

Annex 1 – UK GOVERNMENT RESPONSE

COMMISSION REPORT ON THE PAEDIATRIC REGULATION

(ARTICLE 50(3) OF REGULATION (EC) NO 1901/2006)

Consultation on the experience acquired with the Paediatric Regulation

The UK welcomes the opportunity to express views on the experience acquired and lessons learnt from application of the Paediatric Regulation to support the Commission in drafting its report to the European Parliament and Council in 2017 according to Article 50(3) of Regulation (EC) No 1901/2006 (the Paediatric Regulation).

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?

The UK experience would suggest that legislation is required to produce evidence-based development of paediatric drugs which in this case has been the important first step in covering paediatric therapeutic needs. Although the provisions of the Paediatric Regulation have been somewhat slow to take effect, there is clear evidence that the situation with respect to the availability of authorised medicines has improved, particularly in comparison to geographic areas without similar legislation. There seems to be a slow progression converting PIPs into new drugs on the market. It is questioned whether this is a consequence of the details of the PIP process, the rarity of paediatric diseases, the difficulty in conducting paediatric studies, or the lack of motivation from companies. There is some evidence that companies are deferring studies in order to obtain adult licences, and then not completing the agreed PIP development due to commercial market reasons. The UK considers that perhaps 10 years is not sufficient time to see the conversion of PIPs into marketed products and therefore a further review might be needed to cover the first 15 years of the Regulation's implementation.

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?

Most PIPs are first and foremost for adult indications. It is felt that since paediatrics is not a profitable area for drug development and is also an additional financial risk for the companies, the response to the Regulation has been driven by companies' adult product pipeline, leaving certain needs not addressed for conditions specifically for paediatrics.

In oncology the translation of adult medicines to paediatrics has been limited by the restrictions of class indication, and the lack of consideration of the drugs' mechanism of action. Therefore it is questioned whether a change to the legislation to one covering 'mechanism of action' would help better cover paediatric conditions and diseases.

Paediatric rheumatology has been well-represented in the availability of new medicines because of profitability and the biological mechanisms are shared between adults and children. It is noted that the Paediatric Regulation has been enormously beneficial in mental health since it has been an opportunity to show that conditions with the same definition have different presentations at different developmental stages, and hence promote paediatric drug development.

The UK would be interested to know how many adult licensed products that had a PIP were then used or marketed in paediatrics.

It is noted that national research institutions are well placed to identify funding gaps and areas of research need, and subsequently place broad calls for drug development. Paediatric needs should also be better identified and outlined proactively so that it is apparent to industry where a potential market exists.

The UK supports the need for direct contact between the regulatory agencies and research institutions. Although the PDCO is consulting clinical groups, it is felt there is little power for them to direct industry; and the focus is on established adult drugs rather than undeveloped areas. It is noted that there are examples of paediatric needs being flagged (for example through PDCO priority lists) but that industry is not picking up on them, and better incentives are required.

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?

It is difficult to comment specifically on national availability of drugs without additional work to compare the list of licensed drugs during the 10 year period to clinical guidelines implementation (for example in the UK how quickly BNF-C reflects any changes). Review by NICE, uptake by national health services and rapid reflection in clinical guidelines were other important steps in this process, as clinicians may not be aware of regulatory developments without these. Pharmacists seem better at identifying off-label usage and licensing changes and making suggestions to clinicians. There are more new paediatric cancer drugs but it is difficult to assess whether this is because of the Regulation.

The UK notes the significant issue with paediatric drug discontinuations as actually some licences are being removed due to market reasons, reducing patients' access to medicinal products.

It is concluded that the overall ethos has changed with paediatric drug development being more evident in companies' agendas, but it is felt that more transparency and publicity surrounding paediatric drugs would be of benefit.

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?

Compared to the overall very large sums spent on drug development, the paediatric cost seems relatively small. It is highlighted that as the consultation has identified, the 6 month SPC extension reward can be very significant financially. The UK notes that there is a discrepancy between the investigator costs and industry costs and that clinical investigator costs were a fraction of industry claimed investment. It is also noted that the cost to healthcare systems and payers has not been captured.

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?

Paediatric development, seen as high financial risk, is in need of strong rewards to be successful. We have not seen the Commission's full analysis of rewards, but it seems clear that the paediatric extension to the Supplementary Protection Certificate (SPC) is asymmetrical – giving high reward to blockbuster products, and possibly insufficient rewards to products with low sales, and is unrelated to the costs companies face in fulfilling the PIP.

Further, the link between total sales and the benefit of use amongst children is not necessarily related to sales amongst adults.

It is concluded that the reward system works for adult drugs being considered as a paediatric indication rather than developing products specifically for paediatric need which may have lower sales. Based on the consultation data, the UK considers that more could be done to ensure that industry understands there is a reward for paediatric development and what this involves. It is felt the orphan drug process was widely known about, but PUMA less well-known.

It is noted that companies continue to underestimate the time required to implement the PIP measures (including formulation development, non-clinical studies and clinical trials) and therefore long deferrals are required. It would be preferable for a simultaneous development with in parallel with adults, rather than the paediatric studies occurring later which could have increased companies' costs. For example, toxicity studies should be performed for juveniles at the same time as adult animals.

6. The orphan reward

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

The UK was interested to read that some applicants were choosing to abandon orphan drug status so as to apply under the regular SPC route, in the hope of larger financial reward through 6 month SPC extension compared to 2 year orphan drug status. It is questioned whether this 'playing the system' has resulted in any obvious gaps in drugs, perhaps for very rare diseases, not being brought forward.

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?

Overall the UK agrees that the regulatory process seems to have improved from early days. However there may be a reluctance to modify PIPs as the process is so lengthy, for example, if it is difficult to recruit paediatric patients. The need for more flexibility throughout the paediatric drug development cycle is highlighted and the UK would support an option to proactively approach companies in order to bring back PIPs for discussion. The EMA/FDA collaboration is considered a very positive step for the success of any drug development.

8. Waiver and mechanism of action principles

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?

From the UK experience, there have been a significant number of waivers sought (including class waivers) without of clear consideration of paediatric needs and therefore the UK would support a 'mechanism of action' approach being considered.

Paediatric oncology seems unique in that cancers are defined differently with adult cancers traditionally defined by site whereas in paediatrics currently are more frequently defined by molecular mechanism. It is noted that in enzymatic, metabolic, and chromosomal conditions as well as neonatal disorders, where there was little cross-over with adult conditions, drugs for these populations are developed directly for children

The UK concurs, as noted later in the consultation, that the movement towards 'personalised' medicine may make age less relevant than perhaps genetic disposition to a range of diseases and this would also suggest that such narrow definition of a condition will not really work in the future.

9. Deferrals

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

Based on the UK experience, it seems that such deferrals are commonly sought. It was noted that the 'blockbuster' method of drug development is no longer sustainable and that new business models are needed overall in drug development. It is felt that over time the process may change to parallel development of adult and paediatric drugs. When companies better understand the process then it would be more cost-effective to undertake adult and paediatric studies together, unless scientifically not justified. There is likely to be a transition period while companies move to newer models of drug development and in the meanwhile adult studies will be still performed first. This means a lack of access to medicines for children which, ethically, limits their human rights to effective and safe treatment options. It was also noted that it is preferable for the quality development to be initiated before the PIP application, and that companies need to understand this better.

10. Voluntary paediatric investigation plans

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

The rarity of these types of voluntary applications is noted. The response to question 3 is also relevant here in that consideration needs to be given to incentivising the submission of voluntary PIPs.

11. Biosimilars

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

We are concerned about the security of supply of paediatric drugs since there could be a discontinuation of the innovator product, with the biosimilar products are under no obligation to produce paediatric licensed products. This is largely financially driven and the UK notes the lack of incentives for biosimilar companies to maintain a supply chain for paediatric patients who would not then benefit from reduction in their treatment costs. The production of biosimilars by the innovators is also noted as a commercial decision that might not support paediatric availability.

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?

We agree that the PUMA concept can be described as a failure. It was however also noted that the lack of PUMA uptake was part of a bigger system-wide problem with a number of drivers and factors outside the regulatory process that cannot be tackled by the legislation alone. There is no connected incentive, and even once approved, the drug does not have to be marketed or used in all member states. It is noted that there is a lot of local variation in formulations and that it is cheaper to produce a medicine locally which might be inhibiting PUMAs further. A partnership and realistic approach involving industry, investigators, and research councils has to be put forward as a method of targeting paediatric needs and finding broader funds. The UK considers that there should be a different stronger incentive offered or the development of different regulatory route. The idea of regulators taking the lead by authorising paediatric formulations without unnecessary clinical trials and using existing clinical experience, could stimulate innovation by small companies, otherwise the cost is prohibitive.

The UK also notes that the variety of incentives on offer by FDA while in Europe incentives only apply to specific products.

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?

We agree that overall there has been an increase in paediatric clinic trials but it is noted that these were driven by industry and PIPs and not clinical needs. The majority of research funding is directed to drug related clinical studies rather than basic science such as disease understanding, drugs' mode of action and toxicology. There has been a new wave in paediatric oncology looking for biomarkers and targets but this is mainly driven by academia. The reduction in public funding to academic research is an additional factor influencing negatively the availability of medicines in children.

We consider that it is more cost effective for industry to collaborate more with academia and clinicians as a mutual beneficial way of working. Ideally paediatric drug development should involve consortia of clinicians and patients to identify the needs to be covered, then industry could perform the

basic science studies followed by close collaboration with clinicians to recruit participants.

The UK agrees with the consultation comments about ensuring that the ethics of involving children and young people in trials are kept at a very high level, particularly when many of those children will be agreeing to take part through parents as they are too young to consent themselves. Also, whilst PIPs involve commonly large trials, there has been an increase of PIPs in rare diseases with trials that involve very small numbers of participants, and again the ethics of such trials, meaning that participation crosses over directly with treatment, need to be preserved.

Overall the Regulation has massively improved the number of non-clinical safety and toxicology studies of relevance to the understanding of safe use of medicines in the paediatric population.

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?

The significant investment from public payers to the implementation of the Regulation is noted as an important issue. The UK considers that since wider engagement is desired as paediatric drug development has not been fully integrated yet to the regulatory, clinical and marketing systems, it is not the right time to introduce a fee-based approach. Different sources of funding should be explored.

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?

The UK notes an overall positive effect of the Regulation. There is a need to consider lifecycle-approach to the design of studies, particularly in rare paediatric only diseases. The new emerging methodologies that would further reduce the need of paediatric clinical studies, such as extrapolation and modelling are also a positive benefit of the Regulation.

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?

Pharmacogenetics and the use of precision medicine will have a wide impact on paediatric drug development. However, there will still always be a need for age appropriate pharmacology studies and therefore scope for investment in understanding the diseases’ basic science in the developing body.

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?

The UK considers that there should be incentives for clinicians to take the lead in studies involving off-label use of medicinal products. Companies were reluctant to initiate studies involving off-label use of their products for fear of repercussions and the lack of the return of investments. Furthermore in some countries there are patient-led clinical studies with patients choosing which studies should be undertaken and there is a need for promotion and financial support of such initiatives.