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:

NIHR Clinical Research Network's Children's Specialty Group

Transparency Register ID number (for organisations): _____

Country: 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 the extent of research on the development of paediatric medicines and legislation in the US and the 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 in UK (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 through the NHS 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 – the MHRA has collated data on the new paediatric medicines that have become available since the Regulation came into force.

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.

There have been examples of products that have been found to be effective but which the companies involved did not wish to license due to the potential costs associated with marketing the product, as was seen with Canakinumab for the treatment of some paediatric rheumatological conditions.

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.

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.

2.6. The orphan reward

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

We have no specific comments on this particular point.

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 and we believe that some early problems with implementation have been mitigated.

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?

We suggest that the paediatric oncology community would be well placed to respond to this particular point, however we wonder whether the use of waivers associated with adult cancers may need to be reconsidered.

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. W are aware of examples where companies could have chosen the voluntary PIP route but having chosen not to, were later required to develop a PIP at a later stage.

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.

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).

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. This has resulted from significant work that has been undertaken with research ethics committees and their members since the Regulation came into force.

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?

We have no specific comments on this particular point.

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 introduction and implementation of the Paediatric Regulation has had significant impact on paediatric medicines research within the UK. In 2005 the Department of Health for England, in anticipation of the regulation coming into force, prioritised children's research and established the Medicines for Children Research Network (MCRN). This provided over £20M ring-fenced funding to set up and support the infrastructure required to undertake recruitment to paediatric medicines studies (both commercial and publicly-funded) for the first five years alone, with similar levels of funding provided during the subsequent five years. In addition, significant levels of research funding was allocated to paediatric research to support the development of new studies through a number of funding schemes and programmes dedicated specifically to improve the development of medicines for children. Part of the role of the MCRN was to engage with the life sciences industry to educate companies on the detail and implications of the regulation prior to its introduction in order to support the delivery of commercial studies within the UK and Europe. The MCRN was in operation for ten years before transitioning to the Children's Specialty Group within the National Institute for Health Research (NIHR) Clinical Research Network in 2015, which continues to provide the necessary infrastructure and dedicated resource to support research into paediatric medicines.

Since the MCRN was established, over 520,000 children have been recruited to portfolio studies within the Children's Specialty (12,500 to commercial studies) and currently more than 1700 studies are included within the Children's Specialty, 28% of which are commercially sponsored. The UK has been particularly successful in supporting commercial studies, and achieved 24 global first recruits to commercially-sponsored paediatric studies within the last five years.

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?

We suggest that the following trends that will have an impact on the development of paediatric medicine:

- Precision / stratified medicine – need for more detailed –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

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?

We have no specific comments on this particular point.