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Report on the EMA workshop of pharmacovigilance in the paediatric population

28 April 2014

Introduction

On 28 April 2014, the European Medicines Agency (EMA) convened a first one day workshop on the needs and priorities for pharmacovigilance in the paediatric population.

The objectives of the workshop were to outline the current work performed at the EMA with regards to paediatric safety, and to discuss the potential for improvement in terms of active paediatric pharmacovigilance, and proactive planning with regards to surveying medicines when they come to the Marketing Authorisation phase.

This workshop was organised by the EMA Paediatric Medicines Office and held at the EMA.

18 European pharmacovigilance experts from a regulatory or an academic (university or hospital) background actively participated to this workshop as well as EMA staff from both Paediatric Medicines and Pharmacovigilance Offices.

The agenda is published in the EMA webpage dedicated to this workshop.

Background information

The first half of the morning session started with some background information on paediatric pharmacovigilance to introduce the topic:

- Descriptive overview of paediatric versus adult Adverse Drug Reactions (ADRs) in EudraVigilance (Kevin Blake)

Reports of paediatric ADRs seemed to be more common under the 'general and administration site', 'nervous system', 'skin and subcutaneous disorders' and 'infections and infestations' SOCs. The safety profile in adults is not necessarily reflective of children.

- The PRAC's perspective on paediatric safety issues (June Raine)

It was outlined that some progress in addressing the special challenges for pharmacovigilance in the paediatric population is required. The pharmacovigilance legislative tools create significant potential to

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minimise harms in the paediatric population from strengthened systems but there is a mismatch between clinical trial population and real life use in paediatrics which means a significant knowledge gap. Finally, the paediatric population issues need to be considered in all phases of the pharmacovigilance cycle.

Paediatric pharmacovigilance tools and methodologies used at EMA

The second half of the morning was dedicated to outline the current tools and methodologies used at the EMA with regards to pharmacovigilance in the paediatric population:

- Development of paediatric age group categories of organ maturation tables (Janina Karres)

Information on organ maturation (i.e. specified maturation of key sub-functions, enzymes, main structures within organ – kidney, liver, brain, lung, GI -) allows for better use of EudraVigilance data for paediatric medicines and help identifying maturation related ADRs. It was recommended that the ongoing work should be extended to, immune system, heart, skin, bone, ear and eye. It would be important to look at pregnancy exposure data, if possible.

- Update on the Standard EudraVigilance Paediatric (SEVP) Query Reports (Cosimo Zaccaria)

The initial requirement for issuing such report is when a potential risk in children is raised by the PDCO during a PIP assessment (Art.8 or 30) and it is based on Off-Label Use or known product safety in adults or paediatrics for another indication/condition. The SEVP Query Report is used to evaluate whether EudraVigilance data generate a similar hypothesis. SEVP Query Reports could also be useful for PRAC: triggering signals requiring evaluation which may ultimately lead to better information for healthcare professionals and patients (e.g. labelling), risk communication (emphasising aspects relevant to paediatrics), identification of questions for further investigation through Post-Authorization Safety Studies (PASS) – targeting paediatric ADRs, and follow up of long term studies (detecting drug induced and development disorders).

- Routine signal detection and statistical tools on paediatrics (Cosimo Zaccaria)

A stratification analysis is currently underway to investigate signal detection in vulnerable population including paediatrics. Also a workstream is currently dedicated to the writing of the methodological guidance for signal detection with a focus on describing how to monitor vulnerable population including paediatrics (PROTECT WP 3.8: evaluation of any increase performance in detecting more true positive and/or less false negative: http://www.imi-protect.eu/wp3.shtml). Besides, it was highlighted the need for a priority list of paediatric ADRs and PRR for screening eRMRs, complementary data source to advance knowledge of safety and benefit/risk in paediatrics, and the link between PIP and RMP to monitor risks for children in eRMR. Pharmacovigilance in the premature neonates should be enhanced. Looking at the data there is (in proportion) a higher number of cases reported for neonates reflecting the fact that they are more vulnerable among the paediatric population and close monitoring in this subgroup is warranted. Separating the screening of paediatric ADRs from the rest, might enhanced the monitor in this population particularly for medication error. Reporting of harms resulting from medicines should be encouraged irrespective of whether the use is within the terms of the marketing authorisation. Reports of harms resulting from medications Errors can enable the development of regulatory risk minimisation strategies e.g. better product presentations and/or information for the paediatric population to optimise the treatment of children in the future. Information on posology can be particularly relevant in the paediatric setting.

Paediatric ADRs in a specific therapeutic area

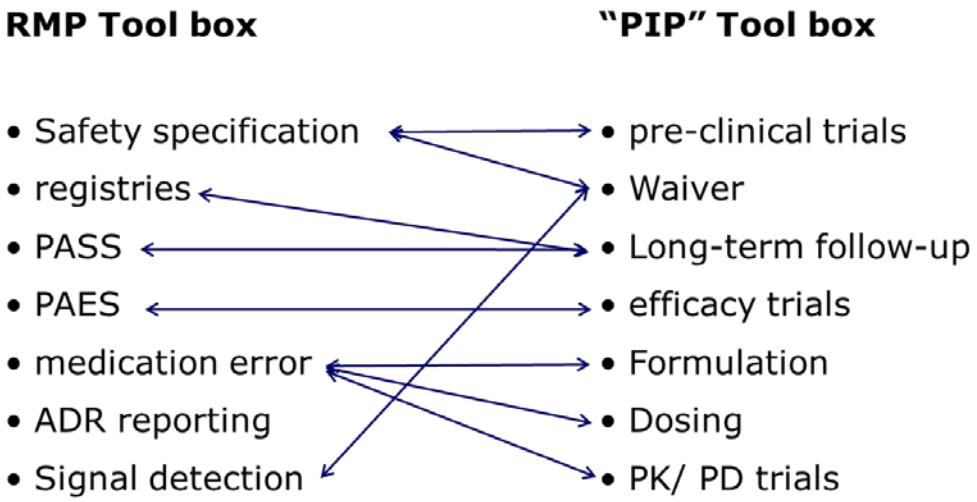
A specific topic focused on ADRs in paediatric oncology (Ralf Herold). In paediatric oncology medicines can be expected to result in ADRs in particular when the maximum tolerated dose is administered. Indications (use) in children are generally different from those in adult cancers. In addition, novel toxicities are suspected (e.g., based on animal studies) which are to be monitored. At present, most paediatric patients are in clinical trials (favourable for understanding safety and for protecting children), with many medicines used Off Label based on experience and evidence. The assessment of paediatric oncology medicines (Article 45) and the first PIP results lead to about 15 anti-cancer medicines updated product information.

An academic perspective

Some methodological challenges faced by academia with regards to paediatric pharmacovigilance were highlighted by the Enpr-EMA PRINTO network, in a presentation, on a pharmacovigilance project in Juvenile Idiopathic Arthritis JIA - Pharmachild the PRINTO perspective (Nicola Ruperto). Pharmachild is a European collaboration on long term outcome and pharmacovigilance for biologics used in Juvenile Idiopathic Arthritis (JIA). The question of setting up product registries or drug related registries as opposed to disease registries was raised. Some proposals derived from the presentation: it would be relevant to combine the existing non for profit and for profit registries for safety into one single international JIA registry for methotrexate ± biologics. Also there would be a need to establish a common platform for an active pharmacovigilance system whose main goals would be safety and effectiveness (e.g. erosions, efficacy, remission, retention on treatment). It was also mentioned a few initiatives to address long term safety studies, and patients' registries: PARENT, IMI project under Horizon 2020, on public private partnership for multiple registries.

Revision of the guideline for conduct of pharmacovigilance for medicines used by the paediatric population

An important element of this workshop was to present an update on the revision of the guideline on conduct of pharmacovigilance for medicines used by the paediatric population (Dirk Mentzer), after the concept paper was adopted by both PDCO and PRAC earlier in April 2014. The revision of this guideline should remain the 2014 main focus for paediatric pharmacovigilance for both Committees. It should be the umbrella covering all activities for paediatric pharmacovigilance.



Interactions between EMA PDCO and PRAC

Beside the collaborative work undertaken on the revision of the guideline, some concrete proposals for strengthening the interaction between PDCO and PRAC (Benjamin Pelle) in specific situations, in which input from either Committee is needed, were presented:

- Monthly screening of PRAC agenda and identification of paediatric safety issues (i.e. establishment of the link between PDCO concerns for long term safety or efficacy and RMP);
- SEVP Query Reports;
- Access to Committee expertise in evaluating product benefit risk issues for safety signals, safety reviews including Art.31 referral to PRAC and safety component of PIP assessment;
- Wider initiatives: Best practice guide on risk minimisation and prevention of paediatric Medication Errors and utilisation of paediatric clinical research infrastructure: Enpr-EMA, EnCePP and Enpr-EMA Working Group 8 on Pharmacovigilance;

It was noted the relevance to optimise the Committees interactions but to strictly respect the different Committees mandates. Also, the proposed interactions would not be implemented in a systematic way but only when input from either Committee is clearly required and in line with their legal mandates. A virtual PDCO/PRAC working group could be created to share information and expertise on paediatric safety issues. The PRAC will be responsible for the safety and benefit-risk evaluation of marketed products whilst the PDCO input could be in sharing information which would be of relevance to PRAC Rapporteurs in the review of RMPs to ensure well adapted to the needs of the paediatric population and in providing insights on therapeutic context for marketed products particularly established products. Moreover, PDCO subgroup expertise would ideally be more visible to PRAC members e.g. on formulation issues.

Actions points:

1. Moving forward with the drafting of the revised paediatric pharmacovigilance guideline:

- It is the umbrella covering all aspects of paediatric pharmacovigilance so it is the main focus of this year;
- First draft to be presented to both Committees by summer 2014;
- Public Consultation by end of 2014.

2. Improving the quality of paediatric ADR and paediatric Signal Detection:

- Quality of reported data should be improved: definition of minimum requirements, and common EudraVigilance dataset;
- Age, co-morbidity, and Date of Birth, should be reported/captured fields in ADRs;
- Stratification by age in ICSR (paediatrics ICH E11) should be looked at; in case the implementation is not possible, to have a tick box as “paediatrics”, “not paediatrics” or “unknown”;
- Age should be retrieved from the AE narratives when mentioned, so that paediatric Signal Detection can be performed;
- Common methods for Signal Detection in paediatrics should be defined;
- Lack of quality/appropriate formulation in Off-Label Use ADRs should be addressed;
- A MedDRA SMQ for Medication Errors should be developed and Medication Errors reporting encouraged.

3. Improving the interactions between PDCO and PRAC:

- A virtual PDCO/PRAC Working Group (with 2 assigned members from each Committee) should be set up to feed information on paediatric safety issues at both Committees and share experience of the therapeutic context.

4. Improving the interactions with specialised networks:

- Utilisation of Enpr-EMA Working Group 8 on Pharmacovigilance should be enhanced;
- Link between GRiP Work Package 2 on Pharmacovigilance and PRAC should be established for a proactive collaboration.

5. Continuing the work performed on Organ Maturation:

- The on-going work should be pursued and extended to, in order of priority, immune system, heart, skin, bone, ear and eye as it is useful for Signal Detection and RMP.

6. Second workshop on paediatric pharmacovigilance:

- It was suggested that a second workshop on paediatric pharmacovigilance could be organised in a year time in order to follow-up on the above action points and reflect on the progress made and gaps minimised with regards to paediatric safety.