16.3. Survey on all existing paediatric uses

One of the legal requirements of the Paediatric Regulation was the collection of available data on all existing uses of medicinal products in the paediatric population. In accordance with Article 42 of the Regulation, the PDCO/EMA requested data from the 27 EU Member States2. The 3 EEA states which are not EU Member States (Iceland, Norway and Liechtenstein) were also invited to provide data.

The majority of the submitted data focused on the existing off-label use in children; the few datasets referring to the existing authorised use of medicines are therefore difficult to extrapolate.

The analysis of these data was subject to a number of limitations, due to format heterogeneity in the submitted data from different Member States, many datasets could only be considered representative for specific paediatric subsets in the different individual countries (e.g. only OTC setting, only hospital, different age groups not equally covered etc.). Some Member States did not submit any data. Several datasets used the terms authorised, unauthorised and off-label use in different definitions. Most datasets could not link the use to treatment of a specific condition.

Both hospitalised children and out-patients are frequently treated with medicines used outside the terms of their marketing authorisation. Higher rates were reported in the premature (up to 90% of prescribed medication) and term neonates and in infants, as well as in patients having serious conditions and being admitted in the intensive care units (both neonates and paediatric). Medicines are mainly used "unapproved" for the treatment of children, with lower figures for prophylactic uses. Not surprisingly, there are differences with regard to the unapproved medicines use across the EU, partially explained by different prescribing habits, but also by the regulatory status (approved or not, in all or some subsets) of the medicinal product in different countries.

The most frequent medicines used off-label and unauthorised belong to the following therapeutic classes: anti-arrhythmics, antihypertensives (rennin-angiotensin inhibitors and beta-blockers), proton pump inhibitors and H2-receptor antagonists, antiasthmatics, and antidepressants (mainly selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and tricyclic antidepressants). A high rate of off-label use of oral contraceptives was encountered in adolescents, mainly reported in Scandinavia. There is extensive off-label use of antimicrobials (macrolides, beta-lactamines plus beta-lactamase inhibitors and carbapenems) in very young children. Corticosteroids (dexamethasone) are frequently reported to be used off-label in the systemic treatment of very young children. Some steroids for systemic use (e.g. dexamethasone) are not even authorised in some countries (Norway). Most other steroids used off-label in children were topical medicines for dermatologic use. There is a need for clinical trials and supporting evidence for safety and efficacy of anti-asthmatics in children, especially since long term safety concerns were recently reported for the long-acting beta agonists (LABA). This is all the more important as asthma affects principally children. The use of anti-infectives requires supportive evidence in the younger age groups. Although scarce, the data submitted confirm that the neonates, in particular preterm neonates, have high unmet needs. The future will have to address those needs through dedicated trials despite the feasibility issues.

The analysis of the pharmaceutical forms shows that both oral and parenteral formulations are being used unauthorised or off-label, pointing out at a common reason which is the lack of appropriate dosages and strengths for the treated age groups.

EMA/PDCO assembled a comprehensive report on this data which is also available on the EMA website. This review is not exhaustive and analysed very heterogeneous data. However, it is clear there are wide unmet needs everywhere in Europe. The outcome does not provide sufficient information on safety.

These data among others are currently also used to revise the inventory of paediatric therapeutic needs in the Paediatric Inventory Working Group of PDCO. This effort is aiming to update information to fulfil the requirements of Article 43 of the Paediatric Regulation, that is, to define research priorities to improve information on use of medicines in paediatrics based on prevalence, seriousness and availability and suitability of alternative treatments.

[2] http://www.ema.europa.eu/pdfs/human/paediatrics/5756962007en.pdf

17. Additional data: Increased information on medicines used in children

17.1. EMA / PDCO workshops on paediatric medicine development

The slides presented for discussion and outcomes are available here: http://bit.ly/H5Fx4W.

Table 27: Scientific workshops conducted specifically on the development of paediatric medicines

No.	Topic	Date	Stakeholders participating (approximate participant number)
1	Ethical considerations for paediatric trials - how can ethics committees in the European Member States and the Paediatric Committee at the European Medicines Agency work together?	29-30/11/2011	Pharmaceutical industry, Ethics committees, PDCO, EMA, European regulatory network experts (95)
2	Expert meeting on clinical investigation of new drugs for the treatment of chronic hepatitis C in the paediatric population	04/04/2011	
3	High-grade glioma expert group meeting	03/12/2010	Paediatric neuro-oncologists, adult neuro-oncologists, neuro-surgeons; biologists; pathologists; experts from PDCO, SAWP and COMP; members of FDA (30)
4	Expert group meeting on paediatric heart failure	29/11/2010	
5	Paediatric rheumatology expert group meeting	17/11/2010	
6	Expert meeting on paediatric gastroenterology and rheumatology	28/06/2010	
7	Expert meeting on neonatal and paediatric sepsis	08/06/2010	
8	Expert meeting on specific immunotherapy	18/01/2010	
9	Paediatric rheumatology expert group meeting	04/12/2009	
10	Paediatric epilepsy expert group meeting	01/09/2009	
11	Meeting of the paediatric diabetes mellitus expert group	17/04/2009	
12	Meeting of the paediatric human immunodeficiency virus (HIV) expert group	26/05/2009	
13	European Medicines Agency workshop on modelling in paediatric medicines	14-15/04/2008	
14	Workshop on FP7 and off-patent medicines developed for children	06/06/2007	

18. Additional data: Other projects necessary for the implementation of the Paediatric Regulation

18.1. Literature related to the Paediatric Regulation

The following key words and limits were used in various combinations to identify scientific publications directly related to the implementation of the Paediatric Regulation or scientific publications on data that explicitly respond to or address the Paediatric Regulation by providing data or methods. The abstracts of literature search results were manually reviewed and relevant publications were categorised by authors' affiliation to either external stakeholders or to the EMA and / or PDCO. The found literature is listed in section 10. "References".

PubMed:

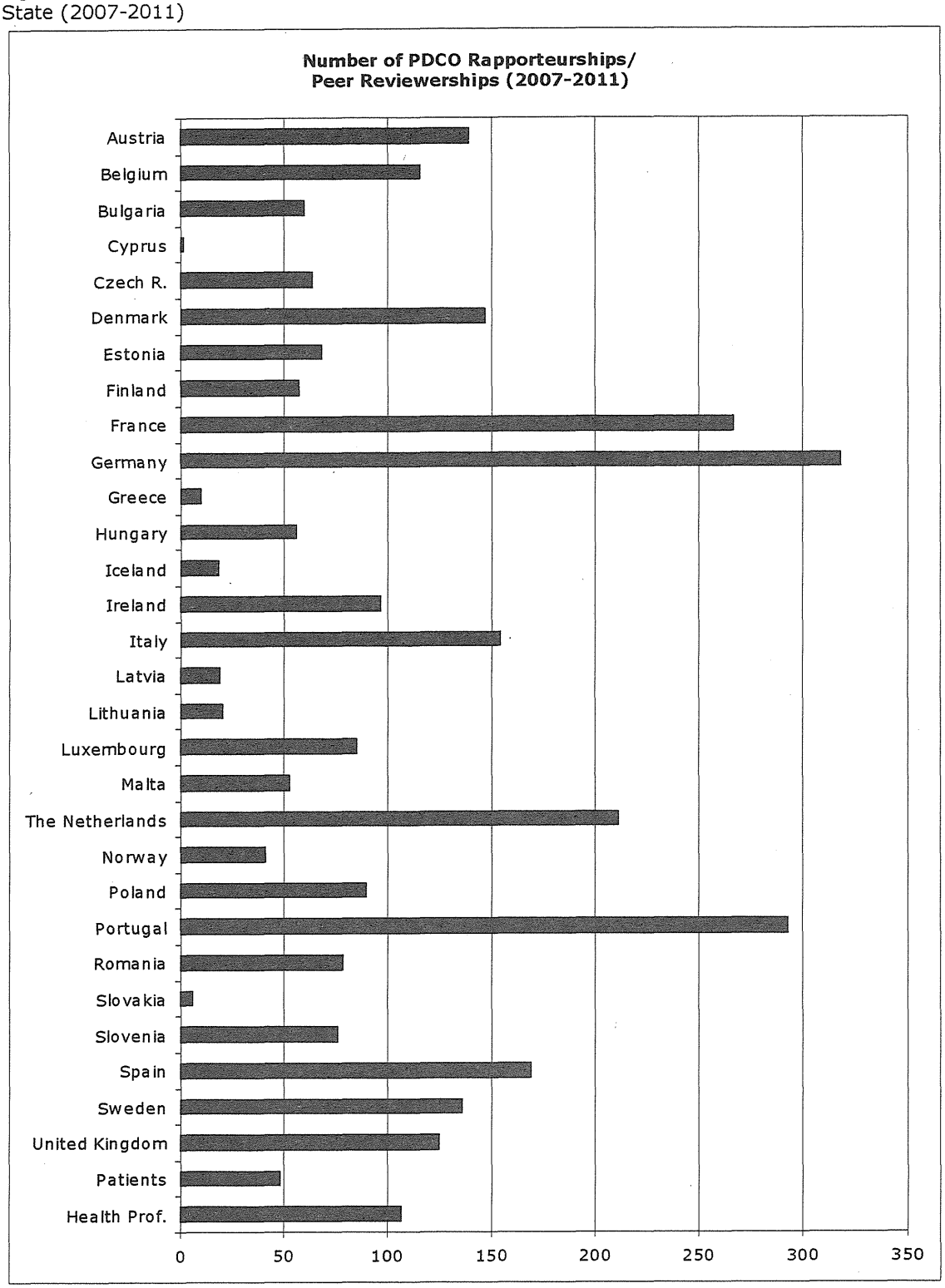
- "Paediatric regulation" OR "Pediatric regulation" OR "Paediatric legislation" OR "Pediatric legislation"
- ("2007/01/01"[PDAT] : "2012/01/31"[PDAT])
- "Clinical trials"[All Fields], "Paediatric trials"[All Fields], "Pediatric trials"[All Fields]
- ("Child"[Mesh] OR "Infant"[Mesh] OR "Infant, Newborn"[Mesh]), (child* OR pediatr* OR paediatr*)
- "Europe"[Mesh], "European Union"[Mesh], "european regulation", "european legislation", "Legislation as Topic"[Mesh], "Legislation, Pharmacy"[Mesh], "Legislation, Drug"[Mesh]
- "Pharmaceutical Preparations"[Mesh]

Embase:

- ("paediatric regulation" or "pediatric regulation" or "paediatric legislation" or "pediatric legislation").mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
- limit 2 to yr="2007 - 2011"
- exp clinical trial/ or exp "clinical trial (topic)"
- (infant <to one year> or child <unspecified age> or preschool child <1 to 6 years> or school child <7 to 12 years> or adolescent <13 to 17 years>))
- *Europe/ ("european regulation" OR "european legislation") {Including Related Terms}, *regulatory mechanism/

19. Additional data: Resources used by the Member States

Figure 6: Number of rapporteurships/peer reviewerships for PIP or waiver applications, by Member State (2007-2011)



20. European Network for Paediatric research at the EMA (Enpr-EMA)

Introduction

Article 44 of the Paediatric regulation required the European Medicines Agency (EMA) to develop a European Network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. To meet this objective the European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA) has been established, officially launched and presented to all stakeholders in March 2011 as a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children (full list of Enpr-EMA milestones below). Enpr-EMA aims to foster ethical research on quality, safety and efficacy of medicines to be used in children. It serves as platform for industry providing access to competent, high quality paediatric research networks and encourages inter-network trans-European collaboration.

In order to aid achieving the successful creation of Enpr-EMA an Implementing Strategy (http://bit.ly/AqfjRV) was adopted in January 2008 by the Management Board at EMA, where the definition of a network was given as a virtual structure defined by a formal agreement between individuals, organisations or structures sharing and collaborating towards the same objectives, goals and quality standards. The implementing strategy was largely based on the outcome of previous discussions/meetings held by the EMA during 2005 and 2006 with representatives of existing or developing paediatric networks.

As a next step, the EMA prepared a formal inventory of paediatric networks, investigators and centres with specific expertise in the performance of studies in the paediatric population. Sixty networks were identified at that time, and these were subdivided in various categories such as national networks, European Networks publicly funded, paediatric sub-specialty networks (e.g. rheumatology, HIV), age-related networks (e.g. neonatology) and activity or structure-related networks (e.g. pharmacovigilance, community-practitioners). The implementing strategy also identified interested 'stakeholders' including patients, parents, families and organisations representing them; Paediatric and other relevant learned societies; Academia (EU and international); National Competent Authorities; Ethics Committees; Paediatric health care providers; Pharmaceutical industry; Clinical Research Organisations and Hospital pharmacists.

The main objectives of Enpr-EMA were identified as building up and strengthening scientific, technical and/or administrative competences in the performance of paediatric clinical trials through effective collaboration in order to avoid duplication of work and efforts, making the use of facilities more efficient and profitable and developing common methods of working with special attention to quality assurance. Additional benefits are the facilitation of recruitment of patients, and avoiding unnecessary studies in children. Finally the EU network aims at strengthening the foundations of the European Research Area by promoting European Commission framework programme applications. For more detailed goals of the network see the implementing strategy published on the EMA website.

Operational structure

From 2009, two working groups with members of identified networks were tasked to elaborate the operational structure of Enpr-EMA and to define recognition criteria which will have to be fulfilled to become a member of Enpr-EMA (http://bit.ly/I6w22Z). Both tasks were completed by February 2010 and a workshop was organised in March 2010 (http://bit.ly/IJdbvW) to present the proposals to a larger group of networks, and to come to an agreement. Twenty-two networks were represented by 27

participants. As stated in the implementation strategy the operational centre of Enpr-EMA is a co-ordinating group (CG) which is responsible for the network's long- and short-term strategy. During the workshop it was agreed that the co-ordinating group should be as diverse as possible to represent various types of networks: networks focusing on specific therapeutic areas, specific needs/age subsets (e.g., neonatal /adolescent networks) or specific activities (e.g., pharmacovigilance), as well as organisational networks (e.g., national networks linking together either several clinical trial centres or community paediatricians), accommodating for regional differences throughout Europe with regards to how the medical care of children is organised. Consensus was reached regarding the total number of members for the CG: 18 networks fulfilling all minimum recognition criteria and 2 PDCO representatives. A maximum of four additional members may attend the CG meetings as observers, including patient/family representatives, representatives of ethics committees as well as the EC.

It was further agreed that Pharmaceutical Industry will not be represented in the Co-ordinating Group; however, regular communication with industry as major stakeholder must be ensured. Membership of the Co-ordinating Group shall be for 3 years only, to ensure sufficient renewal and involvement of various members. The main tasks of the CG were identified as follows: to facilitate access of the pharmaceutical industry to paediatric clinical study centres and experts; to discuss and solve operational and scientific issues for the network; to act as a forum for communication; to identify new networks and inviting them to join Enpr-EMA; to develop common educational tools for children and parents, to increase their willingness to take part in clinical trials; and to report to the Paediatric Committee, which acts a scientific committee of Enpr-EMA.

The European Medicines Agency will provide the secretariat and organise and host the meetings.

For further details on the composition and tasks of the CG please see the Report on Second Workshop (http://bit.ly/IJdbvW).

Recognition criteria to become member of Enpr-EMA

A set of recognition criteria and quality standards were elaborated following the Delphi and nominal group techniques (Ruperto et al. 2011). Six quality criteria were identified: Research experience and ability; Network organisation and processes; Scientific competencies and ability to provide expert advice; Quality management; Training and educational capacity to build competences; Public involvement. Each category was further subdivided with detailed information being requested in each of them. From this list a minimum set of recognition criteria that have to be fulfilled in order to become a member of Enpr-EMA was agreed at the workshop in 2010 and was published on the EMA website allowing networks to assess themselves (http://bit.ly/I6w22Z). Networks submitting a self-assessment are expected to provide evidence for their claims to allow public scrutiny. Self-assessment reports together with the supplementary documentation are reviewed by the EMA secretariat and published on the EMA website once all the potential clarifications/questions have been addressed by the corresponding network. All self-assessment reports have to be annually revised and updated.

Following a call for expressions of interest in 2010, Enpr-EMA published a full list of applicants for membership in January 2011 (http://bit.ly/IvoGI5). To date 34 networks have submitted their self-assessment reports to the EMA (http://bit.ly/IJcz9E). During the reviewing process performed by EMA secretariat networks were classified according to 3 categories: category 1 networks fulfilling all minimum criteria for membership of Enpr-EMA; category 2 networks potentially fulfilling all minimum criteria but in need of clarifying some issues before becoming a member of Enpr-EMA; and category 3 networks currently not yet fulfilling minimum criteria. To date 18 networks are recognised as category 1; 2 are recognised as category 2; and 14 are recognised as category 3 (Table 28).

Table 28: Enpr-EMA networks . Networks were classified according to 3 categories. Category 1: networks fulfilling all minimum criteria for membership of Enpr-EMA; Category 2: networks potentially fulfilling all minimum criteria but in need of clarifying issues before becoming a member of Enpr-EMA; and Category 3: networks currently not yet fulfilling minimum criteria.

Type or therapeutic area of network	Category 1 networks	Category 2 networks	Category 3 networks
National	NIHR-MCRN, FinPedMed, MCRN-NL, MICYRN, Scotmcn, CICPed		IPCRN, NCCHD, BLF, RIPPS, Futurenest CR, BPDN
Oncology (solid / haematologic malignancies)	Newcastle-CLLG, ITCC, IBFMSG, EPOC	CLG of EORTC	
Diabetes / Endocrinology / metabolic disorders / Gynaecology			AMIKI
Gastroenterology / Hepatology			ESPGHAN
Allergology / Immunology/ Rheumatology	PRINTO		JSWG of PRES
Stem Cell and Organ Transplantation / Haematology (non malignant) / Haemostaseology	EBMT		IPTA
Respiratory diseases / Cystic Fibrosis	ECFS-CTN		
Cardiovascular diseases / Nephrology			
Psychiatry / Neurology	EUNETHYDIS		
Infectious diseases / Vaccinology	PENTA, UKPVG		PENTI
Special Activities / Age groups			
Intensive Care / Pain / Anaesthesiology / Surgery		Network of Excellence for research in paediatric clinical care-NL	
Neonatology	GNN		EuroNeoNet, Neo-circulation, INN
European Paediatric Pharmacists			
Special Activities (pharmacovigilance, long-term follow up, community paediatricians)	FIMP-MCRN		
Expertise in Clinical Trial Methodology			TEDDY*, PRIOMEDCHILD*, ECRIN*, GRIP*

* Unable to provide self-assessment report, as based on different objectives

Presentation of Enpr-EMA to all stakeholders

Enpr-EMA was officially launched in 2009 and introduced to a wider audience in March 2011 during a 2 day workshop organised by the Agency (http://bit.ly/Im7Ygg). On the first day of the March 2011 meeting, open to networks only, Enpr-EMA's co-ordinating group was established and Professor Peter Helms, director of the Scottish Medicines for Children Network, was elected as chair of the co-ordinating group. Priority tasks for the CG were defined as establishing Enpr-EMA as platform for communication with industry and patient organisations; linking activities between Enpr-EMA's

members; developing common educational tools for patients/parents to increase willingness to participate in paediatric trials; collaborating with the Paediatric committee (PDCO) on the development of so called "model paediatric investigation plans in selected therapeutic areas; defining a policy of transparency in line with the EMA policy on the handling of potential conflicts of interest (EMA 2012) with the aim to balance the need to ensure that experts involved have no interests which could affect their impartiality with the need to secure the best (specialist) scientific expertise.

The second day of the workshop was open to all stakeholders, particularly patient organisations, clinical researchers, and pharmaceutical industry staff responsible for paediatric studies. More than 160 participants attended. During the second day expectations from various stakeholders were discussed (http://bit.ly/Im7Ygq). The views from pharmaceutical industry were represented by large pharmaceutical industry, small and medium sized enterprises (SMEs) and companies developing medicines for rare disease. The networks perspective was addressed by representatives of three different types of paediatric networks: a large national network, an oncology network and a neonatal network. The parent/patients' expectations were addressed by the secretary general of the Patients Network for Medical Research and Health (EGAN) and one PDCO member representing patients' organisations. Several parallel break-out groups discussed proposals for the effective use of Enpr-EMA.

Following the conclusion of the workshop, the first meeting of the newly form CG took place in June 2011 where the outcome of the workshop and the first tasks identified were discussed. Enpr-EMA also elaborated and submitted a common response document to the Clinical Trials Directive consultation and this was sent to the European Commission. EMA secretariat and the coordinating group worked closely to elaborate the mandate of the coordinating group, the mission statement, the policy on transparency and the working plan for Enpr-EMA, all published on the Enpr-EMA website in early 2012.

In order to fill the identified gap of networks in several therapeutic areas, Enpr-EMA organised a meeting to "kick-start" paediatric research networks in three specialties: Paediatric Cardiology, Paediatric Gastroenterology and Paediatric Diabetes and Endocrinology. The workshop took place in November at the EMA with the aim of bringing together relevant experts in the paediatric specialties mentioned above in order to stimulate the development of European-wide new clinical trials networks (CTNs) in these therapeutic areas by sharing experience with existing CTNs, and scoping the possibilities for networks in these specialties. Representatives for each of the three potentially new networks were selected and will report on the progress of their initiatives at the fourth annual Enpr-EMA-workshop in March 2012.

In addition one of the key areas Enpr-EMA has been working on is to raise awareness on the need to perform ethical research in children in order to ensure that a medicinal product is safe, of high quality and effective for use in the paediatric population. Enpr-EMA has established intense collaborations with the Patients and Consumers Working Party (PCWP) at the EMA, with the result of one of their members (Jose Drabwell) being elected as their representative to interact with Enpr-EMA; Jose Drabwell has now become a co-opted member of the CG of Enpr-EMA.

Other key tasks that Enpr-EMA has identified include the elaboration of Model PIPs. The first step will be to develop a priority list of areas for model PIPs. Another area of work has been to increase the visibility of Enpr-EMA. A logo for Enpr-EMA has been created and a link (to the Enpr-EMA pages) on the EMA website has been established. Enpr-EMA secretariat has submitted two project proposals to the EMA for a website and a resource database that will increase visibility and efficiency of the network. In addition a paper on Enpr-EMA has recently been published in Archives of Disease in Childhood5 as well as a short report in the European Pharmaceutical Contractor.

One of the key tasks for Enpr-EMA is to deal with queries coming from pharmaceutical industry. To this end Enpr-EMA is working to develop an operational procedure to deal with these queries. The potential issues from industry point of view are confidentiality of the information submitted to Enpr-EMA and

how this information will be distributed amongst all the members of Enpr-EMA. This will be one of the major topics in the upcoming Workshop in March 2012, where representatives of pharmaceutical industry are expected to attend and give their views and ideas on how to establish a sound system. From Enpr-EMA side, a conflict of interest policy has been developed and all members will have to sign to a confidentiality agreement to protect Industry interests.

Conclusion

The establishment of Enpr-EMA has been a significant achievement, and even though more work is needed the way ahead for Enpr-EMA is clear. Enpr-EMA aims to become the platform for access to competent, high quality networks with recognised expertise in performing clinical studies in children across Europe. Enpr-EMA is able to provide reassurance on quality of networks being recognised members of Enpr-EMA, and to ensure that networks contacted in parallel for one specific study interact and communicate between each other achieving a high level of collaboration between networks avoiding potential duplication of studies. Enpr-EMA anticipates an ever increasing pool of key players and networks with capacity to conduct paediatric drug trials to provide timely and well informed scientific advice and to act as advocates for the needs of children as far as the safe and effective use of medicines is concerned.

Table 29: Enpr-EMA Milestones

2005-2006:
- Inventory of existing paediatric networks
- Several meetings at EMEA with existing networks
- Voluntary participation
- Understanding the difficulties, the issues, the needs
- Preparing the strategy by discussing objectives

2007:
- 01/2007 Entering into force of Paediatric Regulation
- 07/2007 Establishing PDCO
- Consultation of Paediatric Committee on Network strategy
- Public consultation on strategy

2008:
- 01/2008 Adoption of "Implementation strategy for " The Network of Paediatric Networks at the EMEA" by EMA Management Board
- 07/2008 Call for European Paediatric Research Networks sent to 15 European and International Paediatric and general scientific journals – to identify additional networks

2009:
- 02/2009 first network workshop
- 04/2009 establishing 2 working groups

- "implementation working group" (WG 1) to elaborate on the structure and operational model for the European network and on communication strategies
- WG 2 to define definition of quality standards and recognition criteria.
  - 04-06.2009 WG 2 identified available information on quality standards/recognition criteria for networks
  - 06/2009 WG 1 meeting – deliverable: proposal for structure and communication strategy
  - 07/2009
- WG 2 T-conference: agreeing to use the Delphi Technique and Nominal Group Technique to define recognition criteria.
- first round of Delphi survey sent to all identified networks and learned societies
  - 08-09/2009
- summarising responses from Delphi survey
- preparing second round of Delphi survey
- sending out second round of Delphi survey
  - 09/2009
- Informing learned societies and networks in writing about

i) proposed organisational structure of Enpr-EMA
ii) the need for grouping of existing networks and centres to ensure adequate representation in the coordinating group,
iii) asking for proposals on how and with which other network(s) collaboration could be envisaged

- 10-11/2009: analysing responses from second round of Delphi survey
- 12/2009: face to face meeting WG 1 and WG2: finalising proposal for recognition criteria

2010:

- 01/2010 test phase for self-assessing recognition criteria by network members of WG1 and WG2
- 02/2010 public consultation of recognition criteria
- 03/2010 second workshop:

- agreement of final recognition criteria
- agreement of organisational structure and composition of coordinating group

- 05/2010 Publication of recognition criteria
- 05-09/2010 self-assessment period for networks
- 06/2010 First internal meeting with EnCEPP to discuss ways for collaboration
- 10-12/2010

- checking self-assessment reports submitted to Agency and requesting additional clarifications as needed

2011:

- 01/2011

- Publication of self-assessment reports received and list of networks becoming member of Enpr-EMA
- T-conference with new members of Enpr-EMA to discuss composition of coordinating group (CG) and call for expression of interest to chair CG
- second internal discussion meeting with EnCEPP

- 03/2011 third network workshop:

- first day only networks: election of chair of coordinating group and discuss priority tasks of CG
- second day: first meeting between networks and industry and patient organisations

- 06/2011 First face to face meeting of coordinating group at EMA
- 07/2011 creation of Enpr-EMA Banner on EMA webpage with direct link to Enpr-EMA webpages
- 07/2011 Adoption of Policy on transparency and handling of research Interests
- 08/2011 Adoption of Mandate of Coordinating group (CG)
- 09/2011 Adoption of Enpr-EMA Mission statement
- 10/2011 Second meeting of CG
  - representative of Patients and Consumers Working Party (PCWP) at the EMA agreed to become co-opted member of coordinating group[
- 11/2011 Workshop on emerging networks in the therapeutic area of cardiology, Endocrinology and Gastroenterology

2012:

- 01/2012 Third meeting of CG
- 01/2012 Follow up TCs with 3 emerging networks (in the therapeutic area of cardiology, Endocrinology and Gastroenterology)
- 03/2012 fourth annual workshop
  - first day: open meeting between networks and industry and patient organisations
  - second day: only networks

21. Formulation working group

The Paediatric Committee's (PDCO) Formulation Working Group (FWG) was established in February 2008 as the PDCO identified a need for specialised expertise in paediatric formulations.

Composition

The FWG started with 11 members in 2008, increased to 13 in December 2011. It is composed of formulation experts from the EMA PDCO, the Quality Working Party, assessors from EU national regulatory authorities, experts from hospitals and academia.

Two representatives from the United States Food and Drug Administration (FDA) also attend the meetings by teleconference as observers. Their participation is within the framework of the Agency's confidentiality arrangement with the FDA.

Role

The Group supports the PDCO in the review process of the quality section of paediatric investigation plans (PIPs), through monthly teleconference meetings, the week before the PDCO plenary. At each meeting, recommendations are made regarding age-appropriate paediatric formulations in PIPs for discussion at the next PDCO plenary, and questions for the PIP Request for Modifications as well as key binding elements for the PIP Opinions are proposed.

The FWG reviews the proposed paediatric formulations of a PIP for the first time before the Day 30 PDCO discussion and suggests modifications to the PDCO if appropriate.

The Group's comments are reflected in the summary report and, if endorsed by the PDCO, in the request for modification sent to the applicant.

The FWG is usually also involved later on in the process, once the responses to the request for modification have been received from the applicant, to evaluate the appropriateness of the applicant's proposals and suggest some key binding elements for the PIP Opinion.

In addition, the Group provides advice on formulation-related aspects upon request of the PDCO (e.g. interaction with other EMA committees), or during drafting/revision of scientific guidelines.

Achievements

- The major topics discussed by PDCO FWG relate to the safety of excipients in the paediatric population, the appropriateness of the pharmaceutical form and the intended dosing/need for dosing flexibility. Focus has been put on the youngest age groups, in particular neonates, to optimise formulations with regard to appropriate dose, safe excipients, minimising risk of medication errors and optimising practical handling.
  - Safety of excipients for the paediatric population: Better justification of the chosen excipients, in relation to age and daily dose of excipient, replacement of excipients with potential safety concern. Input from/collaboration with the PDCO NcWG and the CHMP SWP for further discussion of potential excipient safety issues.
  - Appropriateness of the pharmaceutical form: Ensure formulations suitable for children, or appropriately adapted to the relevant age groups. E.g., request of alternative dosage forms to be developed to single unit solid dosage forms. Requesting sufficient testing of palatability and acceptability in children of the formulation proposed.

- Dosing flexibility, accuracy of dosing and practical handling: Focus on practical aspects of administration, feasibility of formulation/dosage form to support correct and accurate dosing in view of needed dosing flexibility, inappropriate manipulation of adult dosage forms and presentations.

- From February 2008 to November 2010, the PIPs were referred to the FWG by Paediatric coordinator or PDCO member on a case-by-case basis. Since Nov 2010, a screening of all PIPs is performed by EMA Quality team, identifying PIPs to be discussed by the FWG, currently applying a more systematic approach.
- Quantitative data: Number of PIPs reviewed by the PDCO FWG:
  - In 2008, from March to December, the FWG discussed 62 PIP applications.
  - In 2009, the FWG assessed 84 PIP applications, 43% of the total number of validated PIP applications (84/195) during this year.
  - 115 and 152 PIPs were discussed by the PDCO FWG, in 2010 and 2011 respectively.
  - Each product has been counted in the year when the last discussion occurred for this product. As each product is generally discussed several times, the figures do not exactly reflect overall activity, however they show the trend of an increased involvement of the PDCO FWG, reviewing systematically all the PIPs raising some quality issues since November 2010.
- Adoption by the PDCO, upon proposal of the PDCO FWG, of standard wording for paediatric formulations key binding elements in PIP Opinions, to better reflect the PDCO's requirements in opinions and avoid the general wording "development of an age-appropriate formulation".
- Implementation of quality questions in the Part A of the PIP application form, to be filled by applicants, to ensure the needed information is provided at the time of the PIP submission, especially the composition of proposed formulations, with qualitative and quantitative data on excipients (http://bit.ly/A6wg0j).
- Implementation of FWG comments/minutes in the EMA Paediatric database, to capture the above data and allow future statistics on paediatric formulations (data entered retrospectively until August 2011 and prospectively since September 2011).
- Support PDCO in the collaboration with other committees by providing recommendations upon specific requests (e.g. PhVWP: medication error issues).
- Annual face-to-face meetings to discuss general issues on paediatric formulations (e.g. state of the art knowledge on paediatric safety of specific excipients).
- 2 workshops for National Assessors on paediatric formulations, in 2010 and 2011, to share the experience with PIP assessment, increase the awareness and understanding of paediatric-specific issues in the development of paediatric formulations and enhance collaboration within the European network. The material of the two workshops has been published on EMA external website (http://bit.ly/HXOoSU and http://bit.ly/I7hbFX)
- Participation in the drafting group of EMA Draft guideline on the pharmaceutical development of medicines for paediatric use (EMA/ CHMP/QWP/180157/2011), published on EMA website in September 2011 (public consultation phase ended December 2011).
- Participation in the drafting group of the revision of European Commission guideline on excipients in the label and package leaflet for medicinal products for human use.

- Comments provided on several guidelines related to paediatric formulations, published by WHO, national agencies or associations.
- Collaboration with European Paediatric Formulation Initiative (EuPFI) through participation to their congresses and a project on acceptability/palatability testing guidance; collaboration with FDA and WHO.
- Overall, the work of the PDCO FWG has raised awareness and deepen the knowledge of the issues specific to the development of paediatric formulations, both among applicants (through the comments on PIP applications) and among the EMA network, such as National Competent Authorities through various workshops or other EMA committees. The participation of experts from National Competent Authorities, hospital and academia in the PDCO FWG meetings is also a bilateral exchange, during which they bring expertise to enrich the global knowledge.

Action plan in the near future

- To continue to support the PDCO by providing recommendations for PIPs, and when needed recommendations to support PDCO's interactions with other committees.
- To maintain a consistent approach and agree on assessment standards that can be applied in evaluation of PIPs.
- To continue participation in the drafting groups of the guideline on "Pharmaceutical Development of Medicines for Paediatric Use" and the revision of the Commission guideline on Excipients in the label and package leaflet of medicinal products for human use.
- To continue collaboration with other stakeholders with an interest in paediatric formulations and forms.
- Develop guidance on acceptability/palatability testing of paediatric formulations (project initiated end of 2010) with input from the European Paediatric Formulation Initiative(EuPFI) and GRIP (Global Research in Paediatrics - Network of excellence) .
- In December 2011, the Committee and its Formulation Working Group were informed that, via the Reagan-Udall Foundation, the FDA is working on a proposal to develop a validated approach to assessing "acceptability/suitability" of formulations in children of different ages. The PDCO FWG may also be involved in this project as part of the paediatric cluster.

22. Non-clinical expert working group

Role

The Non-clinical Working Group (NcWG) was established in November 2008 to complement the Paediatric Committee's (PDCO) work with specialised non-clinical expertise. The NcWG guarantees a high quality consistent approach in the monthly review process of the non-clincal section of paediatric investigation plans (PIPs). Recommendations are made to the PDCO either before adoption of the Request for Modification or the opinion. The recommendations clearly state the respective concern and consequential proposed request and are reflected in the summary report and/or opinion, if endorsed by the PDCO.

Composition

The NcWG is currently composed of 15 non-clinical experts from the PDCO, the EMA Safety Working Party (SWP) and additional members from medicines regulatory authorities in European Union Member States. Two representatives from the United States Food and Drug Administration (FDA) also attend the meetings by teleconference as observers.

Main achievements

Since November 2008, 379 PIPs have been reviewed, which is approximately 69% of total PIPs received (only counting a product once and not including waivers, Figure 7, blue bars) and 117 PIPs have been re-discussed (Figure 7, green bars) when the applicants' responses to the Request for Modification were received and warranted further discussion.

The PDCO generally endorsed the recommendations of the NcWG. All 88 PDCO Opinions adopted between March 2011 and December 2011 were compared to the respective initial application with regards to their pre-clinical strategy and showed the following:

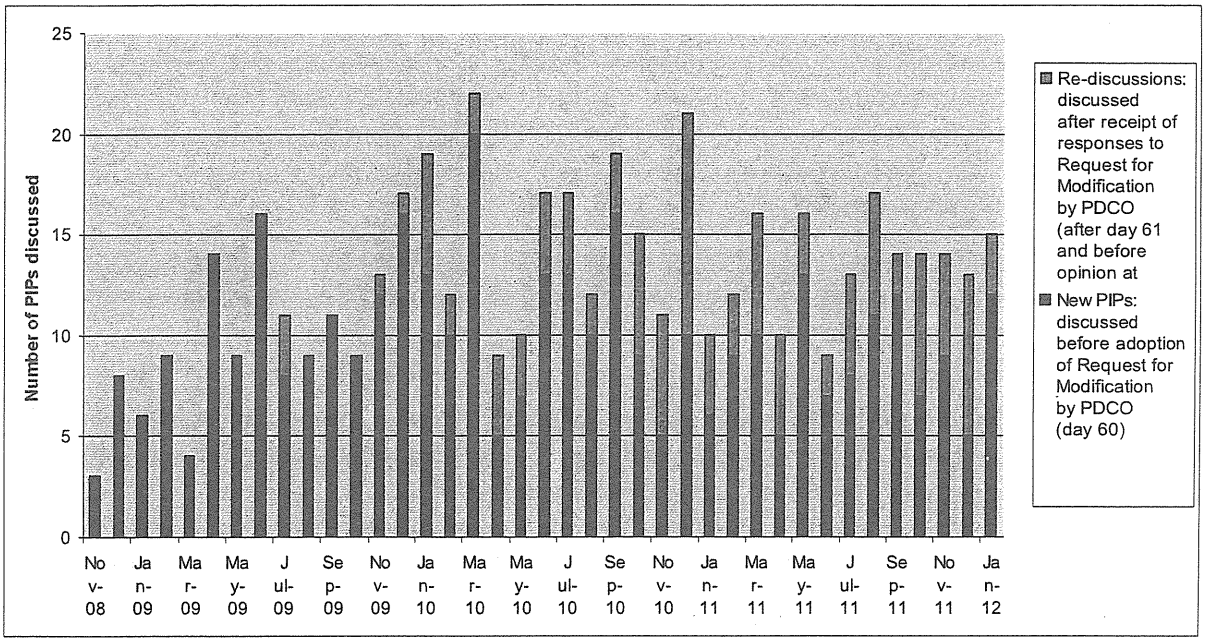
- Juvenile animal studies were present in 19% of the applications for PIPs (17 applications with at least one juvenile study; 30 juvenile studies in total across these 17 applications).
- Juvenile animal studies were required in 25% of the PDCO opinions on PIPs (22 opinions with at least one juvenile study; 37 juvenile studies in total). This means that additional juvenile animal studies were requested by the NcWG/PDCO in about 6% of all proposed PIPs.

A review of all 97 PIPs discussed by the NcWG between November 2008 and May 2010 was recently published (Carleer and Karres, 2011). According to this review, the young age of the paediatric target population was one of the major drivers for requesting juvenile animal studies. In about 14% of the reviewed PIPs, however, the NcWG requested either justifications for, or amendments of the designs of juvenile animal studies proposed by the applicants.

The review also showed that the number of juvenile animal studies required in PDCO opinions was less than the sum of the number of juvenile studies initially proposed by the applicant and of those requested by the NcWG/PDCO in the Request for Modification of the PIP. This reduction of eventually required juvenile animal studies compared to those discussed at any stage of the PIP evaluation, was mainly due to additional data or justifications provided by applicants during the evaluation, such as in the response to the Request for Modification.

It was noted that the PIP applications often lacked information relevant to the non-clinical evaluation.

Figure 7: Frequency of discussions of PIP applications



Review of results of required juvenile animal studies

A preliminary review was performed of reports of 5 completed juvenile animal studies that were required in PDCO opinions for medicines from 4 different classes of oncology products. The review revealed increased sensitivity and unexpected toxicity in 3 of the investigated medicinal products.

Dissemination and public-facing activities

Members of the NcWG and the EMA participated to three international conferences regarding pre-clinical safety aspects for the development of medicinal products used in the paediatric population, organised a training on the need of juvenile animal studies for National Assessors and published two articles describing current experience with requirements for juvenile animal studies in PIPs (Carleer & Karres 2011; Silva-Lima et al. 2010). Furthermore, the NcWG provided comments on the Japanese guideline on non-clinical support for paediatric drug development.

Interactions with the Safety Working Party/CHMP

- When safety concerns regarding the paediatric use of a specific class of medicinal products or excipients were identified by the NcWG, a common approach was decided in collaboration with the Safety Working Party (SWP). Specific examples from the past 2 years are: tolerable daily intake values for the presence of di(2-ethylhexyl) phthalate, benzyl butyl phthalate and dibutyl phthalate within medicinal products; maximal tolerable doses of aluminium hydroxide contained in allergen products; intravenous use of polysorbate 80 in neonates; safety of pegylated drug products for the paediatric population.
- Currently the guideline on Excipients in the Labelling and Package Leaflet (European Commission, 2003) is for revision and the NcWG together with the Formulation Working Group (FWG) of the PDCO and the SWP will contribute to the review of 8 prioritised excipients with potential paediatric issues: (dextran/) cyclodextrins, ethanol, polyethyleneglycol, propyleneglycol (and esters), polysorbates, benzyl alcohol, sorbitol (and other poorly absorbed sweeteners), aspartame.

Conclusions

The NcWG provides a high-quality, consistent approach to the application of the EMA guideline on the need for juvenile animal studies (EMA 2008) and thereby complements the work of the PDCO. The case-by-case evaluation process to determine the need for juvenile animal studies contributes majorly to the protection of the pediatric population during clinical trials and prevents the conduct of unnecessary juvenile animal studies.

Young age of children exposed to the investigated medicinal product was one of the main reasons for requesting juvenile animal studies owing to potentially increased sensitivity toward organ toxicity as several organs or systems of newborns and infants are not fully developed and are maturing postnatally.

The occurrence of increased sensitivity and unexpected organ toxicity in juvenile animals as seen in a preliminary evaluation of completed juvenile animal study reports from PIPs (described above) and as described previously (Bailey and Marien, 2009; Carleer and Karres, 2011) emphasises the general importance of conducting juvenile animal studies. The main values of the results from juvenile animal studies are their contribution to dose predictions in children, their use for risk minimization and for the identification of safety parameters in the pediatric clinical trials to monitor and detect early safety signals.

The collaboration with the FDA (and, occasionally, with the Japanese PMDA/MHLW) increases consistency in pre-clinical safety requirements for the development of medicinal products used in the paediatric population at the international level.

A need was identified for applicants to provide better scientifically-based justifications, when no juvenile animal studies are proposed in the initial PIP submission.

Action plan for the near future

- Continue to support PDCO by providing recommendations for PIPs, and when needed recommendations to support PDCO's interactions with other committees/agencies.
- Continuation of the review of use of juvenile animal studies in different therapeutic areas and product classes.
- Evaluation of the impact of the Paediatric Regulation on the SmPC labelling regarding juvenile animal studies.
- Continuation of the collaboration with the American FDA and the Japanese PMDA/MHLW agencies.

Meeting contributions

- Workshop on "The Value of Juvenile Animal Studies" in Washington, DC. Organised by ILSI Health and Environmental Sciences Institute/Developmental and Reproductive Toxicology Technical Committee (2010).
- Workshop for National Assessors on paediatric formulations, London (2011).
- Biotherapy Development Association (BDA) workshop in collaboration with ITCC, ENCCA and EMA, London. "Innovative Oncology Drug Development for children and adolescents in Europe: Current Status and Where to Go?" (2011).

Meeting organisation

- Workshop organised by EMA for National Assessors on the need of juvenile animal studies for medicinal products used in the paediatric population (2009), to increase their knowledge on the topic and collaboration.

23. Detailed inventory of all medicinal products authorised for paediatric use since its entry into force

Article 50 (2) of the Paediatric Regulation states that *"This [report] shall include in particular a detailed inventory of all medicinal products authorised for paediatric use since its entry into force."*

The inventory includes both medicines that received the initial marketing authorisation since 26 January 2007 and medicines for which the already granted authorisation was varied since 26 January 2007 to include a new paediatric indication. The data for the inventory were collected as part of the survey among Members States used for this report, which have been detailed and aggregated in four sections the Annex II of this report. The summary data are also presented in the section "5. More medicines available for children in the EU" of this report.

Taken together, the following sections form the inventory of all medicinal products authorised for paediatric use since its entry into force:

23.1. Centrally authorised medicines

23.1.1. Initial marketing authorisation (MA) including a paediatric indication

- Line listing in Annex II, section 4.1

For this section, only medicinal products were considered when a paediatric indication was granted as part of the initial MA. Thirty four (34) new medicinal products have been centrally authorised since 26 January 2007 with a paediatric indication at the time of initial MA. Out of these 34 medicinal products, 7 were authorised for a use only in the paediatric population, whereas the remaining 27 medicinal products were authorised for use in adults and in children. For 10 out of the 34 medicinal products, the requirements of the Paediatric Regulation needed to be fulfilled, meaning the corresponding PIP had not been completed.

23.1.2. Extension of therapeutic indication to include the paediatric population

- Line listing in Annex II, section 4.2

The therapeutic indications of 33 centrally authorised medicinal products was extended or amended to include a part or subsets of the paediatric population. 38 changes to the authorised indications were adopted to include a part or subsets of the paediatric population for these 33 centrally authorised medicinal products (several products had more than 1 change to their indications affecting the paediatric population).

23.2. Nationally authorised medicines

23.2.1. Initial marketing authorisation (MA) including a paediatric indication

- Line listing in Annex II, section 7.1

Overall 12 Member States provided data on this question, about 300 data entries covering more than 80 active substances and covering the period from 2006 to 2011 (more than 180 data entries 2011,

less than 35 each for the preceding years). The data provided have been summarised across Member States and presentations by using the English INN for the active substance(s).

The data included medicines that were already authorised in some EU Member States, but became available for use in children through new authorisations in further, new Member States.

The data provided were scrutinised for new medicinal products with new active substances. There were 3 such medicines that could be identified (name of medicinal product): Numeta and associated names, Celtura, Panenza.

The legal basis, under which the medicinal products were authorised, was not requested to be reported, so that no distinction can be made between new medicines linked or not linked to the Paediatric Regulation. Some of the data entries may be for generic medicines, which do not fall under the Paediatric Regulation and thus are not part of this report.

23.2.2. Extension of therapeutic indication to include the paediatric population

- Line listing in Annex II, section 7.2

In total 11 Member States reported a new indication authorisation of a use in the paediatric population for the medicinal products concerned by a total of 33 active substances, none of which is considered a new active substance since coming into force of the Paediatric Regulation. The authorised paediatric indication is reflected in sections 4.1 and / or 4.2 of the SmPC (Table 17 and Table 18 in Annex II, respectively).

Out of the 33 active substances, 8 underwent an Article 29 referral procedure (section 5.2. in the core report) or that have been captured in Article 45 assessments (section 6.1. in the core report).

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Annex II Cumulative data 2007-2011

This is Annex II to the 5-year Report to the European Commission, the general report on the experience acquired as a result of the application of the Paediatric Regulation. The report does not include data for generic, biosimilar, hybrid, homeopathic, traditional herbal and well-established medicinal products - which are excluded from the scope of the mandatory development - unless otherwise mentioned. Recitals and Articles refer to the Paediatric Regulation, if not otherwise stated.

7 Westferry Circus • Canary Wharf • London E14 4HB • United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7040
E-mail info@ema.europa.eu **Website** www.ema.europa.eu