This response is from the founders of Christopher's Smile, a UK registered charity. The founders of Christopher's Smile started the charity after losing their 5 year old son to a brain tumour. The charity funds research into new targeted treatments for childhood cancers. The founders of Christopher's Smile met with the EMA in London in 2010 and attended the December 2011 BDA conference on childhood cancer drug availability.

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?

The Paediatric Regulation can only be viewed as an aspirational piece of legislation from a paediatric oncology viewpoint. While the Paediatric Regulation has the potential to deliver huge improvements in the development of new treatments we can see no evidence whatsoever that advances in the understanding of paediatric disease and any subsequent development of new treatments are directly attributable to the existence of the Paediatric Regulation.

HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

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

From our perspective the regulation has yet to deliver these key objectives and measures of the Paediatric Regulation:

- *to ensure high-quality research into the development of medicines for children*
    - *Why is the research into paediatric oncology targeted treatments dependant on charity funding for its existence?*
- *to ensure, over time, that the majority of medicines used by children are specifically authorised for such use*
    - The general report describes paediatric oncology as an 'unmet need' and documents the timescales as 'on going' – so the term 'over time' does not give any indication of prospective timescales.
- *to ensure the availability of high-quality information about medicines used by children*

    - All cytotoxic agents used in paediatric oncology are used 'off label'. Although side effect information is widely available, the Paediatric Regulation did not expedite it's availability. The availability of quality data on any new agents used in paediatric oncology will yet to be seen.
- *the requirement, when applying for marketing authorisation for medicines and line extensions for existing patent-protected medicines, to submit data on the use of the medicine in children in accordance with an agreed paediatric investigation plan*
    - New oncology agents developed in recent years have been produced for large market diseases and any paediatric use has been largely ignored and waivers have been obtained as a matter of course.
- *a system of waivers from the requirement for medicines unlikely to benefit children and a system of deferrals of the timing of the requirement to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults*
    - Waivers have been used by pharmaceutical companies to circumvent the Paediatric Regulation as waivers are based on disease and not on mechanism of action. This is documented in section 7.3.3 of the general report on the Paediatric Regulation.

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?

For Paediatric Oncology older drugs tend to be non-targeted and have toxic side effects. Should any older drug be identified to have a therapeutic effect on a particular childhood cancer type the market would be small. Therefore any financial incentive would not be attractive due to the size of the market. We feel that there needs to be either a major rethink on the PUMA incentives or completely withdraw it.

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.

Pharmaceutical companies continue to apply for waivers in preference to applying for a PIP for oncology drugs. While this option is available there is no incentive to apply for a PIP as any paediatric market will be tiny compared to the target adult market. Therefore we believe that pharmaceutical companies will not allow new agents to be delayed by PIP applications and subsequent PIP process.

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?

Pharmaceutical companies will not develop any new agents to specifically target and treat a childhood cancer. The market is small and there would not be an economic return on the development costs.

It is actually in pharmaceutical companies' best interests not to make their latest agents available for paediatric academic pre-clinical testing. The reason is that if the intention is to apply for a waiver, the application would fail if there was a documented paediatric indication gained from academic pre-clinical testing.

It is for this reason that paediatric oncology drug development is totally dependent on adult drug development.

From the General Report I quote the following paragraph:

"The review of the applicability of a class waiver is also an opportunity for the PDCO to recommend medicines development in paediatric conditions with unmet needs, when the mechanism of action of the medicine justifies development. This was particularly the case for medicines used in adult oncology that can be used, based on their mechanism of action, in different cancers in children with high unmet needs. The PDCO recommended development for a number of medicines. Sadly, no PIP application was received in response to such PDCO recommendations."

THE BURDEN/REWARD RATIO —A BALANCED APPROACH?

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

The current incentives for pharmaceutical companies are totally inadequate. Evidence for this comes from the General Report as it repeatedly states that paediatric oncology is a huge unmet need. If incentives were adequate this would not be the case.

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?

What benefits would a pharmaceutical company see in having to share data on their latest agents with competent authorities? While waivers can be obtained based on disease rather than mechanism of action, the data on new drugs for children will be only become available when drugs are made available for paediatric testing.

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?

In our experience paediatric oncologists are desperate for new drugs to treat childhood cancers. The current treatments are not effective and cancer is the biggest killer by disease of children. Current treatments also leave a legacy of issues and are almost exclusively used ‘off label’.

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?

We believe this is the area in need of the biggest change for the following reasons.

- The stream of children seeking participation in clinical trials outside of the EU of treatments for childhood cancer continues unabated.
- There is no single source of funding for paediatric trials
- In the case of paediatric oncology, ethical committees seem to be over zealous in their scrutiny of trials for new targeted agents whilst seeming to ignore the poor efficacy and horrendous side effects of current treatments.
- There is no 'fast track' process to ensure the speedy implementation of paediatric clinical trials for agents in the 'high unmet need' class.
- The time to set up clinical trials is far too long.

UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

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

The PIP process is seen as a huge burden for any pharmaceutical company especially when there is no guarantee that the agent under trial will be successful. Any amendments to the PIP process which results in a lower administrative burden in the early phases of a trial should be encouraged.

PIPs which are uncompleted should be reviewed to ensure a paediatric trial has not been ceased purely due to poor efficacy in the adult trial. In these cases the pharmaceutical company should be approached to enquire if a way can be found to continue the paediatric study if the paediatric results are good.

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?

We do not believe that the Paediatric Regulation has contributed to a richer framework of paediatric expertise in the EU. In paediatric oncology the formation of networks exists both within Europe and beyond. Truly international research networks have been established. These networks have developed based on the quality of scientific output rather than geographical location. While the Paediatric Committee exists in a purely regulatory basis we see no evidence that its existence has improved the quality of paediatric oncology research.

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?

As stated earlier, the Paediatric Regulation should be regarded as a piece of aspirational legislation as in its current form it cannot deliver its full objectives. It fails to address the fact that pharmaceutical companies see paediatric specific diseases which have a small market as not worth pursuing. It is an uncomfortable fact that it is more economical for a pharmaceutical company to withdraw a drug during clinical trials due to poor efficacy in adults than to proceed with a product that may only benefit a tiny paediatric market. In fact the way the legislation is written with regards to waivers, it is better for a pharmaceutical company to not allow a new drug be made available for paediatric pre-clinical testing until a waiver has been secured.

There needs to be real incentives for pharmaceutical companies because unless there is significant change paediatric oncology will still be regarded in the 2017 report as an area of unmet need. Changes need to happen now and not wait until 2017. In fact waiting until 2017 for a review of the Paediatric Regulation clearly shows how out of touch the regulators are.

The regulation also does not take into account the huge improvements in technology and understanding especially in the field of paediatric oncology. These developments have resulted in a need for more clinical trials which are

targeted at specific populations. Currently the level of bureaucracy to set up clinical trials is unacceptable and needs change. When this subject is raised regulators immediately retreat to their standpoint of 'we must make sure that new medicines are safe'. This position completely ignores the fact that treatments used currently in the field of paediatric oncology have poor efficacy, horrendous side effects and are used off label. This hypocrisy must stop now.