Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company:

European Network of Paediatric Research at the European Medicines Agency (EnprEMA)

Transparency Register ID number (for organisations): _____

Country: EMA (based in United Kingdom)

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Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

- ✓My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication
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Please indicate whether you are replying as:

- o A citizen
- o A business
- o A non-governmental organisation (NGO)
- o An industry association
- o A patient group
- o A healthcare professional organisation
- ✓Academia or a research or educational institute
- A public authority
- o Other (please specify)

If you are a business, please indicate the size of your business Not applicable

Please indicate the level at which your organisation is active:

- o Local
- o National
- o Across several countries
- o ✓EU
- o Global

2. PART II – CONSULTATION ITEMS

(You may choose not to reply to every consultation items)

2.1. More medicines for children

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?
Yes. There is a clear difference between the extent of research on the development of paediatric medicines and legislation in the US and EU. In the rest of the world the absence of legislation is accompanied by a lack of research. Legislation is only one driver and has a particular effect on industry.

2.2. Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

Legislation is necessary but not sufficient for the development of medicines that are appropriate for children.
In the ideal world the reach of the legislation would be extended so that companies are required to consider paediatric needs rather than extending from adult developments.
However, this leads to a number of challenges:

1. Market failure cannot be addressed solely through legislation such as the Paediatric Regulation. If companies are required to develop medicines then it is reasonable for companies and children that those medicines will be made available. Access to medicines depends on many factors most of which are not within the scope of the Regulation, or even the competences of the European Union.
2. Medicines development is expensive and risky. The costs and risks of research are borne by children, health care systems and families, as well as by the companies. An unmoderated requirement to consider all possible uses in children could lead to unnecessary costs and risks for all parties

The Regulation has contributed to the availability of new treatment options across a number of therapeutic areas. For example, Ivacaftor, an extremely effective CFTR modulator drug for approx 6% of people with cystic fibrosis (those with gating mutations), dramatically improving outcomes for responsive individuals in this life shortening disease, is now approved licensed and available in England from the age of 2 years upwards (with appropriate granule formulation for pre-school children). Studies were performed in these age groups directly because of the EU Paediatric Regulation. It is likely that without this regulation it would only have been tested/approved so far in adults/children aged 12 years and above. The clinical benefits seen in children receiving this drug are dramatic for this severe condition.

2.3. Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

Yes

2.4. Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

Costs vary considerably between programmes.

Companies do not meet all the costs of drug development programmes. Children, families, research teams and health care systems provide significant contributions.

Many PIPs have included measures that do not directly inform prescribing and so have led to unnecessary costs (and risks) for children, families, health care systems as well as companies.

We have sympathy with the view expressed by some companies that costs incurred during paediatric development would not be excessive as long as there was a guaranteed way to recoup those costs through market access. In this sense, expenditure on paediatric drug development can be wasted if products are not placed on the market.

The same considerations apply from the perspective of children, families, research teams and health care systems. All these groups make investment in drug development that is not fully reimbursed by the companies. The investment (and exposure to risk) is wasted if products are not available.

The situation is complicated by the fact that many products developed through the Regulation do not primarily meet the needs of children but are extended from adult indications. Unfettered market access for inappropriate products may not be appropriate. This goes back to the point about whether companies should be directed more forcefully to targeting paediatric needs

The EMA's inventory of the needs for paediatric medicines could be better exploited and disseminated. The methodology to define a therapeutic need by the EMA could be reviewed.

Incentives and strategies to focus private investments towards research in the most relevant therapeutic needs are needed.

2.5. Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

We can only comment on this point from the perspective of non-commercial Sponsors, e.g. during FP7 products designed to support PUMA applications.

Many factors influence whether strategic planning will ensure that a company receives a reward. One of these factors is the implementation of the Regulation through the actions of the PDCO. In our experience the decisions of the PDCO can occasionally mean that strategic planning does not ensure a Sponsor receives a reward. While many factors impact on the results of strategic planning, decision-making by PDCO can sometime have a strong influence on the outcomes of drug development. This influence is independent of, and additive to, forces beyond the control of the PDCO.
For example the Metfizz Project (metformin for treatment of polycystic ovary syndrome in children) was unable to proceed due to the requirements of the PDCO rending the project unfeasible, and therefore it was unable to go forward as planned. There was similar experience with TINN (Treat Infection for NeoNates and their programme related to ciprofloxacin).

2.6. The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

Evidence shows that the orphan reward is not as attractive as expected by the various legislations. In the same time, it has to be acknowledged that the development of a medicine to treat a rare disease in a paediatric setting could be very difficult (e.g. inborn errors of metabolism affecting children from very early life). For this reason a reward strategy gathering the orphan and paediatric perspective, specifically addressed to companies developing a plan of paediatric studies for a rare disease could be explored.

2.7. Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

Yes, implementation has improved over time.

Examples: early interaction meetings, public workshops and meetings presenting relevant novelties in the regulatory field (e.g. the Reflection paper on extrapolation of efficacy and safety)

Other problems with implementation remain.

Examples: awareness of the incentives and possibilities given by the Paediatric Regulation among local institutions (e.g. ethics committees and regulatory agencies) has not been a straightforward process. For example, up to 2011 more than 80% of ethics committees in EU did not know the Paediatric Regulation (Altavilla A. et al 2011)

For this reason, a widespread and continuous information campaign among stakeholders is recommended.

2.8. Waivers and the 'mechanism of action' principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

Individual member networks will respond to this question.

2.9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?

Yes, we agree with this assessment of deferrals. We see no intrinsic reason to defer the study of a medicine in children (including neonates) until adult development has been completed.

The initiation of clinical studies in children should be determined on a case-by-case basis, taking account of the drug and the clinical need. Dose selection in children can be informed by studies in adults and pre-clinical models, particularly when drug disposition can be reliably predicted qualitatively and quantitatively between populations. However, when drug disposition cannot be reliably predicted it may be more useful to start studies that inform dose selection in different age groups in parallel rather than in sequence. Given the widespread agreement that safety cannot be extrapolated from adults to children it makes no sense to complete adult studies before opening studies in children on safety grounds. Therapeutic confirmatory / Phase 3 studies in children should start when an appropriate formulation is available, there is a rational basis for dose selection and the necessary assessments for inclusion criteria and outcomes are in place.

Deferrals should reflect the scientific and clinical realities of these considerations rather than commercial planning.

2.10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?

The implementation of the Regulation may be a disincentive to voluntary PIPs, as may the lack of a clear relationship between effort and reward discussed in Item 5.

2.11. Biosimilars

Consultation item No 11: Do you have any comments on the above?

We are aware of examples (e.g. in paediatric rheumatology) where children may be missing the opportunity to have access to suitable biosimilars because companies have chosen not to study these in the paediatric population.

Unnecessary studies in children have to be avoided and paediatric age-appropriate formulations/strengths should be available, irrespectively from the Marketing Authorisation Holders.

The request to develop additional biosimilar formulations/strengths has to be evaluated only if critical aspects exist with the already existing pharmaceutical preparations (e.g. costs, poor stocks, storage, etc.).

If there is evidence of paediatric off-label use for the originator, additional studies could be requested to develop the product in paediatric and/or to develop medicines formulation/strengths to cover other paediatric age subsets..

2.12. PUMA — Paediatric-use marketing authorisation

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

Yes, the PUMA concept is a disappointment. The incentives are not sufficient but market access is more important. The absence of research into off-patent medicines in children is a complex problem. This problem needs a multifaceted approach affecting multiple policy areas. In the absence of other policy initiatives the PUMA concept was unlikely to succeed. This problem can be analysed with respect to “push” and “pull” factors. In brief, research into off patent medicines for children requires funding and infrastructure (push). This funding will only come if there are markets (pull). The markets will only develop if there is an incentive to use a product with a PUMA when other products are available. From the perspective of health care systems an emphasis on marketing authorisation may have unintended consequences if the introduction of product with an MA leads to a significant increase in price. The future of the PUMA concept depends on the policy context: much of that context is not within the competence of the EU (e.g. access to markets).

We believe that for the PUMA concept to be effective, the Commission would need to provide sufficient funding to support the initiative.

We note that there have been some successes in relation to the PUMA concept (e.g. propranolol) and some particular disappointments (e.g. buccolam, which is not widely available).

2.13. Scientifically valid and ethically sound — Clinical trials with children

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

We believe that the introduction of the Paediatric Regulation increased the focus on paediatric research and changed the mind-set of the clinical research community from a position of believing that research on the paediatric population was unethical to the current commonly held view that it is unethical not to undertake research involving children.

In general: the Regulation has stimulated research and discussion of the application of new methodologies. We are uncertain that the best use of new methodologies has occurred – we get the impression that EMA has shied away from novel methods (CHMP as well as PDCO) and that many Sponsors are conservative because of institutional inertia or commercial pressures. Optimal implementation of the Regulation has not occurred yet.

Difficulties: using sites optimally has not developed – need to overcome barriers to working across specialties within each site and set up infrastructure that can be used by multiple studies and multiple specialties in each site.

Multiple studies in a limited population: the companies appear to be the bottleneck. Diabetes. Hepatitis C. More recent experience within Oncology is exciting. Further analysis is needed to examine this problem and to define policy solutions. Amending the Regulation may not help.

Lack of harmonisation about ethics is a major and unnecessary barrier to the development of medicines for children in Europe.

EnprEMA is uniquely placed to addressed these issues but is hampered by very limited funding.

2.14. The question of financial sustainability

Consultation item No 14: Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

It is important that adult development continues to subsidise paediatric development because of the flawed market in paediatrics. For example life-time benefits to the child, family health care system and society and are not always included in pricing decisions. Additional costs arising from fees to EMA would hinder paediatric development by small companies and academic groups.

The PDCO and EMA paediatric team are not resourced adequately.

We are unable to comment on the pressures within EMA. We can draw comparisons between EMA and FDA during international strategic initiatives. For example the EMA's contribution to the International Neonatal Consortium has been significantly less marked than the FDA's contribution (despite the valiant efforts of some individuals, particularly Dr. Ralph Bax).

2.15. Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

The Regulation has given overdue attention to children. 18% of studies added to EudraCT in 2015 plan to recruit at least one child – up from 8% in 2005. The studies added to EudraCT in 2005 planned to recruit 3,648 children while studies added in 2015 planned to recruit 211,302 children, an increase of close to 6000%. Between the 2012 and 2015 the studies added to EudraCT planned to recruit 0.7% of all European children to a medicines trial (assuming each child is recruited to a single trial). More and more Sponsors are realising that they cannot do business without paying attention to children.

The drive to capture medicines that are driven by adult needs has led to under achievement.

Paediatric drug development needs to be driven by the needs of children.

Effects of the Regulation have not been prominent because of latency and delays.

Many PIPs have not been feasible leading to delays as PIPs are revised.

The impact of the public funding for PUMA research has been less than anticipated. This resulted from a number of features including: the structure of the call which was intended to meet multiple policy goals (for example the exclusion of large Pharma stimulated the involvement of SMEs but reduced the chances of academics linking with relevant expertise); the fundamental inflexibility of FP7 funding which made it a poor choice for the management of a programme of clinical trials (despite the best efforts of individual scientific officers to overcome the limitations of FP7); the lack of understanding among academics of regulated drug development; problems with developing paediatric formulations in a timely way; poor preparation of academic centres to contribute to drug development (long delays in signing contracts etc.).

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2.16. "Mirror, mirror on the wall" - Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

Trends that will have an impact on development of paediatric medicine include:

- Precision / stratified medicine – need for more detailled –omic studies; resources; co-development of devices and medicines; quality assurance; smaller populations will be even more difficult to study
- e-Health: resources; regulatory framework
- Real world data: resources; regulatory framework; impact on benefit-risk assessments
- m-Health / wearables etc.: resources; co-development of devices and medicines; quality assurance; regulatory framework
- Need to develop all of these in a global context
- Possibility of altered regulatory system in the US
- Drug repurposing

It is not clear how the Paediatric Regulation will impact on these trends.

2.17. Other issues to be considered

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

The implementation reflects many initial expectations. However, the implementation revealed some points that need to be considered in the future.

1. The way in which Regulation was implemented had significant effects and changes to implementation led to significant changes in the effects. Changes to implementation should be the default way to address concerns raised during the consultation

2. The absence of robust mechanisms to assess feasibility during PIP development, evaluation by the PDCO and PIP implementation has led to many unfeasible PIPs and studies. The European Union needs to ensure that mechanisms to assess study feasibility are developed and maintained by EC funding, national funding or a combination of the two.

3. In the absence of robust feasibility assessments experts have had a significant role in the work done by companies and the PDCO. Dr. Janet Woodcock, Director of CDER at the FDA has commented “Don’t just rely on experts, they are usually wrong, due to sampling bias”. The role of experts in advising about feasibility and methodology may need to be revised.

4. Clinical Research Networks (such as the members of EnprEMA) can contribute evidence-based information about feasibility in addition to clinical and methodological feasibility. Clinical Research Networks need to be developed across Europe and all specialties. This requires funding and a system for coordinating multiple networks.

EnprEMA has considerable potential to promote successful implementation of the Regulation. EnprEMA has not had dedicated funding beyond some time for EMA staff members and facilities and reimbursement for one annual meeting. Despite this, EnprEMA has made significant advances bringing networks together and sharing good practice: this reflects commitment from EMA staff and the enthusiasm of network members. Investment in EnprEMA will promote the continued success of the Regulation.