Safeguarding public health

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UNITED KINGDOM GOVERNMENT RESPONSE TO THE EUROPEAN COMMISSION PUBLIC CONSULTATION ON PAEDIATRIC REGULATION

Please find the attached the United Kingdom Government response to the European Commission's consultation on experience acquired and lessons learnt from the Paediatric Regulation

Yours sincerely,

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GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION

(ARTICLE 50(2) OF REGULATION (EC) NO 1901/2006)

'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT'

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 2013 according to Article 50(2) of Regulation (EC) No 1901/2006 (the Paediatric Regulation). This Regulation has been hugely important for addressing the needs of children for properly researched and authorised medicines through its requirements for a paediatric investigation plan (PIP). Implementation of the Regulation and meeting its obligations has required considerable resource both on the part of the regulatory network and pharmaceutical industry to meet its aims.

1. A change of culture: nowadays paediatric development is an integral part of product development

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?

We agree that the Regulation has initiated a change in approach to the development of medicines for children. Historically, paediatric medicines were developed after the adult programme and after marketing of the product for the adult population. The Regulation has stimulated development of children's medicines earlier in the product lifecycle and this will lead to children being able to access authorised products sooner than they might otherwise have done. We are aware that a number of companies have embedded paediatric development in their overall R&D programme and are setting an example to other manufacturer's in this regard.

2. Has the Regulation delivered in terms of output? Too early to judge

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

We agree that it is too early to fully judge the delivery of the Regulation in terms of output for the reasons set out in the consultation document. However, there are encouraging signs after this first five year period. In the UK as of September 2012, marketing authorisations for 9 products had been updated as a result of studies fully compliant with a paediatric investigation plan (3 with a new paediatric indication, study data added for 4 and new dosage forms for 4). These are in addition to the centrally authorised products listed by the EMA in its 5 year report (13 new medicines, 30 new indications, 9 new pharmaceutical forms as of end of 2011).

We also acknowledge that setting a bench-mark for measuring a shift from off-label to authorised use as a consequence of the Regulation will be a challenge. In the UK we plan to do this by comparing the situation before and after the Regulation using medicines listed in the British

National Formulary for Children as an outcome measure. However, this survey will not be able to reflect changes in actual clinical usage of newly authorised products.

3. The PUMA concept: a disappointment

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?

We do share the view that the uptake of Paediatric Use Marketing Authorisations has been disappointing, particularly as older medicines are widely used in children either off-label or as unlicensed products. We believe that there are a number of reasons for this:

- Traditionally in the UK, oral liquid medicines suitable for use by children have been produced by smaller niche companies with little experience of interacting with the European regulator, and they have found procedural aspects of submitting a PIP daunting.
- Differences in paediatric clinical practice between Member States has led to the perception that a PIP for a particular product might not be agreed at European level.
- The additional legal data protection and marketing exclusivity have in reality not proved sufficient incentive as competitor products supported by their own data package can be authorised through alternative routes.
- Funding for research and development has been considered restricted and expertise for commercial product development lies within companies rather than academia, although there are good examples of partnership which could be extrapolated further.
- Commercial incentive is insufficient for development of products with relatively low usage.

There is clearly a continuing role for the EMA Small and Medium Enterprise Office in facilitating scientific and regulatory advice for smaller companies wishing to develop PIPs. National competent authorities should be encouraged to take a similar approach. EMA and some Member States offer free scientific advice for paediatric development. However, unless more can be done to improve the commercial attractiveness of PUMAs, we do not foresee the number of applications increasing in the coming years.

4. Waiting queues? No evidence of delays in adult applications

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.

We are aware of some instances where validation of a Marketing Authorisation application has been delayed due to the need to demonstrate compliance with a PIP. This has mainly been due to misunderstandings by the applicant of the obligations when the Paediatric Regulation was first introduced. In these circumstances, cooperation between the competent authority and EMA has helped to resolve situations as rapidly as possible. Likewise, the operation of the system of deferrals and the ability to modify a PIP to ensure compliance with key binding measures has only become fully understood more recently with the benefit of experience. Work by the EMA on clarifying the modification process and simplifying key binding measures to facilitate compliance should further reduce the risk of delays to MA applications.

A deeper question is whether paediatric development delays the adult development programme within the pharmaceutical industry sector.

5. Missing the point? Paediatric development is dependent on adult development, not paediatric needs

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

We recognise this as an issue where paediatric conditions either have a different cause to the adult disease or where there is no equivalent in adult patients. Childhood cancers are a particular example of the latter. We are aware that the Paediatric Committee has often encouraged applicants to conduct studies in therapeutic areas of particular concern but there is no legal obligation on companies to conduct studies outside of the intended adult indication. This is disappointing as there are some clear unmet paediatric needs which are thus not addressed by the Regulation. Encouragement of submission of PIPs and future MA applications on a voluntary basis would be welcome as are the steps being taken by PDCO to update the class waivers in the oncology area.

6. The burden/reward ratio — A balanced approach?

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

The key issue is the extent to which the reward to companies is proportionate to the benefit conferred by the development/implementation of a PIP. An obvious risk is that, in the case of certain medicines with very large sales (so-called blockbuster drugs), the effect of granting six months' additional monopoly will confer a reward which is excessive, and hence which imposes unnecessary additional costs on payers. At this stage, it is too early to draw definitive conclusions in this respect. We have, however, made some preliminary calculations on the basis of experience in the UK so far, and our view is that (i) a similar exercise should be undertaken across the EU as a whole; and (ii) a process of monitoring experience at regular intervals should be established, so that at the time of the next review in 2017, an adequate base of information exists on which a proper determination can be made.

7. Articles 45/46: the hidden gem of the paediatric regulation

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?

The compilation of existing paediatric data, facilitated by EMA, and submission for assessment by competent authorities on a work-sharing basis is in principle an efficient mechanism for updating product information. As of September 2012, out of 100 products, new paediatric indications had been recommended for 11, safety information updated for 5, study data added to 12 and paediatric information revised for clarity or consistency across products and member states for a further 45. Implementation of the recommendations remains a challenge for all brand-leaders and generic versions of the products. Whilst this is a significant achievement, much more data remains

to be assessed. A continuing difficulty will be the ability of member states to continue to put resource into this work which is not directly remunerated.

Until results can be transferred to EudraCT, the study data is not yet in a form that is readily accessible to the interested public. A significant proportion of the information is in the form of published literature which is not suitable for inclusion in a clinical trial database.

For newer studies arising from Article 46 of the Regulation, further thought is needed on the most efficient way of assessing these data where the studies result from an on-going paediatric development programme such as a PIP.

8. Lost in information: Healthcare professionals not as receptive as expected

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?

Much has already been done at UK national level to highlight the need for better research into children's medicines, particularly through a UK Paediatric Strategy and the work of the Medicines for Children Research Network (see response to question 11). MHRA uses a number of tools to communicate to healthcare professionals updated information on the use of particular products in children through its website, distribution of Drug Safety Update and by working with the British National Formulary for Children which is now published electronically and can therefore be updated on a more frequent basis. MHRA regularly engages with its expert advisory group on paediatric medicines and representative bodies of healthcare professionals with the aim of ensuring a good understanding of the regulatory requirements for paediatric development, but there is a continuing need to raise awareness.

Although this problem may need to be primarily addressed at national level, further collaboration between senior healthcare professionals across member states may help to secure and direct funding to the most appropriate areas of paediatric research to meet priority needs.

9. Clinical trials with children: no specific problems detected

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?

Overall the UK shares the views on paediatric clinical trials expressed in the consultation. In the UK, our figures for paediatric clinical trials have seen at least a 30% increase in the number of trials involving children since the introduction of the Paediatric Regulation. We believe this increase has resulted from the concerted efforts of the regulator, clinical research networks and professional bodies in the UK to emphasise the requirements of the Paediatric Regulation and importance of high quality research on children's medicines.

The developments have been fundamental and lead to a mindset change in the approach to trials in childhood. Now thought needs to be given to the coordination between regulators and research

programmes to avoid duplication effort but also in identifying the most pressing research priorities from a treatment point of view.

10. Unnecessary efforts? Non-completed paediatric investigation plans

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

Whilst we recognise that the need to stimulate early development of paediatric products may result in non-completed paediatric investigation plans, steps should be taken to minimise wasted effort both on the part of the regulatory network and the pharmaceutical industry. It is also essential that children should not be recruited needlessly into clinical trials and that paediatric trials should deliver results which are meaningful for the population as a whole.

We believe that a better understanding of how to conduct a good quality paediatric development programme and clinical studies in children has evolved since the Regulation was introduced through dialogue with all interested parties including the Paediatric Committee, industry, regulators, investigators and research networks. Better and earlier identification of efficacy and safety issues and appropriate timing of paediatric studies using the deferral system should minimise unnecessary trials taking place where adult development eventually has to be abandoned. Applicants should be encouraged to seek scientific advice from competent authorities to help refine their paediatric development programmes.

11. Sophisticated framework of expertise achieved

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?

UK has a well-developed Medicines for Children Research Network which has engaged fully with the aims and objectives of the Paediatric Regulation in facilitating the necessary research to support paediatric development programmes. The Paediatric Regulation has stimulated a wide framework of paediatric expertise in the EU with the establishment of Enpr-EMA but more widely within the regulatory network and healthcare professionals.

12. Any other issue?

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?

Overall, the Regulation has met our expectations and understanding of its potential limitations outlined in the responses above. One area not specifically addressed above is the need for suitable dosage forms for the different subsets of the paediatric population (age-appropriate formulations). There is evidence of innovative product development taking place in industry and academia but the challenge is translating this research into cost-effective medicines. The issue of suitability of certain excipients in medicines for children is an area where more information is

urgently needed and the database being created by the European Paediatric Formulation Initiative (EuPFI) is to be welcomed in this regard as well as the initiative being led by the EMA to revise regulatory guidance on use of certain excipients. Research funding in this area needs to be encouraged.

Finally, long-term follow up of the efficacy and safety of medicines used in children will remain a challenge and alternatives to controlled trials, such as registries, will need to be explored. The new pharmacovigilance legislation provides an excellent opportunity to focus on gathering good quality safety information for paediatric medicines to ensure their best possible use.