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: **Cancer Research UK**

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- o A non-governmental organisation (NGO) – Medical Research Charity

Indicate the size of your business

- o Large (250 employees or more)

Please indicate the level at which your organisation is active:

- o National

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?
Cancer Research UK agrees that specific legislation supporting the development of paediatric medicines is necessary. However, we feel that the current regulation is underperforming, and requires amendment to ensure that it fully achieves its aims. The implementation of the regulation has seen only a 10% increase in the number paediatric marketing authorisations as a proportion of all marketing authorisations awarded[1]. Furthermore, within the field of paediatric oncology, only 2 medicines with innovative mechanisms of action, Votubia (Everolimus) and Unituxin (Dunituximab), have been

[1] 10-year Report to the European Commission: General report on the experience acquired as a result of the application of the Paediatric Regulation. https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

approved through a Paediatric Investigation Plan (PIP).

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?

Despite cancer being the leading cause of death by disease in the young population over the age of one, with 6000 young patients dying of the disease in Europe each year[2] just 2 paediatric cancer medicines have been approved through a PIP.

We do not agree with the Commission's conclusion that this is 'dependent on factors that can hardly be influenced by legislation'. Article 11(1)(b) of the regulation allows for the requirement to complete a PIP to waivered on the grounds that the condition does not occur in children. However we are becoming increasingly aware that the mutations found within a cancer are of greater relevance to treatment and prognosis than the tissue or organ in which the tumour is located.

According to analysis of the minutes of the EMA Paediatric Committee, between 2012 and 2014: 214 class waivers were discussed, 72% of these were for an oncology drug, of which 95% were granted waivers (i.e. 147 drugs). Alarmingly, 63% of drugs receiving waivers were relevant to paediatric malignancies on the basis of mechanism of action[3].

This will be discussed further in section 2.8.

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?

Within the field of oncology, the number of new paediatric medicines available in Member States has not substantially increased. We are aware of just two new medicines with innovative mechanisms of action, Votubia (Everolimus) and Unituxin (Dunituximab), have been approved through a PIP.

[2] Vassal G. et al. (2016) The SIOPE strategic plan: A European cancer plan for children and adolescents. Journal of Cancer Policy

[3] Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin.

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?
We have no specific comment on the costs for pharmaceutical companies. However it is encouraging that the Commission has noted herein a critical flaw in the regulation that permits companies to abandon agreed PIPs if they decide to abort the adult development programme. The result is that new medicines showing promise for children are not adequately researched after a drug fails to show potential in an adult indication. We would like to see better regulatory requirements and rewards for early PIP completion that will help to establish an evidence base for the paediatric population even if the adult development program is aborted. This is discussed further in sections 2.5 and 2.9.

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 do not think that the current reward system incentivises development of innovative paediatric oncology medicines. The reward is not sufficiently motivating for companies to complete PIPs in a timely fashion. An analysis of paediatric oncology PIPs performed in June 2012 found that the start had been deferred in 82% of cases[4]. For companies, the current reward for completing a PIP is a secondary consideration relative to the need to comply with the Regulation as a prerequisite for obtaining a marketing authorisation. Failure of a drug to show positive results in an adult cancer therefore leads to the corresponding PIP also being cancelled. It is crucial that PIPs are started early in the product development cycle and that agreed timelines for completion are adhered to. Possible amendments to the reward system that could be considered: 1) Enable the current reward to be awarded in two stages to encourage companies to start PIPs earlier 2) An additional reward that incentivises the completion of a PIP where development for adult indications has failed

[4] Vassal g. et al. (2013) Is the European Pediatric Medicine Regulation Working for Children and Adolescents with Cancer? CCR Perspectives in Drug Approval. Vol 19. Issue 6.

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 comment on this issue.

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?
The area that we feel that there is the greatest need for improvement in implementation is the requirement of Regulation Article 16(1) that PIPs should be submitted "not later than upon completion of the human pharmacokinetic studies in adults". A 2012 analysis of paediatric oncology PIPs found that the start had been deferred in 82% of cases[5]. Failure of a drug to show positive results in an adult cancer leads to the corresponding PIP also being cancelled so it is crucial that PIPs are submitted early in the product development cycle and that agreed timelines are adhered to.

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 urge the commission to introduce the 'mechanism of action principle' to the Regulation. We find it concerning that Article 11(1)(b) has led to so many missed opportunities for paediatric cancer medicines as a result of waivers given on the basis of a lack of the presence of the disease in children. Few paediatric cancer drugs are used in the same indication as for adults. Indeed, more than 90% of anticancer drugs used in paediatric malignancies are used to treat a different adult cancer[6]. According to minutes of the EMA Paediatric Committee, between 2012 and 2014: 214 class waivers were discussed, 72% of these were for an oncology drug, of which 95% were granted waivers (i.e. 147 drugs). Alarmingly, 63% of drugs receiving waivers were relevant to paediatric malignancies[7]. Therefore for paediatric cancer medicines it is vital that mechanism of action is taken into account.

[5] Vassal g. et al. (2013) Is the European Pediatric Medicine Regulation Working for Children and Adolescents with Cancer? CCR Perspectives in Drug Approval. Vol 19. Issue 6.

[6] Vassal g. et al. (2013) Is the European Pediatric Medicine Regulation Working for Children and Adolescents with Cancer? CCR Perspectives in Drug Approval. Vol 19. Issue 6.

[7] Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin.

One such example is the drug Crizotinib. Crizotinib is a targeted anticancer drug for the treatment of ALK+ lung cancer. The drug received a PIP waiver as lung cancer does not occur in children. However, we do know that ALK+ mutations are found in a number of paediatric cancers such including anaplastic lymphoma, soft tissue sarcoma, and neuroblastoma. This is just one example of a missed opportunity as a result of a waiver granted under Article 11(1)(b).

2.9. Deferrals

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

We urge the commission to more strongly enforce the requirement of Regulation Article 16(1) that PIPs should be submitted "not later than upon completion of the human pharmacokinetic studies in adults".

Cancer Research UK agrees that deferrals based on a genuine need to gather additional safety information in the adult population are valid. However, as previously mentioned, an analysis of paediatric oncology PIPs performed in June 2012 found that the start had been deferred in 82% of cases[8]. Failure of a drug to show positive results in an adult cancer leads to the corresponding PIP also being cancelled so it is crucial that PIPs are started early in the product development cycle and that the agreed timelines are adhered to.

We are concerned that at present there appears to be few barriers, and no penalty, for late PIP submission. Furthermore the current rewards do not appear to incentivise timely PIP submission or completion. Possible incentives are discussed in section 2.5.

2.10. Voluntary paediatric investigation plans

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

We agree with the commission that some companies do submit and develop voluntary PIPs as described.

However, whilst voluntary PIP development can, and sometimes does, happen we do not feel that this process is anywhere near efficient enough to satisfy the need for innovative medicines for paediatric cancer.

This is again linked back to the issue of paediatric development being coupled to the adult development of the drug. Voluntary PIP development only happens once the adult indication has been established, leading to delays in paediatric medicines reaching children.

An additional reward that incentivises the completion of a PIP where development for adult indications has failed, as suggested in section 2.5, would support voluntary PIP submission.

[8] Vassal g. et al. (2013) Is the European Pediatric Medicine Regulation Working for Children and Adolescents with Cancer? CCR Perspectives in Drug Approval. Vol 19. Issue 6.

2.11. Biosimilars

Consultation item No 11: Do you have any comments on the above?
This is not currently an area of relevance for paediatric oncology.

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?
Unfortunately it does not appear that the PUMA concept was successful. We are only aware of two PUMAs (Hemangiol and Buccolam) that have been awarded in the past 10 years across all paediatric diseases. Nevertheless there is still a need to continue to generate data on off-patent medicines. This will generate new academic knowledge to be published and disseminated to the academic community in order to improve practices.

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?
Cancer Research UK would encourage pharmaceutical companies to work in collaboration with cooperative groups and networks, including during early interaction to best design PIPs with regards to needs and feasibility. Competing companies often develop drugs with the same mechanism of action; this could easily lead to a multitude of Paediatric Investigation Plans targeting the same condition. Without mutual consultation between companies these PIPs would prove infeasible to complete due to the small patient populations involved. We would like to see the EMA coordinate discussions that would lead to prioritisation of the most important PIPs.

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 comment on this question

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?
Unfortunately, as mentioned previously, the Paediatric Medicines Regulation has not had the anticipated beneficial impacts on paediatric oncology research.

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?
Cancer Research UK, working in partnership with pharmaceutical companies, is leading the way in precision medicine research. Through precision medicine we have the ability to classify individuals into subpopulations that differ in the biology that will have implications for their prognosis, or in their expected response to a specific treatment. Interventions can then be concentrated on those who will benefit, sparing side effects for those who will not. Incorporating the 'mechanism of action principle' within the Regulation, as discussed in section 2.8, would prove highly complementary to advances in the field of precision medicine.

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?