European network of paediatric research at the European Medicines Agency

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Human Medicines Development and Evaluation

Response to:

General report on experience acquired as a result of the application of the paediatric regulation of 19 September 2012 submitted for public consultation by the European Commission on 'experience acquired' and 'lessons learnt'

Submitted by The European Network of Paediatric research at the EMA (Enpr-EMA)

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1. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Consultation Item 1:

Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

Paediatric development still seems to be an extension of adults needs instead of addressing specific paediatric needs as a significant number of new products are only relevant to very small numbers of children with adult-like diseases of low prevalence in the child population. Examples include auto-immune disorders, hyper-lipidaemia and idiopathic hypertension. Proposed trial protocols are also proving challenging to deliver as outcomes may require significant adaptation and consideration given to frequency of monitoring and nature of the investigations required.

HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

Consultation Item 2:

While the Paediatric Regulation has led to a certain amount of new authorisations that include paediatric indications, the regulatory instrument is recent and the data does not provide a sufficient basis for a comprehensive review. It will probably take at least a decade before the regulation can be judged in terms of its output. That said, it will always be a challenge to establish appropriate benchmarks for comparing off-label use with and without the Paediatric Regulation.

Do you agree with the above assessment?

Not entirely. Translating PIPs into clinical trial protocols that practising clinicians would be comfortable to recruit to is proving challenging. Issues include those outlined in Response 1 and the requirement to compare active products with placebo controls. Furthermore, healthcare systems with affordable access to medicines and the requirement to demonstrate symptoms at trial entry pose problems. Many clinicians would prefer to be engaged in comparator studies with existing established therapies than against placebo alone.

The regulation has not reduced off-label use in children. The regulation has worked well for medicines new on the market (which use has never been off-label), but due to the long deferrals granted to study children, it may take years before the effects will be seen in practice. New information on old medicines is not/poorly generated under the regulation. Measures to address old (off-patent) medicines are insufficiently executed.

THE PUMA CONCEPT: A DISAPPOINTMENT

Consultation Item 3:

THE PUMA CONCEPT: A DISAPPOINTMENT.

Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

Yes, the PUMA concept is a disappointment. Most off-patent medicines are currently delivered on the market as generic medicines. Pharmaceutical companies of generic medicines are not well equipped for research and development.

The paediatric population in which the "PUMA' drug is used is often too small to make up for the costs of research and registration. Moreover, the small number of drugs for which a PUMA has been acquired are infrequently used drugs in children. As such they have only addressed a small medical need.

Academic networks have a track-record in doing research, but may be unaware of possibilities to register for a PUMA as a academic network. If aware of this possibility at all, they will likely have problems complying with registration requirements and costs. Data protection is not an incentive for academic networks.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS.

Consultation Item 4:

Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

As the focus of Enpr-EMA is entirely on facilitating clinical trials with medicines for children we are unable to comment on this point.

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

Consultation Item 5:

Do you have any comments on the above?

Although the general goal of the regulation is to address paediatric needs there is too much emphasis on marketing authorisation to fulfil these needs. Paediatric development programs of new drugs do not necessarily solve this problem. Many drugs for which PIPs are agreed upon are developed for adult indications, e.g. antithrombolytics, antihypertensives, etc and do not present major paediatric needs. A significant proportion of diseases seen, particularly in young children, such as acute bronchiolitis and croup, diseases specific to the new-born and chronic symptoms with the same diagnostic label as adults but with different responses to therapy (e.g. pre-school wheeze) pose additional problems in the design of appropriate studies and targeted clinical trials.

It is also questionable if many me-too drugs (drugs in the same class and for the same indications) should be studied in children at the same time. Ultimately children benefit from high quality data on the safe and effective use of medicines for their specific needs, not solely from marketing authorisations.

6. THE BURDEN/REWARD RATIO — A BALANCED APPROACH?

Consultation Item 6:

Do you agree with the above?

Whereas it is true to say that the impact of paediatric regulation in terms of impact of the rewards is as yet unclear, experience with the FDA regulation has estimated the economic benefits in terms of sales and extended use of products in which extension studies into children have been performed (Li et al : JAMA, Volume 297(5).February 7, 2007.480–488)

For specific indications patient populations are often very small. Experience suggests that these patient groups are much smaller than the number of patients required when every company needs to study their own same class and same indication drug. This imposes a significant burden on children, which may not be warranted by the benefits accrued to that specific patient group.

Smarter study design approaches, including Bayesian methods, adaptive study designs, modelling and simulations, should be considered, to reduce the number of children exposed rather than always following the traditional drug development paradigm of Phase 1, 2 and 3 trials.

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

Consultation Item 7:

Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?

This should be the "hidden gem", but unfortunately misses the point in delivering paediatric data, useful to the public. Pharmaceutical companies often only forward the studies sponsored by the company. A search on PUBMED for additional paediatric data on the medicine is rarely performed, either by the company or by the Committee for Medicinal Products for Human Use (CHMP).

Such assessments often conclude that there is no evidence of efficacy/safety in the paediatric age group, despite an extensive and accessible body of relevant academic data. Considering the selection bias mentioned above, the validity of the conclusion proposed in this consultation item is dubious.

If the assessment leads to the addition of paediatric data in the summary of product characteristics (SmPC), data are mentioned in section 5.2 (instead of section 4.2), leaving the physician or pharmacist with no conclusion at all on dosing and not solving the off-label issue.

The Dutch Paediatric Formulary has some examples where good evidence for use in children is available, but the assessment reports on paediatric data conclude 'no evidence of efficacy and safety'. Although the level of evidence may be insufficient for marketing authorization (MA) in children, comments such as "no evidence of efficacy and safety " is not helpful to the public, since most products will be used anyway.

A European paediatric formulary might be helpful in disseminating knowledge derived from art45/46 procedure on paediatric use of medicines, when there is not enough evidence for paediatric MA.

The lack of interest in updating SmPCs on a voluntary basis is a concern. Approaches such as the British National Formulary for children (BNFc) might be an approach to consider in order to make the

information contained in the study reports more widely available. The involvement of clinicians together with regulators for the update of SmPC seems warranted.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Consultation Item 8:

Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

No, we do not agree. The accessibility and presentation of information is key. The online Dutch paediatric Formulary provides evidence-based information on the use of medicines by children and is used over 4000 times/day by unique users. Professionals need clear consolidated advice on dosage, safety aspects and daily practice. As they will not themselves search for (new) evidence, review available data and make a final conclusion, they need a translation from available evidence to daily practice.

Paediatricians are in general aware of the off-label status of most medicines, but this will not influence prescribing, as they often have no choice other than to prescribe off label.

A European formulary would be a solution for other countries without a national paediatric formulary.

The Paediatric Regulation will not, at least in the short term, reduce off-label prescribing, although could in the longer term provide scientific evidence on the use of off-label medicines and in doing so promote responsible off-label prescribing.

We do agree that healthcare professionals could be more interested in paediatric clinical research. Historically, paediatricians other than those managing childhood leukaemias and cancers do not have long-standing experience with clinical drug trials in children, as they were just not done. Although they might be interested in research, they do not have the experience to understand what it means to participate in a clinical drug trial, including PDCO/EMA and GCP requirements. Hence when approached by companies to participate a gap in expectations becomes evident and hampers much needed collaboration.

Moreover, as many current paediatric industry-initiated protocols impose more of a burden than deliver benefit to the individual child, many paediatricians are reluctant to enroll their patients. Although this may not have been a major issue for oncology phase I/II trials, where a potential benefit may be life-saving, for other less critical drugs, this may be a major issue for study feasibility. This roadblock may be overcome by smarter study designs and early involvement of practising children's doctors, who see patients on a daily basis.

Healthcare professionals could be encouraged to engage in paediatric clinical research through nationally supported child research networks such as being encouraged within ENPR-EMA. Such networks require a minimum level of support in order to encourage participation in building the evidence based base through well designed and well supported clinical trials. Member states should be encouraged to develop and disseminate formularies specific to needs of children in a similar way to child specific formularies such as the BNFc in the UK as available in the UK and Netherlands.

Similar challenges have been identified in the USA following the introduction of the 1998 "Pediatric Rule" and some of the responses and subsequent developments may provide some useful pointers to

possible developments in EU member states. Despite the lack of a national healthcare program, the USA has put in place some foundational elements to encourage participation. First, paediatricians are required to be recertified by the American Board of Pediatrics (ABP) in order to continue in active practice. In order to be recertified, they are required to engage in quality improvement projects/programs, and the ABP credits 30 of the required 40 points if a clinician is involved in a clinical practice research network -- a strong motive! Second, there is a strong move towards quality and safety and the value of networks is increasingly being recognized. The term being used is "Collaborative Outcome Improvement Networks (COINs)", but the work and goals are the same -- generating and using evidence to improve care and health outcomes. Outside of the well-established Children's Oncology Group and the Cystic Fibrosis Therapeutics Development network, the best example would be the Crohn's & Colitis improvecarenow (ICN) network. The ICN network currently extends to approximately 40 specialist paediatric GI centres including Great Ormond Street Children's hospital in London UK. By standardising management practices participating centres have seen the proportion of children in full remission increase from 49% to 78% over the 5 years of the network. The network is supported by a modest annual centre fee of $22,000 which enables independent annual assessments of quality and, the agency which lists "the best children's hospitals in America" gives credit towards their rating for full participation in ICN.

As most of the common diseases of young children such as croup and bronchiolitis are managed by general paediatricians not aligned with major academic centres, where the majority of specialty networks are based, the American Academy of Pediatrics has dedicated significant resources to support infrastructure for the Pediatric Research in Office Settings (PRIS) network.

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

Consultation Item 9:

Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

This is a particular problem for products within the same class, developed at the same time by different companies for the same indication and where the number of eligible children will be significantly smaller than eligible adults. The potential crowding of the market for such studies in a small number of children could be overcome by the use of comparator studies i.e. using the different products within the same class for the same indication. Although this is an unpopular approach for industry this is the most practical solution to the problem for clinicians. Other approaches could be the development of sequential trials with a single product within the class followed by a number of smaller studies to demonstrate comparability.

The design of clinical trials does not often comply with daily practice in terms of standard treatment of care, measurement of outcome parameters and burden to the patients.

Also, see the above comments at 7 and 8.

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

Consultation Item 10:

Do you have any comments on this point?

An important issue here is the early involvement of paediatric expert clinicians across the EU. There are clearly issues relating to protecting intellectual property but these concerns could be dealt with within the context of well regulated and supported Paediatric Research Networks.

As the workload of the PDCO is already high, it seems reasonable to consider a two-step program in which a preliminary program can be submitted and a full review on the PIP only performed when the proposed program has been shown to be feasible. Such an approach would be more balanced than current practice as many products are not considered by clinicians to address urgent and unmet paediatric needs.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

Consultation Item 11:

Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union?

A network of existing European networks has been established, facilitated by the paediatric regulation. It is not yet clear to what extent this network has contributed to clinical trials and expertise in Europe.

Furthermore the majority of Networks registered within Enpr-EMA rely on enthusiasm of a small number of individuals with little or no infrastructure support. Member states such as the UK and its four devolved health administrations have demonstrated how such support can increase participation in trials, can contribute to the education of healthcare professionals and increase the pool of expert advisors to the regulatory process. Without such support it is difficult to see how the aims and objectives of Enpr-EMA will be met in the medium to longer term. In this regard the experience of networks following the introduction of the 1999 "Pediatric Rule" in the USA outlined in response to question 8 has clear lessons for Europe.

Consultation Item 12:

Overall, does the implementation of the Regulation reflect your initial understanding / expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?

Variations in ethical opinions and health service approvals reflect wide variations in the expertise and experience of research in children. What is acceptable and ethical requires not only prior knowledge and experience but also access to views and attitudes of children and young people and their parents/guardians. Many professional and lay members of ethical committees and health service managers are unaware of work in this area resulting in lengthy discussions and not infrequently negative opinions for trials and medicines-related research in children. The development of public engagement including the establishment of Young Persons Groups is a priority within Enpr-EMA and for which support is currently not available.