GENERAL REPORT: ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION (ARTICLE 50(2) OF REGULATION (EC) NO 1901/2006)

'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT' SUBMITTED FOR PUBLIC CONSULTATION

Subject: PCPD/12/01 — Public Consultation on paediatric report
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This response is from the NIHR Medicines for Children Research Network (MCRN), which coordinates medicines research conducted by health professionals in England

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MCRN responses to questions raised in the consultation document:

1. A change of culture: nowadays paediatric development is an integral part of product development

Consultation item No 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?

The Paediatric Regulation has, without a doubt, led to a fundamental change in the approach that companies are taking to develop medicines, giving children an elevated position in company approaches to drug development. Through industry studies conducted (MCRN have worked to support 213 industry studies) and licensing decisions to-date (including Losartan potassium (Cozaar), Tocilizumab (RoActemra), Latanoprost (Xalatan), Kalydeco (Ivacaftor) and the Menveo vaccine), we have already seen evidence that more child-appropriate medicines will be developed as a result of the Regulation, which is very encouraging. Occasionally, we discuss research programmes with companies based in non-EU countries who are not aware of the Regulation. In these cases, we refer them to EMA documentation so that they develop their understanding.

2. Has the Regulation delivered in terms of output? Too early to judge

Consultation item No 2: Do you agree with the above assessment?

Following studies that MCRN have supported, we have seen a small number of products licensed for children to-date. Despite low numbers of approvals, this is encouraging and shows that the Regulation is starting to deliver, and we expect many more products to be licensed over the coming years. Please note that a study of medicines trials registered in ClinicalTrials.gov with start dates between 2006 and 2011 shows 59% of children's trials to have been conducted without industry funding compared with 35% of adult trials (Bourgeois *et al*, Pediatrics 130(2), 285–92 (2012)).

3. The PUMA concept: a disappointment

Consultation item No 3: 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?

The number of successful PUMAs granted is disappointing and we would have expected to have seen more approvals by now. Anecdotally, we understand that the requirements for work to be undertaken to obtain PUMA approval is considered to be excessive by some companies relative to the potential rewards, although we have no direct evidence of this. In terms of detailed reasons for the disappointing uptake and views on whether PUMA will become more attractive in coming years, it would be more appropriate for companies to comment. However, it should be noted that academic networks have successfully taken forward projects to develop off-patent medicines under PUMA with EU Framework funding. Could more be done to develop academic/industry partnerships to encourage further PUMA approvals? Stimulation of clinical trials by award of paediatric exclusivity (by the US

Food and Drug Administration) has led to trials matching the distribution of the medicines in the adult market, but not the pattern of prescriptions in children. This suggests that market considerations, and not child need, continue to dominate pharmaceutical thinking (Boots *et al*, Eur. J. Pediatr. 166(8), 849-855 (2007)).

4. Waiting queues? No evidence of delays in adult applications

Consultation item No 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.

We are not well placed to comment on this point. Comments from industry and others are more relevant.

5. Missing the point? Paediatric development is dependent on adult development, not paediatric needs

Consultation item No 5: Do you have any comments on the above?

Many conditions in children will not have adult forms and for some that do, the causes will be different. For those conditions where the causes of childhood and adult forms are the same, it is important for advice to be provided by experts to ensure that the paediatric development will provide the information that health professionals require and that studies are feasible (please also see section 9). Expertise is provided by EMA/PDCO, with MCRN also willing to provide additional input as one of the Enpr-EMA networks.

To address concerns where the children's disease is different from the adult form or there is no adult form, we would like to see more PIPs that are driven by disease in children and an increase in basic research on many childhood conditions. We would welcome collaboration from pharmaceutical companies to partner funding for research from charities and other non-commercial funders. This work is likely to include the preparation of model PIPs (by networks, professional societies and others working with Enpr-EMA), as currently being undertaken by the European paediatric oncology community.

It should also be noted that key formulation developments for children will also be of relevance for adults, in particular older adults, so the establishment of the Regulation has applications well beyond its initial intention.

6. The burden/reward ratio — A balanced approach?

Consultation item No 6: Do you agree with the above?

We are not well placed to comment on this point. Comments from industry and others are more relevant, although we probably need to wait for detailed economic evaluations of the Regulation before changes are made to the incentives available.

7. Articles 45/46: the hidden gem of the paediatric regulation

Consultation item No 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?

We agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and for making it available to the competent authorities. We recognise the impressive work conducted through the work-sharing project, but wonder if different/further sources of information (including article 45/46 data, other data submitted to regulators for licensing purposes and other relevant data (e.g. in the UK, the National Neonatal Research

Database)) could be integrated, reviewed and made public (through collaborations involving academics, regulatory authorities, companies and others) to ultimately inform practice?

8. Lost in information: Healthcare professionals not as receptive as expected

Consultation item No 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?

The provision of new scientific information is of critical importance for healthcare professionals. This is probably most appropriately addressed at a national level, but there are opportunities to harmonise across EU (except in some areas e.g. antimicrobials where region-specific patterns will continue). In the UK, the British National Formulary for Children (BNFC) and other initiatives are addressing concerns. Moving forward, we need to ensure that all product approvals under the Paediatric Regulation are rapidly registered in the BNFC. In addition, the programme of industry and academic research conducted across the MCRN (approximately 400 studies) is further highlighting to healthcare professionals the need to generate more evidence on medicine use in children. Going forward, we should work to embed research into clinical practice as much as possible. Related to point 5 above, if drug development is exclusively focused on adults, paediatricians will not be able to participate in studies and evidence generated will not be relevant for children, which will in turn result in off-label use. The EU Framework-funded Global Research in Paediatrics (GRiP) initiative (in which MCRN is an active partner) will also help educate healthcare professionals about the importance of licensing medicines through training courses and other initiatives, including road shows.

9. Clinical trials with children: no specific problems detected

Consultation item No 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?

In contrast to the information presented in the consultation report, the MCRN has seen a massive increase in the number of industry studies conducted, from 4 in first year (April 2006- March 2007) to 55 (April 2011- March 2012). In total, we are now supporting/have supported 213 industry studies, with approximately 90% of studies taken on currently being related to PIPs.

Points raised on alternative methodologies and the duplication of studies (with different PIPs) do need to be addressed. Potentially, companies could collaborate to study multiple products in the same study (an approach that EMA is considering). To further limit unnecessary studies, consideration should be given to the level of information that health professionals need to prescribe products. In some situations, e.g. type 2 diabetes studies, large randomised-controlled studies are specified by the PDCO, but some experts consider that PK, safety and longer term pharmacovigilance data may only be required for older subsets of children due to the experience of products in adults. More advice (early in development cycles) could be obtained by EMA and companies from experts linked to MCRN and other Enpr-EMA networks. Associated with this point, feasibility is a major consideration for many studies that we support and patient numbers should be considered when study designs are suggested; again Enpr-EMA networks can help. Similarly, concerns raised in the report on the involvement on the youngest age subsets can be addressed by working with appropriate experts. Another recurrent issue is the application of inappropriate adult-orientated endpoints, for example, focussing on FEV1 in trials of drugs for asthma in children. Again, these issues could be avoided by appropriate input at an early stage of PIP development. To avoid the unnecessary and unethical duplication of studies, collaborative work between EMA and payer organisations (e.g. in the UK, the National Institute for Health and Clinical Excellence (NICE)) should be undertaken to ensure cost-effectiveness is considered (Pignatti *et al*, Lancet Oncol. 12(10), 930-1 (2011)). This work could include the joint selection of study endpoints, set pre and post-marketing standards and agree programmes of studies. Related to the points above, consideration should be given to early market access for new children's medicines, which in some situations may be appropriate (e.g. in serious and some rare disorders). In addition, it would be useful to explore if more data generated by investigator-led studies could be used by regulatory agencies to direct the licensing of products.

10. Unnecessary efforts? Non-completed paediatric investigation plans

Consultation item No 10: Do you have any comments on this point?

We are not well placed to comment on this point. Comments from industry and others are more relevant.

11. Sophisticated framework of expertise achieved

Consultation item No 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?

We agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the EU. Expertise extends from EMA/PDCO and Enpr-EMA to the developing knowledge of health professionals in EU member states within health systems, universities, networks and companies. It should be noted that the level of funding that MCRN receives from the UK government is unique across the EU, and this has allowed MCRN to develop an effective infrastructure and for the UK to capitalise on the Paediatric Regulation. Colleagues in other parts of the EU consider that more funds should be made available from their governments or from central European budgets to develop their network capacity or a pan-EU infrastructure.

12. Any other issue?

Consultation item No 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?

The implementation of the Regulation reflects our initial understanding/expectations, with products for children being licensed and more in the pipeline. In the future, we would like to see more PIPs that are driven by disease in children and an increase in basic research on many childhood conditions (point 5), although recognise the Regulation will not be responsible for all activities. Ensuring that studies approved by the PDCO are feasible and meet the requirements of patients and health professionals are key goals for the future (point 9), and MCRN is pleased to help facilitate these goals. Related to study feasibility (and point 9), it would be beneficial if companies, charities, health service and academic groups could collaborate further to join up/develop more comprehensive patient registries, as increasingly they will be required to support medicine development. Regulation on children's devices is likely to be required too, but this is clearly out of the scope of the current medicines legislation under discussion.