatric Requirements

The meeting started with a presentation on the current situation in USA and International aspects of paediatric clinical trials. The following discussion focused on consistency between FDA & EMEA on Paediatric Requirements.

- There is high-level desire & commitment in EMEA and FDA to have **one compatible** paediatric plan.
- There are potential issues which regulatory authorities do not control. This may lead to differences in the paediatric program in US and Europe. E.g. ethics committees may have a different view in US and Europe. Recently an USA IRB (ethics committee) did not approve a study in an FDA-approved paediatric program.
- There may be potential changes in the US laws when the paediatric legislation goes through the re-authorisation process in 2007.
- Regarding the possibility of a double reward both in the US and the EU for paediatric programs ongoing 2007, EMEA and EU have no objection as both systems do not take other rewards into consideration.
- FDA and EMEA agreed that the most important step from the industry to minimize the risk for differences in the paediatric programmes between US & EU it to send the paediatric programs simultaneously to FDA and EMEA. This will make it possible to have discussion between companies, FDA & EMEA and allow FDA & EMEA to reach consensus and potentially have one global paediatric program.

The Netherlands Medicines for Children Research Network (MCRN)

In the Netherlands there has been recently a lot of activity resulting in the creation of a Netherlands MCRN. It is clear that the Dutch government, the pharmaceutical industry and the deans of all medical universities are supportive of this initiative. The idea is to have a one-stop-shop for investigators and industry to go to with research questions. Scientific rigor, feasibility and ethics of the proposed research will be examined and if all aspects are viewed favorably there is an infrastructure available consisting off academic and non-academic paediatric wards. That infrastructure will guarantee the conduct of the study according to GCP in a timely fashion. That way both investigators and industry will get the results of their study proposal in a timely fashion.

PAED-Net (German Paediatric Clinical Trials Network)

The German PAED-Net is an already established network of experts with the infrastructure to professionally plan and perform multicentre paediatric studies in six paediatric units and is part of the German Coordination Centres for Clinical Studies (KKS). They are located in Cologne, Freiburg, Heidelberg, Leipzig, Mainz and Muenster, are coordinated in Mainz.

The KKS network with 12 Coordinating Centres for Clinical Trials and more than 307 employees (interdisciplinary team: clinical pharmacologists, paediatricians, biostatisticians and informatics, clinical data manager, study nurses, monitors) provides scientific and operational support for clinical trials throughout Germany. KKS and PAED-Net offer planning, conducting and evaluating clinical trials in compliance with internationally accepted quality standards.

PAED-Net studies are conducted since 2002 in the disease areas of intensive care, gastroenterology, immunology, preventive medicine, allergology, metabolic diseases, cardiology, nephrology, diabetes, pulmonology, dermatology, oncology and neurology.

Further progress of PAED-Net will be the implementation of paediatric trial experience in all 12 Coordination Centres for Clinical Trials and the support of building up a pan-European network of clinical excellence for the execution of European studies in the paediatric population. The PAED-Net structure could serve as a model for building-up a European network efficient networking and could provide:

- organisation model
- communication structures
- study logistics
- tools and examples of agreements and contracts
- paediatric SOPs including templates for patient information consent and assent

- pharmacovigilance procedures in trials
- covering national legal aspects concerning application and reporting to authorities and ethics committees
- training and education curricula
- IT-structure for study data base
- qualified study centres in Germany
- recruitment procedures
- transfer of knowledge & experience in planning and conducting clinical trials

Paediatric Research Network Situation in Poland

Marek Migdal explained that a network is in the building up phase and is expected to be established in 2007 using the Children's Memorial Health Institute in Warsaw as a base. A short description on the facilities of the Institute was presented. It is the largest paediatric hospital in Poland and is involved in numerous research grants and multicentre trials.

MediChildren & EU Networking

MediChildren aims at a pivotal role in coordinating EU-wide paediatric research and started as an informal network to prepare for the EMEA network. A French network (RIPPS) has received funding from the French government through the Medical Research Institute. It offers connections and expertise to a multitude of French and European paediatric academic research centers.

TEDDY

TEDDY has received 4.45 Mio € from EU DG research as a network of excellence. Based in Italy, it coordinates a number of European academic centers and is funding several work package projects, including detailed documentation of off-label drug use in children in Europe. A first paper "Medicines for children licensed by the European Medicines Agency (EMA): the balance after 10 years", has been published online in the European Journal of Clinical Pharmacology. Due to high workload, the representative of TEDDY had to cancel its scheduled representation and John van den Anker kindly presented some information on the TEDDY project on their behalf.

PRINTO (Paediatric Rheumatology International Trials Organisation)

www.printo.it / www.pediatric-rheumatology.printo.it

The paediatric rheumatic diseases (PRD) are rare conditions associated with substantial morbidity, consequence on the quality of life, and costs. Many studies on the impact and outcome of PRD have shown that this group of diseases is associated with important morbidity and therefore should be the target of intense research aimed at finding new more effective therapies. However, in the past it has always been very difficult to perform controlled trials in PRD for two main reasons: a) the rarity of the diseases and therefore the need to perform large international studies in order to gather sufficient patients to obtain clinically and statistically significant results in a relatively short-time; b) the difficulty in securing funding since the pharmaceutical industry has little interest in the small paediatric market. This picture changed substantially in recent years for two main events: 1) the organization of large international networks for clinical trial in PRD; 2) the approval of the pediatric exclusivity by the FDA.

In 1996 PRINTO was founded and initially included 14 European countries (now 47 countries with more than 180 centres world wide). PRINTO is composed of academic, clinical centers actively engaged in the care of children with PRD. PRINTO has four main vertical structures: the Advisory Council that provide leadership and guidance for PRINTO research activities; the International Coordinating Center whose main task it to facilitate the flow of logistic and scientific details needed to design, launch and manage multi-centered, multi-national, collaborative studies; the National Coordinating Centers (one per country) whose tasks are to facilitate the participation of the greatest number possible of individual centers and to provide the translation of all the forms to be completed by the parents/patients; and finally the Individual centers that constitute the main support structure to obtain a critical mass of data for on-going and future research.

EU Plans to Finance Off-Patent Paediatric Medicines Research

The EU commission plans to finance research on the paediatric use of off-patent medicines as per the Paediatric Regulation, through the 7th Framework Programme. Detailed plans will be published in due course. The FP7 Health work programme will also include support of developing paediatric formulations of drugs against HIV, Malaria and TC; research in the treatment of the combined forms of diabetes mellitus; research into knowledge gaps in pregnant mothers with malaria; and innovative approaches for neonate medicines and vaccines.

Working Group 4

The EU CT Directive has strongly affected clinical research in Europe. Its implementation has considerably increased the amount and complexity of formal and operative requests with which the study centres have to deal and for which often the necessary know-how is underdeveloped. This holds especially true for paediatric clinical trials, including multicentre ones. The following key issues were discussed:

- Informed consent: the signature of both parents is often an almost insurmountable challenge
- Pan-European Ethics Committee: In international multicentre paediatric trials, it would be highly desirable to have one European Committee that could decide on a proposed study protocol, instead of collecting the feedback from 25 different ethics committees. This would facilitate enormously paediatric clinical research in Europe
- The necessary infrastructure for paediatric research in Europe needs to be built up. At present it is not sufficient
- Insurance premiums for clinical trials have significantly increased and have made paediatric research for paediatric academia very difficult and in some instances even impossible. A desirable solution would be a pool insurance on EU level (for example paid jointly by pharmacy industry association, EU member states, University Hospitals)
- The definition of the sponsor of a clinical trial has proven to be quite confusing.
- For paediatric studies standard operating procedures (SOP) are requested. A harmonization for many SOP's would be desirable.
- Funding of investigator initiated clinical trials is almost impossible since the financial support from Universities is low. National and EU funding opportunities for clinical trials including in particular orphan drugs are urgently needed.

Working Group 5: Expectations from Industry on Paediatric Networks and their Level of Preparedness

- Industry expects competitive research networks. Academic networks must be competitive against each other as well as against CROs
- Academic researchers have less experience with GCP compliant studies
- Realistic feasibility testing is necessary regarding recruitment capacities
- Networks also expect collaboration for basic research

Working Group 6: EU Academic Paediatric Research

Working group 6 discussed the many issues to be addressed as paediatric research in Europe prepares to meet the challenges of the new legislation. Present in the discussion group were representatives from all sectors, academic, regulatory health authorities and industry. All agreed that the common goal is to provide meaningful product information for the safe use of medicines for children. The group listed several areas of key interest

- Pediatric Research covers different types of clinical trials, the purely academic, the purely regulatory or often a mixture of both within a given protocol. It is important for the broad community to understand that paediatric research requires its own infrastructure and there are limits to the ability of adapting an adult clinical trial infrastructure
- Networks can be generic or disease specific, and in Europe many are in the process of being established. The challenge will be to ensure that these networks are set up in collaboration and not in competition with

each other. There was also discussion of the role of a European Network that would enable uniformity of investments, standards of care and training.

- Training was a major concern as paediatric research programs are established. There was agreement that national training efforts for paediatric clinical trials should be supported with European training conferences with participation from all sectors [academic, industry and regulatory authorities]. GCP compliance and training was mentioned specifically.
- Funding will remain a main concern as new networks become established. How will sufficient funds be assured? There is a need for continued awareness both at a national level as well as within the European Framework.
- Academic research needs an assured source of funding. Basic research is a cornerstone of all work and is often the hardest to fund. Data generated from such research should be shared to advance understanding of normal childhood development as well as to create opportunities to minimize the numbers of trials needed in children.

Report from Working Groups & Plenary Debate

After the consecutive presentations by the 3 working groups, no additional comments were provided, but there was the feeling that stopping for discussion after each report would have been useful. Next year's meeting will allow discussing each working group's presentation

©2006 EFGCP

For any information, contact:

Klaus Rose, Chair, EFGCP Children's Medicines Working Party

Klaus.rose@efgcp.be

EFGCP Secretariat

Square de Meeûs

Rue de l'Industrie, 4

B-1000 Brussels - Belgium

Tel: +32.2.732 87 83

Fax: +32.2.503 31 08

E-Mail address: secretariat@efgcp.be

Website: www.efgcp.be