EPTRI
EUROPEAN PAEDIATRIC TRANSLATIONAL RESEARCH INFRASTRUCTURE

EPTRI meeting with MEB experts

Date: October 05, 2018
Location: MEB offices,
Graadt van Roggenweg 500
3531 AH Utrecht
The Netherlands

List of Participants:

- Donato Bonifazi (Consorzio per Valutazioni Biologiche e Farmacologiche, EPTRI Coordinator)
- Giovanni Migliaccio (EATRIS ERIC, Consorzio per Valutazioni Biologiche e Farmacologiche)
- Martin de Kort (EATRIS ERIC)
- Erik Steinfelder (BBMRI ERIC)
- Miriam Sturkenboom (Universitair Medisch Centrum Utrecht)
- Caitlin Dodd (Universitair Medisch Centrum Utrecht)
- Fenna Mahler (Radboudumc Nijmegen)

Several other members from the MEB participated in the meeting.

The meeting was initiated by a round of introductions to englihten roles and expertise of the participating individuals. G. Migliaccio presented a short introduction to the ID-EPTRI project to clarify the background of the consortium and the reason why the informal discussion was requested to the MEB office of external affairs.

Scope of the meeting:

An informal discussion on a list of questions related to paediatric drug development with background information.
G. Migliaccio introduced the list of questions identified by ID-EPTRI coordination group and presented for discussion. The discussion started with some general questions and went through with some specific items to the end.

General Questions

Specific issues have been identified by a survey performed during the Spring-Summer 2018 in the framework of the ID-EPTRI project, aimed to collect interest and map potential service providers and research units to be included in the future European Paediatric Translational Research Infrastructure.
Most of the current drugs are developed for adults and retrofitted for the use in children, given the physiologic differences between neonates, children and adolescent, we propose to increase the development starting from leads identified in the specific sub-population stratified by age and relevant biomarkers. The following points were raised as gaps in the current research framework in need of a concerted response and in alignment with regulatory agencies.

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Q1: What does the agency perceive as challenges in assessing drugs for paediatrics, where research should and can be strengthened?

The number of patients enrolled in clinical trials is often too small to allow a thorough Benefit/Risk assessment. International cooperation between regulators and international compatibility of clinical research requirements are needed for ethical and methodological reasons. For products that are intended for a very rare paediatric indication, duplication of clinical studies with the same product and similar objectives should be minimized as much as possible. Collecting all the patients in a single trial would help to increase the significance.

For determination of the efficacy of a product in children, limited paediatric efficacy data is often supported by extrapolation of adult data to children. Therefore, knowledge of the PK and PD of the product in children (all relevant age groups) and adults is needed. Database of biomarkers to define the stage of maturation of various organ/tissue during the human development might be helpful to determine the relation between PD and maturation stage.

Although the regulators try to have a standard division of the paediatric population per age group, it was noted that between different guidelines the subdivision of the paediatric population was not consistent. The MEB will give attention to use consistent terms and definitions for subdividing the paediatric population by age. However, they also mentioned that in some cases due to the mode of action of a product or to the concerned disease, one needs to deviate from the standard subdivision. In those cases, the chosen subgroups need to be scientifically justified.

For efficacy (pharmacodynamics) there is no specific guidance; whereas for safety/toxicity there is strict guidance.

Q2: Can we, as EPTRI, support/help developing strategy/operational plans to achieve goals?

As mentioned in question 1, collaboration between stakeholders is important in paediatric medicine development, it would help to design optimal paediatric development programmes that are supported by physicians, ethical commission and patients and which meet regulatory requirements across regions. For this to be achieved, interaction between different stakeholders is needed. The MEB maintain the informal consultation with stakeholders mostly inside the framework of the EMA activities. Regular consultations meetings are held in the oncology field. The HESI group (specifically the Developmental and Reproductive Toxicology (DART) committee) based in the USA is cited as another entity acting as a forum for discussion between the industry, academics and the regulatory agencies.

Furthermore, for support of the discussion with regard to the development planning it would be useful that all involved stakeholders, including regulators, have access to all available data. In general, it would be helpful to the regulators if combined data available are shared (by open sources).

Q3: Which are the plans of the Agency to help the paediatric community in general?

Mostly through the participation to the international groups and activities organized in the EMA. In addition, two meetings are organized at the MEB each year for an update of all the upcoming general issues regarding drug development, including the paediatric applications.

The MEB works in collaboration with the Dutch 'kinderformularia', several paediatricians within the network of the Dutch "kinderformularia" can be consulted during assessment- and Scientific

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Advice procedures, to obtain their clinical input and consider those during decision making. Whereas the MEB informs Dutch paediatricians with regard to the paediatric regulation and the remaining challenges concerning paediatric clinical studies and assessment of the paediatric data.
Furthermore, the MEB is involved in 19 PhD projects (not all specific on paediatric research).

Q4: Which regulatory research the Agency would like to see in place for this special population?
No guidance has been prepared for the PD aspects as the attitude is to leave leeway to the developers to come up with solutions case by case for each new drug product. A better of stratification into smaller paediatric target populations would help. The development of novel alternative and better predictive models is encouraged, preferably using technologies like organ on a chip to reduce the need for animal studies, HTS platforms including cell lines (e.g. foetal cells, iPS for early stage markers) or zebrafish screening platforms to study effects on maturation and developmental biology, among others. These studies would require comparability studies. Juvenile animal models that answer the correct research question are equally valuable.

Q5: What type of evidence does the agency would like to see more?
In the clinical trial application, more attention should be given to the results from trials with similar products in the paediatric and adult population. In the case that the adult endpoints are not applicable, new endpoints should be validated before application in clinical trials.

Specific questions

Q6: *Existing guidelines refer to preterm-post term infants, toddlers, children and adolescents but such stratification of the subjects is not homogenous or constant across guidelines. There is a lack of understanding of the physiological differences between foetal, neonatal, children and adolescent physiology, in terms of hormonal, growth factor and intracellular regulatory pathways respect to adult individuals. Recent technology advances have opened the treatment to the foetal stage, no existing guideline is treating this age group. Moreover, the existing EU guidelines refer with different terminology and criteria to the staging of the paediatric population. (Ref. WC500236640.pdf; WC500147002.pdf; WC500003066.pdf)*

Is this stratification based on scientific criteria or other criteria? Would it be useful to define better the various stage of the human development in relation to drug development?
The Agency mentions the new guideline ICH-S11 on the use of animal models in the non-clinical development of drug for the paediatric population which contains tables indicating the comparability of development for various organ and tissues. The lack of consistency is likely to be due to the different revision timeline for the general guidelines. For a point to consider dedicated to the novel foetal applications, the PDCO at EMA should be consulted. In any case, the animal model should be fit to purpose and chosen on the basis of the specific application.

Q7: *There is a lack of specific guidance for the application of novel technologies to the various sub-groups of the paediatric population. Moreover, there is a lack of reference data for different ages and of a measure of variability between different racial sub-populations. In particular imaging could be useful to assess in a non-invasive way foetuses, infants and toddlers (i.e. imaging tracer etc.). The current guideline for diagnostics by the EMA mention "children" only in the safety section to limit their exposure to radioactive probes. (ref. WC500003581.pdf)*

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There is a lack of dedicated paediatric biobanks, especially for normal samples. The search for paediatric biosamples, in the Biobank European research infrastructure BBMRI, have identified few instances of paediatric ones and all are linked to specific clinical studies.

Does the agency agree with these evaluations and their relevance?

The Agency agrees with the usefulness of non-invasive methods for the assessment of specific biomarkers, especially if all the variables are controlled and the data made available in a public database for pre-competitive diffusion. It is also mentioned that ISO is producing a new standard for biobanking expected to be available on November 2018.

Q8: *Most pharmacologic studies are done on small rodents of adult (post sexual maturation) age. The use of juvenile animals is also frowned upon for ethical consideration with an increased burden on the researchers. Reliable models of the foetal, neonatal and juvenile stages of development are needed and require validation for the correspondence to the human targets. (ref. WC500003305.pdf)*

However, the reference to human adult safety data use limits the stringency of the request allowing for a justification of their absence. This approach is practical, but it is designed for the enlargement to the paediatric population of drugs designed for adults, not for the development of novel drugs designed around lead targets specific for the paediatric population. In alternative is proposed the development of in vitro methodologies (organs on a chip), using cells with characteristics present in foetal, immature stages of human development. No guidance is available on the validation of these models for the paediatric population. In addition, the purported foetal characteristics of cells derived by iPSC are considered a hindrance and not a possible tool.

Does the agency agree with this evaluation and its relevance justifying an effort in validating novel animal models? Or in vitro models with human cells?

The agency mentions the new ICH-S11 just released for consultation as a mean to make these instances noted and addressed.

Q9: *Lack of an easy pathway to the recognition of new pre-clinical models on the predictability of safety / efficacy of new drugs. The current model of validation for an animal model would require clinical data. As most of the clinical trials are done in execution of PIPs for other adult based drugs it makes the effort quite challenging.*

Which alternative pathway could be used to establish paediatric specific animal models?

It is suggested to check the US-EPA database of animal toxicology data (Toxicology Reference Database). It is also mentioned that the issue should be divided according to safety and efficacy prediction.

Q10: *Consistent guidance is given for the development of paediatric drugs however most of the current clinical studies are part of PIPs for the translation from adult to the paediatric population. (Ref. PK/PD guidance ref. WC500003066.pdf; Reflection paper on extrapolation ref. WC500236640.pdf; Guideline for the development of paediatric drugs ref. WC500147002.pdf; ICH guidance for paediatric drug development ref WC500002926.pdf)*

What is the feasibility of Phase I studies in healthy paediatric population with drugs specifically developed for the paediatric population?

As there are no prescription possible to request the development of novel drug for specific population this pathway is applicable only in few cases (i.e. for the common infective diseases of childhood).

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