GENERAL REPPORT ON THE EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION
Experience Acquired and Lessons Learnt Vertex Pharmaceuticals

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?

Vertex agrees with the assessment that the Paediatric Regulations has paved the way for paediatric development, making it a more integral part of the overall product development of medicines. This earlier consideration of paediatric development is not isolated just to the European Union as attempts to standardize paediatric development of medicines are a global initiative for most Sponsors. Despite the success of the paediatric regulation, there remain issues for future EMA consideration. For example, submitting a PIP "not later than upon completion of the human pharmaco-kinetic studies in adults." While in concept, this is admirable, in reality, Sponsors would prefer to obtain Proof-of Concept data to ensure that a therapy is active in the target disease before undertaking the work associated with the PIP. A therapy which does not achieve Proof-of-Concept would most likely have its development stopped (See Consultation No. 10). For therapies for which development advances, it should be noted that the PIP requires months of discussion and planning prior to submission to the PDCO and following submission, the PIP assessment procedure is quite lengthy (up to 9 months in some instances when factoring in the Day 60 clock-stop). The impact of the procedure duration places a burden on small to medium enterprises which have limited resources and thus, could delay adult development if tight resources are re-directed to the PIP. A potential solution would be for the EMA should encourage the PDCO to work with Industry to develop more standard PIPs for a variety of disease areas, similar to successful efforts made for H1N1 pandemic influenza vaccine and allergen extracts for immunotherapy. Another alternative could be making clinical trial study designs that are encouraged by PDCO publicly available through PDCO workshops or online resources, for example the diseases in which randomised withdrawal clinical studies are warranted. A third example where the PDCO could be more transparent on their current thinking is, for example, paediatric pharmacokinetic (PK) studies and the allowable frequency and amount of PK sampling in the paediatric sub-sets. Transparency of this type of information would enable in more comprehensive PIPs and potentially result in fewer questions at Day 60 and translate into shorter assessment procedures. This reduces burden on both the PDCO and Industry.

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

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

Vertex agrees with the EMA that it will probably take at least a decade before the regulation can be judged in terms of its output. Data from prescribing clinicians and pharmacists could potentially contribute to an evaluation of the impact of the regulation. However, adjustment to the regulation (like the ones proposed in item No 1) should already be made now.

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?

In concept this is an attractive pathway for off-patent products; however Vertex has not explored PUMA and cannot comment on its future attractiveness at the current time.

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.

While there may be no evidence of delays from an agency perspective, Industry may have a different opinion. As noted in Consultation item No 1, the PIP burden on small and medium enterprises is difficult to quantify. In addition, companies working on rare diseases may in fact be experiencing delays. Rare genetic disorders are manifested from birth, so companies will be developing the product for paediatrics. All the Paediatric legislation does is to add an additional burden of costs to the development of such products. The EC is encouraged to consider waiving paediatric requirements for orphan drugs, or for orphan drugs for genetic diseases. A scheme similar to that followed by the United States Food and Drug Administration's application of the Pediatric Research and Equity Act to medicines with an orphan designation would seem appropriate. This could result in a win-win situation and spur development in rare diseases while also advancing paediatric development. The compliance check required prior to submission of an MAA is an additional burden which can cause a delay in submission of MAAs; perhaps there is a way that compliance with the PIP could be done during the MAA assessment.

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
Please see responses provided to Consultation items No. 1 and No. 4.

6. **The burden/reward-a balanced approach**

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

In Vertex's experience, the regulatory processes of the PDCO have not been simplified. Given the large range of expertise of the member-state appointed PDCO participants, PIP requests/questions are not consistent from procedure to procedure. In our experience, some PIPs have required more information than other PIPs in the same disease area, for example submission of non-clinical reports or more binding elements regarding clinical trials. It must be noted that PIPs include early iterations of development programmes which often evolve as new information becomes available. Moreover, due to the single clock-stop during the procedure, it makes it difficult to introduce new information. As a result, modifications become necessary. The modification process is time-consuming and presents a significant burden because the procedural, it is not well developed. The PDCO could consider amending the modification process and make it more flexible – perhaps by having multiple modification categories such as major and minor modifications; similar to the substantial and non-substantial amendment process for clinical trials. PDCO guidance on what qualifies as a major or minor modification would reduce burden on both the PDCO and Industry.
Vertex has also experienced rigidity of individual PDCO members and for the scheduling of PDCO hearings. In one case a requested TC for 5 am US East coast time was cancelled a few minutes prior to the meeting leaving a team of company participants waiting in a conference room at Vertex facilities. In another case a PDCO hearing was scheduled for Monday morning London time forcing company participants to spend the whole weekend traveling and away from their families. Such events lead to unnecessary frustrations and increased cost of development.

Vertex have not yet experienced the benefit

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?

Vertex has no comment on this item.

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?

There has been some feedback that parents are not so receptive to having their children involved in clinical studies. However, this experience differs depending on the severity of the condition to be studied and the burden the study puts on the family.

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?

Based on our experience, the regulation has in some aspects made paediatric clinical trials easier to receive regulatory approval from EU Competent Authorities. Having an agreed-upon PIP and providing the PIP in the Clinical Trial Application has, in our experience, led to smoother clinical trial assessments with fewer questions from Competent Authorities. However, this has to be put into perspective with the additional burden, as pointed out in responses to items Nos. 1 and 4.

10. Unnecessary Efforts? Non-completed Paediatric Investigation Plans.

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

In order to avoid the unnecessary efforts of preparing a PIP and having the PDCO review the PIP would be to encourage Industry to submit their PIP after Proof-of-Concept has been achieved (in cases where adults are being evaluated). For therapies being developed for a paediatric population only, one possible solution is a staged approach, in which the PDCO assesses an initial PIP containing development through Proof-of-Concept on a shorter procedure schedule with an acknowledgement that a modified PIP inclusive of the remaining development program would be provided later (as a binding element). This type of scheme could expedite develop in paediatric-specific therapies.

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?

Vertex is not in a position to comment on this item.

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?

The implementation of the regulation closely reflects our understanding of the legislation. The intent of the legislation was to ensure that medicines are evaluated in the paediatric population in a timely manner and in that regard the regulation has met expectations.