Date: 27Nov2012
Commented by: Finnish Investigators Network for Pediatric Medicines, Finland
Enpr-EMA membership: Yes, since 2010.
Network status: Non-profit network without legal status, hosted by CRI HUCH Ltd.
Pages: 4.

COMMENTS:

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?

Comment: It is too early to state that paediatric development has become an integral part of the overall product development of medicines in EU. With the results so far it may be justified to say that PIPs have become that, but it remains to be seen to what extent the companies are willing to perform the studies of the PIPs and seek labelling for children.

Additionally, it is not seen in practice yet. Pharma companies (including CRO`s) do not seek enough expert opinions nor help for the protocol development, i.e.ready plans without amending possibilities. The protocols are still planned with very narrow perspective and with inadequate expertise leading to the fact, that those are mostly suitable only for a few therapeutic areas not meeting the actual clinical needs of the pediatric patients. Multicentre studies may be difficult to conduct, if the indication is not relevant (i.e. such diseases do not exist so widely among children – like DM2) or the protocol is not suitable for national standard care and practice. The original purpose of integrating the overall product development is difficult to see at this point when the PIPs are submitted too late and medicinal product design is based on adult population medicines.

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

Comment: Yes

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?

Comment: Yes, we consider it unlikely that PUMA will become more attractive in coming years. We consider PUMA to be of less importance than the incentives/requirements/rewards concerning new medicinal products and developing new ways to provide incentives for medicines of primary interest for children not for adults.

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.

Comment: Yes

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

Comment: New ways have to be found to increase the development of medicines primarily needed by the paediatric population.

Despite all possibilities are screened, ensuring the potential use of adult medication, the pediatric trials are quite difficult to conduct if there are not enough patients, investigators or trial sites, only because the primary target is incorrect (clinical need, IMP, disease, diagnose, medical or ethical practice etc.)

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

Comment: Yes

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?

Comment: Data, which is important, should be in labelling and SmPC. Those are the only places where such data is easily and effectively available for the prescriber. The hard work of the regulatory assessments is largely wasted, unless means are found to include important information in labelling/SmPCs. Means should be found to do that.

Patient Organisations (patients, parents, administrators) and generally citizens, are now looking for the safety information and research publication of all new medicines for children (eg. from websites). This is very important aspect, and more data / information (non biased and independent i.e. not from Pharma Companies) should be openly available, especially when POs try to inform and encourage parents to take part to clinical trials in order to increase the safety and efficacy information about new medicines.

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?

Comment: Off-label use is not simply a question of information. Off-label use has dominated paediatric prescribing, because it has so often been the only option. Generations after generations of paediatricians, and other paediatric prescribers have had to adapt to “off-label culture”, starting from medical school. The situation has not changed significantly yet (as stated in the report Item No:2), so how could the medical practice have changed already? The problem is not one of information, but of changing practice. Change of practice is not achieved by provision of information; appropriate measures (educational interventions that have been shown to be effective) have to be instituted before change of practice can be expected.

As stated in Item No 5. , the reason not to be interested taking part to pediatric clinical trial is not depending on lack of interest towards new scientific information nor the restricted knowledge of off-label medicines use – on the contrary – they are seeking scientific information to cure this very problem, but if the trial proposed do not meet clinical or scientific interest, i.e. the actual clinical

need among the paediatricians or other doctors treating children, the engaging is more than challenging. Another problem for conducting the trials is limited resources (financial, personnel).

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?

Comment: As stated earlier, real increase in number of paediatric trials has not happened yet, so it is too early to make conclusions on problems or lack of them. However, it is worth noting, that our network has received too many proposals for clinical trials that have been badly planned, and some even unethical.

Additionally, the open competition between the companies (especially CRO`s) has led to problematic request practises, as two or three different companies try to find investigators and patients at national level to the same protocol (same study) – competing on who can win the feasibility contest and achieve the final agreement to administrate the requested (multicentre) study in Europe or globally. At that point, the potential investigators cannot – and are not willing to – fill 2 to 3 different feasibilities and answering multiple questions regarding to one and the same trial. In Finland, the situation is more important due to small population, a low number of potential investigators and trial sites. The duplicate trials are very rare and not easily performed in Finland.

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

Comment: Regarding to a normal drug development pipeline, the risk of discontinuations is existing fact – it has always been, also before the regulation. The argument of unnecessary efforts is not valid if the whole development pipeline is seen for both use groups; children and adults at the first place.

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?

Comment: It would be more appropriate to say that Paediatric Regulation has contributed substantially to an increase of paediatric expertise in the European Union. Calling the current situation an establishment of a comprehensive framework of paediatric expertise in the European Union is a gross overstatement. Europe is still far away from a comprehensive framework of paediatric expertise when it comes to development and scientific study of paediatric medicines. Key problems are the short and limited experience and lack of theoretical knowledge of many of the new experts (including many members of PedCo). The evidence suggests that the development in EU has been more a crash-course building of minimum capacity to manage the new challenges than establishment of expertise. Insufficient opportunities for high quality capacity building are available, and environments where experience can be gained under appropriate supervision/mentoring are scarce.

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?

1) It is becoming quite apparent, that if the PIPs with deferrals really lead to the clinical trials that have been planned, as is to be hoped, the available infrastructure of networks and centres that are able to perform high quality studies within the EU is insufficient. The infrastructure aspect of building research capacity was discussed during the development of the Paediatric Regulation, but no solution whatsoever was proposed (EnprEMA is not infrastructure). Building of European research infrastructure for paediatric clinical trials was left completely to the discretion of the Members State, with the result that it has, with the significant exception of the UK, been ignored. The experience from EnpEMA has shown, that such infrastructure cannot be built to sufficient levels to meet future needs on the basis of revenue from industry sponsored trials, simply because such income will only become available when studies are performed. Part of the success of the US paediatric legislation can be assigned to the early creation of an infrastructure in the form of PPRUs. The success of the UK MCRN also documents the value of developing a good infrastructure in time.

2) The implementation of the Regulation may have increased some awareness and understanding among the regulative, administrative (e.g. hospitals) and networking collaborators. Nevertheless, due to the lack of allocated funding it is quite difficult and very slow to operate with limited resources at the national level, which leads to unbalanced economical possibilities between the European networks of Enpr-EMA (i.e. big differences in national and private supporting funding for networks) to full-fill the requirements of the Regulation.

3) While it can be said, that the paediatric obligations have had no impact on timelines in adult development, including marketing authorisation. However, it becomes increasingly evident, that many new medicines likely to fill important paediatric needs will become available with regulatory approval for children, and particularly newborns, after long delays if at all. It is easy to get the impression, that too many too long waivers have been granted, probably with the good intent of preferably erring on the safe side, but with many children suffering and even dying while waiting for the new innovative treatments. At this point it is certainly too early to make a judgment, but then it is also already too late for many paediatric patients.

Behalf of the Executive Committee,
Pirkko Lepola, Executive Secretary of FINPEDMED

Finnish Investigators Network for Pediatric Medicines - FINPEDMED
Clinical Research Institute Helsinki University Central Hospital Ltd.
c/o University of Tampere, School of Medicine, Tampere Center for Child Health Research
Biokatu 10, FM 3, 3rd floor
FIN-33014 University of Tampere, Finland
Phone: +358-50-5142646
e-mail: pirkko.lepola@uta.fi
www.finpedmed.com