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Human Medicines Development and Evaluation

Report on annual workshop of the European Network of Paediatric Research at the EMA (Enpr-EMA), 27 & 28 June 2013

On 27 & 28 June 2013 the European Medicines Agency (EMA) convened the annual two-day workshop of the European network of paediatric research at the EMA (Enpr-EMA). Enpr-EMA is a network of research networks, investigators and centres with recognised expertise in performing clinical studies in children, with the aim to foster high-quality ethical research on quality, safety and efficacy of medicines to be used in children.

Day one of the workshop, organised with the assistance of The Organisation for Professionals in Regulatory Affairs (TOPRA), was dedicated to strengthen the links and communication between all stakeholders: patient/parent organisations, network representatives, pharmaceutical industry staff responsible for paediatric studies and regulators. The open meeting was followed by the Enpr-EMA members meeting.

Day two was dedicated to the Enpr-EMA coordinating group meeting to analyse the outcome of day one, and to discuss and define priority tasks for the year 2013-2014.

Day 1

The morning session started with a report by the outgoing chair of Enpr-EMA coordinating group (CG) , Prof. Peter Helms, on the activities in the past year, including:

- Young person's groups (survey among Enpr-EMA members completed and report written).
- Link with EMA SME office, to help establishing collaboration between networks and SMEs.
- Increase visibility of and publicity for Enpr-EMA; a peer review paper has been published and resource slides have been prepared for members to be downloaded from the Enpr-EMA webpage.
- Collaboration with PDCO included development of standard PIPs for rhabdomyosarcoma and acute myeloid leukaemia, participation at expert meetings in the field of cystic fibrosis and type 2 diabetes mellitus.
- Continuing support of new specialty networks in the fields of gastroenterology, cardiology, and diabetes/endocrinology

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- Corporate response to EC consultation on 5 year review on Paediatric Regulation.
- Corporate response to revised Clinical Trial Regulation.
- Election of new chair , Dr. Mark Turner, Associate Director for International Affairs, Medicines for Children Research Network (UK).

Challenges encountered in the past years included:

- Advocacy at EU level (Parliament, Commission) regarding paediatric specific needs and challenges related to paediatric trials, including difficulties with obtaining Ethics Committees' approval across Europe when conducting multinational trials.
- Need for core funding for establishing and maintaining efficient functioning of national / specialty networks.
- Active involvement of CG members.

Preliminary results of a survey on collaboration between industry and Enpr-EMA networks for the conduct of paediatric clinical trials was presented, followed by a discussion involving two representatives from industry, one from large pharma and one from a SME, on their expectations and requirements for collaboration with networks.

A SME is looking for:

- Access to a pool of investigators who have done industry-sponsored RCTs before, have the needed research infrastructure (e.g., research nurses) at their institution, which allows them to operate more efficiently (shorter timelines, greater recruitment), deliver better quality research, and better quality data.
- Networks which have already identified the most productive investigators/institutions within their regions; multiple networks combined that offer instant geographic diversification.

The second speaker from a large pharmaceutical company pointed out that there is a need for better advertising of Enpr-EMA. At present communications with Enpr-EMA and its members are difficult. The process for consultation is not clear. It is difficult to find out who to contact. It is not clear as what Enpr-EMA and their members can offer. The website of Enpr-EMA was criticized as difficult to access. It is very difficult to find information on the website. A searchable website, providing industry with easy access to relevant information of individual networks was requested. In addition, to allow better interaction between EnprEMA, industry should be represented within the coordinating group. In the following discussion, it was clarified that according to the Enpr-EMA Implementation strategy adopted by the EMA management board, *"Industry is not represented in the Coordinating Group through membership, but is expected to be a major stakeholder in the discussions."* The comments received clearly indicate an urgent need for improving communication with industry.

Representatives from two successfully established and operating clinical trial networks (CTNs), the Paediatric European Network for Treatment of AIDS (PENTA-ID) and the Medicines for Children Research network, The Netherlands (MCRN-NL) reported about challenges with running their networks and solutions found and applied.

A common message from both networks was the need for building good relationships with industry and with individual investigators, and for the involvement of investigators ideally at an early phase of the clinical trials to increase their motivation and interest in participating to studies, and consequently, to ensure feasibility of proposed studies. Building good relationships takes time and requires proof of successful and efficient functioning of the network. Good relationship with a company in one therapeutic area may be different in other areas. Networks need to get more organised with a single

contact point for industry, a clearer structure and to collaborate with different overlapping clinical networks (e.g. neonatology/oncology). There is a need for rigorous site selection to ensure high quality and timely conduct of studies. Network representatives clearly expressed their interest and their perceived need to be involved as early as possible in the PIP development and encouraged industry to use their expertise, not only for facilitating the conduct of clinical trials but much earlier, in designing the paediatric development. Networks would like to proactively approach industry, but often have difficulties on how to get in contact and to communicate with companies.

The afternoon session was dedicated to panel discussion focusing on three topics:

1. What can Enpr-EMA contribute to bridge regulators, academia, industry, and patients?
2. What can Enpr-EMA contribute to raise awareness on the need for paediatric research in the general population?
3. Communication between Enpr-EMA and ethics committees.

What can Enpr-EMA contribute to bridge regulators, academia, industry, and patients?

- There are many examples of good practice; one major task for Enpr-EMA is to gather such examples and facilitate sharing of good practices.
- Enpr-EMA should facilitate communication between industry and networks, provide industry easy access to information about capacities of individual Enpr-EMA networks, and increase visibility of individual networks.
- Networks are very interested in helping PDCO in prioritising therapeutic needs and candidate medicines when several compounds with similar mode of action are being developed for the same condition in a limited patient population. Patients/parents should be involved in priority discussions (and in discussions involving types of paediatric formulation).
- There is a need to define scientific valid methodology on how to set priorities and to base them on available evidence.
- PDCO needs to receive feedback when difficulties with implementation /conduct of clinical trials agreed in paediatric investigations plans (PIPs) arise or when ethic committees disagree with studies agreed in PIP decisions. Several important questions were raised: Do Enpr-EMA members have a role in alerting PDCO? Challenge: How to deal with confidentiality? How to solve conflict of interest. How to create safe environment for communication?
- Modifications of agreed PIPs can only be requested by companies. Companies and networks should ideally work closely together when preparing requests for modifications, in order to provide sound justifications based on evidence. Feedback on feasibility issues, current best practice and standard of care, available evidence should be provided through consolidated network positions and not through the opinions of individual experts.
- Should Enpr-EMA act on the European Commission 5-year report on Paediatric Regulation, that "*some* studies *published suggest a failure on the part of practitioners to recognise the actual amount of off-label prescribing to children. It is claimed that the prescribing habits of practitioners are often strongly influenced by personal experience rather than by evidence-based information for paediatric medicine. Such observations may point to a substantial hurdle in achieving the goal of the Paediatric Regulation."* It was agreed that it is beyond Enpr-EMA's remit to change every day clinical practice. This has to be accomplished on national member state level through learned societies and national paediatric associations. However, Enpr-EMA could develop more core educational material, not only on Enpr-EMA, but on Paediatric Regulation, on PDCO role and

activities, etc., for downloading and to be used for scientific conferences, for discussion with national paediatric associations, and learned societies.

What can Enpr-EMA contribute to raise awareness on need for paediatric research in general population?

- Early involvement of patients/parents is necessary to raise awareness of the need for clinical trials, to improve feasibility of, and improve recruitment into, trials. There are several examples of good practice for such involvement. Enpr-EMA should facilitate sharing those experiences.
- The need to raise awareness among the general population of the need for clinical trials without duplication of existing initiatives was emphasized by patient group representatives. The Innovative Medicines Initiative (IMI), a public/private partnership between the European Commission and EFPIA, funds the European Patients' Academy on Therapeutic Innovation (EUPATI), a patient-led academy that will develop educational material, training courses and a public Internet library to educate patient representatives and the lay public about all processes involved in medicines development. However, Enpr-EMA could collect and disseminate what educational tools are available. Francois Houyez, from Eurordis volunteered to act as link between Enpr-EMA and EUPATI.

Communication between Enpr-EMA and Ethics Committees

- How to optimise dialogue and interaction with ethics committees regulated by national legislations? How to raise awareness among members of ethics committees on children/adolescents' specific needs? How to disseminate existing good practice when dealing with children and young people between ethics committees? Does Enpr-EMA need to draw up a common strategy, guidance document for ethics committees on requirements for paediatric clinical trials? How can Enpr-EMA contribute to guidance for ethics committees if the European Commission is mandated to prepare such guidance by the Clinical Trials Regulation? Should Enpr-EMA lobby to allow non-written consent information (e.g. video, pictures, drawings) and for updating their guidance on patient information leaflets?
- Because of the very heterogeneous landscape of how ethics committee' approvals have to be obtained among EU member states, it was proposed to start with gathering examples of good practice, with a focus on those networks that are active in countries with only one single national ethics committee. GRIP (Global research in paediatrics) are piloting advice for investigators when dealing with ethics committees.

Based on the discussion points and the questions raised, it was agreed to set up several ad hoc working groups (WG) tasked with addressing the most important of the needs listed above. The purpose of these working groups is to develop pragmatic responses to each need that can be implemented within six months. The focus is on what networks can do, rather than developing comprehensive guidance. As there is already good practice in many of these areas Enpr-EMA needs to focus on disseminating this good practice rather than developing new solutions. The agreed list of WGs set up during the meeting is as follows:

WG 1: Approaches to priority setting:

- To develop proposals for how networks can contribute to prioritising therapeutic needs and candidate medicines when several compounds, with similar mode of action, are being developed for the same condition in a limited patient population;
- How networks can contribute to scientifically valid methodology about how to set priorities and base them on available evidence. Can networks contribute to the available evidence?
- To scope how networks can contribute to the EMA PDCO priority list of off-patent medicines.

WG 2: Broad engagement in priority setting:

- To develop recommendations for how networks can facilitate:
  - the involvement of patients/parents in priority setting discussions;
  - discussions involving types of paediatric formulation.

WG3: How to establish communication between Enpr-EMA, networks and industry:

- To develop recommendations for how Enpr-EMA can:
  - facilitate communication between industry and networks;
  - provide industry with easy access to information about capacities of individual Enpr-EMA networks;
  - increase the visibility of individual networks;
  - make contact with a range of industry partners (big Pharma, SMEs, biotechs, CROs etc.).

WG4: **Dialogue and interaction with ethics committees:**

- To gather examples of good practice when ethics committees consider trials relating to children and young people.
- To develop proposals to disseminate examples of good practice to ethics committees.

WG5: Sharing good practices within Enpr-EMA and with industry partners:

- To gather examples of network involvement in good practice for the development and implementation of clinical trials in children and young people.
- To develop proposals to disseminate examples of good practice to EnprEMA members and industry partners.

WG6: A framework for networks to interact with industry and regulators when implementation/conduct of clinical trials agreed in PIPs is no longer possible

- What can networks offer to industry when they submit requests for modifications to agreed PIPs because conduct of agreed studies no longer feasible?
- How can networks feedback to PDCO/regulators (national competent authorities) to help them assess the request for modification of an agreed PIP?
- What information are regulators looking for when considering requests for modification to PIPs?

Additional tasks:

- The Enpr-EMA secretariat will generate a table listing all networks with direct links to their websites and core information on networks capacities. The latter information will have to be filled in by the networks themselves.
- The Enpr-EMA secretariat together with CG chair to develop mandate for all working groups.
- The Enpr-EMA secretariat will look into the feasibility of adding 1 day at next year's annual workshop to run a training course for Enpr-EMA members on clinical pharmacology (the GRIP "roadshow" is one potential source and to extend the invitation to European Paediatric Formulation Initiative.

Before closing the meeting the group thanked Peter Helms for his excellent chairmanship of Enpr-EMA during the past 2.5 years.

Day 2:

Day 2 was dedicated for the annual face-face meeting of the coordinating group.

At this meeting it was agreed to establish two additional ad-hoc working groups, one on Neonatology and another on Pharmacovigilance. The scope of these two working groups will be further discussed at the next coordinating group meeting.

The agenda and meeting minutes are published in the EMA webpage dedicated to this Workshop.