Document submitted by aPODD Foundation

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 medicines in the European Union?

Yes we agree with the statement above.

Overall, the regulation has undoubtedly had a positive impact on paediatric drug development as industry is now obliged to plan and fulfill a paediatric development as pre-condition for a marketing authorisation of the new drug. An additional positive aspect has been the increased awareness in the industry about the needs of paediatric drug development. This effect is shown by the creation of paediatric development groups within pharma and biotech companies and the recruitment of relevant experts.

2 Has the regulation delivered in terms of ouput? Too early to judge

Consultation item 2: Do you agree with the above assessment?

Yes, we agree with the above assessment. We agree that the Regulation has led to a general increase in paediatric industry sponsored studies. This positive impact, however, did not occur in all therapeutic areas. Since the obligation to conduct paediatric studies is referred to the primary adult indication, we have seen a positive effect primarily for those diseases that affect similarly adults and children. In the area of oncology, however, the impact on paediatric drug development has been much more limited, largely in view of the differences between adult and paediatric cancers (more at point 5).

In paediatric oncology, the biggest burden in terms of poor prognosis and lethality is given by diseases that typically occur in childhood and adolescence and are generally not seen in the adult population. These are, for example, solid tumours such as neuroblastoma, soft-tissues sarcomas and certain CNS tumours. We still have limited therapeutic options for these diseases and we have not observed a clear improvement in survival rates over the past 20-30 years for certain subsets of paediatric patients.

If we analyze the PIP-related decisions in the oncology area between Jan 2007 and March 2012 (as provided by the EMA website) we see that out of 77 PIP decisions and 33 approvals, only approximately 5 PIPs were approved for one of the above cancers primarily affecting children.

From a patient prospective it seems fair to say that the Regulation has not yet delivered a substantial improvement in therapeutic options (approved or in development) for children with cancer.

3 The PUMA concept: a disappointment

Consultation item 3 Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? It is likely that PUMA will become more attractive in the coming years?

We agree that the impact of PUMA on paediatric drug development has been limited, despite considerable funding from the European Commission. Perhaps with a change that requires a significant amount of funding to be given to SMEs this might result in PUMAs coming through with public funding. This change could be taken further with SMEs required to become the applicant to drive these products through to license.

Whilst several years ago there has been considerable funding of specific oncology products, none of these products have got to a license. The reasons for this should be considered. Ideally, we would like to see some additional funding committed to oncology. Perhaps the 'rewards' are a deterrent to the considerable time and cost in taking these product through the regulatory and development process.

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 authorization applications for reason of compliance with the paediatric obligation?

No comment

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?

It is true that the whole drug development process is dictated by adult development rather than paediatric needs. Pharma/biotech companies do not specifically develop compounds for paediatric cancers. Most of the oncology drug candidates currently being developed by industry are for indications that are not seen in children (e.g. breast cancer) and, therefore, are eligible for a waiver and fail to have an impact on pediatrics. The situation is often made more difficult by the need of further pre-clinical work to support studies in children for different cancers and find appropriate resources for paediatric clinical development. It is fair to admit that the Regulation in its current form is unable to create sufficient incentives for paediatric development in the oncology area. At present there are no compelling incentives for the presentation of "voluntary" PIPs for specific childhood cancers.

The situation would be very different if compound evaluations by EMA were mechanism-driven rather than disease-driven. This change is probably not unreasonable in view of the increasing trend of segmenting target indications according to specific biomarkers.

6 The burden/reward ration – A balanced approach?

Consultation item 6: Do you agree with the above?

It may be difficult to evaluate the burden/reward ratio as this is probably subjective and dependent on the resources of the specific drug development agent (e.g. large pharma *vs* small biotech). However, it seems fair to comment that whereas the burden is met relatively early in development, the reward may only come in the future and is also linked to the inherent risk of adult clinical development. The compound may be dropped during clinical development in adults, thereby making the extra 6-months exclusivity useless. The balance is probably tilted toward the burden aspect for most companies.

One idea could be the conception of a "multi-staged" PIP, where the company would initially present a shorter plan covering only pre-clinical and early clinical development, followed by a second PIP with the details of full clinical development. In practice, the second plan would be drawn once more data from adult studies will become available. This approach would probably alleviate the burden for the company and facilitate the whole planning process.

Furthermore, an appropriate modification of the "voucher' approach envisaged by the legislation recently approved in the US ("Creating Hope Act") may create more powerful incentives for companies willing to present a voluntary PIP for paediatric-specific cancers, even though their compound had been originally developed for an adult indication. The voucher would be transferable and could be spent for 'fast-track' review by EMA of another drug candidate chosen by the pharma company.

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, vi a databases , to the interested public?

No comment

8Lost 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 the 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?

Health care professionnls dealing with children in general paediatric medicine still have to prescribe a high amount of off-label drugs as most of these drugs are off-patent and the interest of investigation into these medications is very limited (see PUMA). So for general paediatrics, there is still an unmet need.

In our experience healthcare professionals dealing with special paediatric diseases (e.g. immunology, oncology , cardiac disease) are very aware of new scientific information in paediatric drug development, but still a lot of drugs for these subgroups are still not labeled for paediatric use as there have not been any investigations undertaken (PUMA) Additionally information is not always clear as to what licensed products are available and dissemination of this information at a national and local level as new products receive a paediatric license is critical as well as ensuring that patients are moved to licensed products where available and appropriate

9 Clinical trials with children: no specific problems detected

Consultation item 9: Do you have any comments in development in clinical trials with children following the adoption of the Regulation and in the view of the above description?

It is generally agreed that no specific problems have been seen in this area so far. In paediatric oncology, however, the access to patients for clinical evaluation may be challenging and is dependent on international collaborations through multi-site trials, because of the relatively low numbers of children with cancer. Given the limited impact in oncology, specific delays caused by the regulation were not seen. However, if and when more powerful incentives are created leading to a substantial increase in paediatric evaluation of anti-cancer compounds the situation will change. We will need more compound prioritization and a more collaborative approach among all stakeholders in order to assess the industry pipeline.

10 Unnecessary efforts? Not-completed paediatric investigation plans

Consultation item 10: Do you have any comments on this point?

This is clearly a risk, which cannot be avoided given the current legislative requirements. From an industry prospective, if indeed the PIP is an obligation and a necessary step in order to be eligible for approval, then this is not exactly an unnecessary effort. On the other hand, from a paediatric patients' prospective it is potentially a waste of opportunities since many interesting compounds may not progress in the clinic and will never reach the patients.

The only possible improvement would be given by the possibility of gaining access to these discontinued compounds by third parties, in those cases where the PIP is discontinued solely because of failure of adult development and the compounds still hold promise for the relevant diseases in children (assuming that the company has no interest in pursuing a paediatric indication alone in this scenario)

11 Sophisticated framework on 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?

We agree that the regulation has generally facilitated this process

12 Any other issues?

Consultation item 12: Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of the legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?

In paediatric oncology the real challenge lies in the creation of powerful incentives through new business models and strategic partnership between the relevant players (academia, non-profits, industry).

From a regulatory point of view it may be hoped that appropriate modification to the regulation will be introduced to take into account the above limitations that affect paediatric oncology, or any other area where the paediatric disease is fundamentally different from the adult one. For products where development is stopped for commercial or scientific reasons for the adult indication, it would make sense if these products could be independently acquired by third parties for paediatric assessment particularly in oncology.

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