Consultation in relation to the Paediatric Report

1. PART II – CONSULTATION ITEMS

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

1.1. 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?

- AIEOP agrees that the EU Paediatric Regulation changed the overall landscape for paediatric drug development.

- However, most pharmaceutical companies continue to consider paediatric development in oncology as a regulatory requirement to comply with rather than a full research and development program addressing the needs of patients.

- In oncology, only two (2) medicines with innovative mechanisms of action (Votubia™ and Unituxin™) have been approved, so far, through a Paediatric Investigation Plan (PIP).

- Cancer remains the lead cause of death by disease in the young population over the age of one and 6000 young patients die each year of cancer in Europe.

- There is a clear need to accelerate the development of innovative drugs for children with cancer.

- Thus, AIEOP agrees that a legal framework is needed, but it should be modified and improved significantly to address current hurdles and limitations.

1.2. 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?

- For many years the same anticancer drugs have been (and still are) used in adults and children for the treatment of cancers, despite the fact that malignancies occurring in adults and children differ in terms of pathology.

- AIEOP agrees that there are therapeutic areas such as paediatric rheumatology which clearly benefited from the Regulation.

- This has however not been the case for paediatric oncology. A major reason is that the Regulation considers only drugs developed in adults and in the situation where the condition is the same in children and in adults.

- AIEOP disagrees with the statement that this state of affairs was hardly influenced by the legislation. Indeed, as waivers can be granted according to article 11.b) on the simple grounds that the condition does not occur in children, the Paediatric Regulation is responsible for several scientifically and medically unjustified waivers of anticancer drugs, such as crizotinib.

- Thus, the Regulation did not deliver at the level of expectation for children and adolescents with cancer, at the time when cancer is the 1st cause of death by disease in children over 1 year of age and there is an ongoing explosion in the number and type of new anticancer drugs developed and authorised in adults.

1.3. 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?

- In paediatric oncology, the number of available approved new medicines has not increased significantly during the last 10 years under the Regulation. Few new drugs, such as the BCR-ABL inhibitors and soon blinitumumab have been introduced in the treatment of leukaemia, and one drug in neuroblastoma (Unituxin™). There have been no new medicines approved for the treatment of the vast majority of paediatric malignant solid tumours.

- Unfortunately, AIEOP is unable to provide information on accessibility of approved drugs after their marketing authorisation because extremely few new anticancer drugs have been approved for paediatric use.

1.4. 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?

- AIEOP has no comment regarding the costs for pharmaceutical companies, but we note with interest that the average cost of a PIP is 20 M€, far less than the development of a drug in adults.

1.5. 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?

- According to ongoing dialogue with pharmaceutical companies, the obligation to submit PIPs before filing in adults is the real stimulus driving the design and implementation of the PIPs, rather than the probability of a reward.

- AIEOP understands that once the reward is granted, it must be submitted in each Member State for actually prolonging the supplementary protection certificate (SPC). The published data available on the website of the European Commission show that it is a lengthy and complex process.
- There is a unique type of reward linked to the completion of a PIP that is independent of its results. This creates an incentive to comply with the PIP even though it may have started late during drug development due to deferrals.

- The reward is awarded when the trials are delivered according to the PIP (compliance check). The same reward is awarded in the following cases:
  - A company starts paediatric development late, after first marketing authorisation in adults is granted, thanks to a deferral (almost all Oncology PIPs have deferrals);
  - A company submits a PIP early, i.e. at the end of adult phase I trial, when dose and pharmacokinetic data are available, in agreement with the requirements of the Paediatric Regulation;
  - A company develops a voluntary PIP, i.e. in a paediatric indication different from the adult indication, while a class waiver could have been obtained.

- The rewards should be revised in a way that goes beyond just complying with the Regulation (i.e. delivering data compliant with the PIP) in order to better incentivise companies willing to address paediatric needs through R&D programmes in a timely fashion.

- A system to reward companies investing in paediatric oncology drug development in partnership with cooperative groups should be installed.

1.6. The orphan reward

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

- Each type of malignancy in children is rare and all childhood malignancies together fall within the definition of a rare disease.

- Paradoxically, the Orphan Drug Regulation did not impact the development of new anticancer medicines for children, both before the Paediatric Regulation was in place and since it is up and running.

- There is a need to set up a reward to incentivise development of oncology drugs which will be specific for paediatric malignancies and first marketed in children. The successful US Priority Review Voucher illustrates that such types of reward are able to speed up in incentivise paediatric drug development.

1.7. 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?

- AIEOP agrees that the implementation of the Regulation has improved over time; however, there is still a need for progress.

- Currently the process of evaluating the PIPs is too long and should be simplified and shortened.

- More information on the content of the PIPs should be made publically available, as this is mainly a non-competitive field;

- The European Medicines Agency (EMA) and its Paediatric Committee (PDCO) should more often require PIPs outside of the adult indication when scientifically and medically justified.

- PIPs should be submitted at the end of phase I trial (as requested by the Regulation) and not a few months before filing in adults for a first marketing authorisation.

1.8. 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?

- Those arguing that "changes to the waiver concept risk endangering the objective of disease-agnostic statutory rules as well as the predictability of paediatric investigation plan decisions with regard to the expected scope of paediatric research" are running the risk of overlooking the reality of the needs of children with cancer.

- It is crucial to waive the development of a medicine if it is unsafe, unlikely to address a need, or unlikely to be better than existing treatment.

- BUT: Essentially, article 11. b) is an absolute contradiction with the goal of the Regulation, which is clearly stated in its Recitals: to address the urgent paediatric needs. Waiving drugs with relevant mechanism of action is against the principle and the philosophy of the law.

- Example: scientifically and medically unjustified waiver: crizotinib

Crizotinib is a targeted anticancer drug for the treatment of ALK+ lung cancer. Lung cancer does not exist in children and the drug has been class waived for its development in the paediatric population. ALK rearrangements are observed in several paediatric malignancies: anaplastic lymphoma, soft tissue sarcoma, neuroblastoma, making crizotinib a relevant and important drug to evaluate in children based on its mechanism of action.
Consequences:
-- The paediatric development of crizotinib started in the US in December 2009 and showed high level of activity in children and adolescents with lymphoma and sarcoma as well as some activity in children with neuroblastoma.
-- In Europe, children and adolescents with ALK+ relapsed malignancies have been denied access to an ALK inhibitor until ceritinib, another ALK inhibitor, has been voluntarily developed in children (February 2013).
-- Currently, there are major inequalities in Europe for children accessing crizotinib as: i) very few academia-driven trials are ongoing; ii) the drug is prescribed off label in some countries; iii) most children with an ALK+ malignancy do not have access to an ALK inhibitor.

1.9. Deferrals

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

AIEOP agrees that deferrals for any (real) reason other than safety result in delaying the start of trials and access to innovation. This is of particular and major concern in the situation of life-threatening diseases.

1.10. Voluntary paediatric investigation plans

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

- We agree that the Regulation (hopefully) does not prevent the paediatric development of a drug outside of its adult conditions, even though a class waiver may have been granted (for legal reasons).

- We agree that some companies submit and develop such voluntary PIPs, which are often successful. We applaud these companies.

- However, the provided comment suggests that since it is not forbidden and it happens, the current situation with regards to waivers is acceptable.

- There is then a fundamental question about the goal and the philosophy of the Regulation as it was introduced by EU institutions: is it really to ensure that better medicines are developed and authorised for children, since it ignores a large part of the paediatric development of adult compounds, leaving this critical aspect to the goodwill of pharmaceutical companies?

1.11. Biosimilars

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

In paediatric oncology, we are unfortunately not in the situation of having biosimilars of monoclonal antibodies approved for paediatric use, since we do not have monoclonal antibodies at the end of their patent.

1.12. 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?

- In paediatric oncology, we identified early that the needs for research on off-patent anticancer drugs that could fall under the PUMA concept were:
  - Age appropriate formulation of oral anticancer drugs
  - Dosing of chemotherapy below one year of age
  - Long term toxicity in childhood cancer survivors

- Some research projects on pharmacokinetics of oncology drugs in the very young children have been conducted but did not contribute (yet) to change of labelling. No PUMA has been granted for an age-appropriate formulation of an off-patent anticancer drug. Long term toxicity is addressed outside the field of PUMA through large consortia and EU projects such as PanCareSurFup (http://www.pancaresurfup.eu/), PanCareLIFE (http://www.pancarelife.eu/), ENCCA (http://www.encca.eu/).

- Indeed, the PUMA concept did not work, since only 2 PUMAs have been granted in 10 years for all paediatric diseases. It did not work in paediatric oncology either. It does not mean that there is no

more need to generate data on off patent medicines. EU research framework programmes should continue to allocate funding to study on off patent medicines. This will generate new academic knowledge to be published and disseminated to the academic community in order to improve practices.
It is important to take into account the following: if an old drug becomes available through a PUMA at a rather high price, it is likely that paediatricians will continue to prescribe the more economic off-patent medicine that they are used to prescribe, unless changes in the formulation have been done through the PUMA.

1.13. 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?

- Paediatric development by pharmaceutical companies should be systematically done in collaboration with cooperative groups and networks, including during early interaction to best design PIPs with regards to needs and feasibility.

- Networks should have structural resources to facilitate enrolment of patients as well as their referral to investigating centres, especially when patients are rare.

- Parallel paediatric development of "me-too" drugs or similar drugs by different companies should be avoided. Processes should be put place to prioritise and avoid duplication in order to better fit the needs of patients and considerations of feasibility.

- In paediatric oncology, clinical research is structured through clinical trial groups addressing the needs by disease and across disease areas, but there is a need for funding to support efficient referrals when needed.

1.14. 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?

- Experts should be compensated for additional work performed outside of their daily job.

- If agencies are compensated to do work on adult programmes, they should also be compensated to do work on paediatric programmes. There is no reason why paediatric drug development should be cheaper.

1.15. Positive impact on paediatric research in Europe

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

- In paediatric oncology, the Regulation did not change clinical research since the community has been successfully running academic clinical trials (the vast majority without participation of pharmaceutical companies) over the last 50 years – a long-standing cooperation that clearly improved outcomes.

- However, the Regulation did significantly increase interactions between pharmaceutical companies and the paediatric haemato-oncology community including academia and parents/patients, which led to an increase of new drugs available in trials within or outside PIPs.

- In addition, collaboration between parents and academia has been instrumental to elucidate the positive effects as well as the limitations of the Regulation and to propose solutions to accelerate new paediatric drug development;

- Thus, we can say that the Regulation significantly changed the landscape in paediatric oncology; however, it is far from addressing the needs of children with cancer due to existing loopholes and drawbacks. There is a need to modify the law and its implementation.

1.16. "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?

- The field of oncology drug development is rapidly changing, taking into account new biology knowledge generated through high-throughput technologies. Adapting drug development and patient treatment to molecular alterations identified in patients' tumours become a hallmark of innovation, especially in the field of targeted therapies. The use of biomarkers is key to provide each patient "the right" drug or drug combination he or she may benefit from. The number of master protocols as well as basket and umbrella protocols is rapidly expanding and new design and methodology are developed to address the issue of rarity of adult patients.

- This is occurring as well in paediatric oncology. Cooperative groups have set up programmes to generate comprehensive molecular and immunological information from the relapsed or refractory tumour of each patient and try to match therapies in clinical trials with the identified alterations.

- It is crucial that a larger number oncology drugs enter early phase trials in children in order to increase the capacity of matching treatments to individual tumour molecular portraits, and to streamline drug development. We are developing master protocols to speed up in the introduction of innovative compounds in early drug development in children with cancer.

1.17. 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?

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