Christopher's Smile

coz kids get cancer too

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Response to

Targeted stakeholder consultation on the experience acquired with the Paediatric Regulation

Reference:- PCPM/16 — Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: __**Christopher's Smile**_____

Registered UK Charity 1129906

Transparency Register ID number (for organisations): _____

Country:__United Kingdom_____

E-mail address:___info@christopherssmile.org.uk_____

Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

- My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication ✓
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- I do not agree that my contribution will be published at all

Please indicate whether you are replying as:

- A citizen
- A business
- A non-governmental organisation (NGO) ✓
- An industry association
- A patient group
- A healthcare professional organisation
- Academia or a research or educational institute
- A public authority
- Other (please specify)

If you are a business, please indicate the size of your business

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
- Medium-sized enterprise (under 250 employees)
- Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- Local
- National ✓
- Across several countries
- EU
- Global

2. PART II – CONSULTATION ITEMS

Please note that responses to the questions below will be provided within the context of paediatric oncology

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?

Specific legislation is necessary to guarantee evidence-based paediatric medicines.
Paediatric oncology represents an extremely small potential market for new agents developed to treat adult malignancies. The cost of the development of these new agents is high and so the companies that develop new agents want to bring them to market at the earliest possible opportunity. Therefore, there would be no voluntary testing phase as part of the development cycle if there was an increase in cost or timescales. The small market segment of paediatric oncology would be completely ignored in the drive to bring new cancer therapeutics to market if specific legislation did not exist.
Specific legislation is needed to ensure evidence-based data on new agents is produced at the earliest opportunity as part of the adult development programme.
In the 5-year report to the European Commission, the EMA stated:
"*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.*"

This is why effective legislation is needed.

5-year Report to the European Commission General report on the experience acquired as a result of the application of the Paediatric Regulation
http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

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?

From a paediatric oncology perspective, the Paediatric Regulation has not delivered the aspirations set when the regulation was introduced in 2007. While the EMA and the European Commission can produce statistics on the number of PIPs completed across all therapeutic areas since 2007, the sad fact is that for the disease that kills more children than any other in Europe, the paediatric regulation has been a complete failure.
This can be attributed to naive legislation and underestimating the unswerving commercialism on the part of the pharmaceutical industry to exploit loopholes.

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?

For paediatric oncology no legacy treatments have been replaced by new licensed treatments so from this perspective the regulation has been a failure. Furthermore, any improvements in the survival rates of children diagnosed with cancer across the EU is not due to the Paediatric Regulation but largely attributable to ongoing trials and the introduction of a few new agents that have been made available to paediatric researchers. These new agents have mostly been made available after a drug has been approved for adult use – years after potential testing in the paediatric population could have been started.

In fact, in the 10 Year report to the European Commission the EMA stated:

However, only a fraction of medicines that recently became available for adults were presented by pharmaceutical companies for discussion of the potential relevance for children with cancer, and this cannot be improved through regulatory obligations in the current framework. For such medicines, the revocation of the list of class waivers was envisaged to stimulate paediatric discussions, but this remains to be followed-up.

Section 6.3

https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf

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

Pharmaceutical companies have a responsibility to deliver a return on their shareholder's investment. While we must be mindful that commercial organisations have this responsibility we must also be mindful that the earliest availability of safe effective lifesaving drugs for children should be as, if not more important, than profit.

The lifeblood of pharmaceutical company profitability is product patents and the earliest approval of new products. Sadly, time is money and any delays in gaining approval of a product for a large potential market can cost a company dear, as all the while the patent clock is ticking.

Legislation that could delay the approval of a very profitable agent because testing needs to take place for a tiny potential market will never be popular.

There will never be a sound business case for undertaking paediatric development of a drug developed for adults but companies should be prepared to shoulder this burden. The PIP process will never be cheap but we think that the EMA must be prepared to explore avenues where efforts are shared and some of the work is undertaken by the academic sector. In taking this approach the academic sector must also be prepared to meet industry's expectations of delivery timescales and agreed deliverables.

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 the reward system works at all well for paediatric oncology.
The current reward system allows pharmaceutical companies to apply for and obtain a class or product specific waiver for a drug whose mechanism of action is proven to be applicable to a paediatric cancer. Pharmaceutical companies can deny access to a drug to academic paediatric researchers, thereby delay any paediatric preclinical trials and subsequently perform a voluntary PIP years later during the patent period and subsequently obtain a 6 month SPC. This would all be possible by careful strategic planning on the part of the pharmaceutical company!!

The rewards system in its current format provides pharmaceutical companies with a 6-month Supplementary Protection Certificate for completing a PIP. The rewards from an SPC would compensate a company for the cost of taking a drug through the PIP process but it would not be enough to compensate for any delay in adult approval or to develop an agent specifically for a paediatric disease.

The reward system needs to be overhauled extensively and there should be no reward for any company which obtains a class or product specific waiver based purely on an adult disease and no consideration is taken of a drug's suitability in the paediatric community.

There should also be incentives in place to encourage companies to continue the development of promising drugs in the paediatric population in the event that adult studies have failed due to lack of efficacy.

2.6. The orphan reward

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

The way the orphan reward legislation has been worded, there is little or no incentive to use this legislation on rare conditions as a company can only receive exclusive marketing authorisation for 10 years as defined by the Orphan Drug Regulation ", *the Community and the Member States shall not, for a period of 10 years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product"*
Many childhood cancers only have a few hundred cases per year in the EU making the incentive unattractive. For this reason, the Orphan Drug Regulation has had no impact on paediatric oncology during the life of the Paediatric Regulation.

REGULATION (EC) No 141/2000 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL
http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2000:018:0001:0005:en:PDF

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?

We agree that the implementation of the Regulation has changed over time but the fundamental weaknesses of the legislation have never been resolved.

The amendment of the class waiver list by the EMA has resulted in a number of agents losing their class waivers but this will not happen until 2018 at the earliest due to the 3-year delay between notification and waiver removal. There is also no change in the process for companies to apply for a product specific waiver.

Until Article 11 – 1 (b) of the regulation has been amended and brought into line with up to date scientific practises, the implementation of the Paediatric Regulation will continue to be outdated and not serve the needs of the paediatric oncology patients, parents or academic research community.

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?

As stated above, Article 11 – 1 (b) needs immediate revision as it has allowed pharmaceutical companies to obtain class and product specific waivers for drugs whose mechanism of action is applicable to childhood malignancies.

In the consultation for the 5 Year Report 3 responses specifically mentioned the failing of the Paediatric Regulation by awarding waivers based on adult disease and not mechanism of action. These responses were by Christopher's Smile, ITCC and SIOP Europe. Despite these direct comments there was no mention of waivers based on mechanism of action in the 5 Year Report ".*Better Medicines for Children From Concept to Reality*" produced by the European Commission.

Example - Olaparib

Olaparib, a PARP inhibitor is an Astra Zeneca product that received marketing authority for ovarian cancer. Trials for Olaparib started in 2007.

Olaparib was granted a waiver by the EMA in December 2012

http://www.ema.europa.eu/docs/en_GB/document_library/Minutes/2013/01/WC500137361.pdf

However, when the waiver was granted by the EMA, there existed a published scientific paper that stated that Olaparib could be beneficial to patients with Ewing's Sarcoma.

http://cancerres.aacrjournals.org/content/72/7/1608.long

This paper was published in April 2012, 8 months before the decision by the EMA to grant Olaparib a waiver. As this article was available to the research community how can Astra Zeneca, the EMA and the scientific research members of the Paediatric Committee not be aware of the paper's existence?

Finally, the eSMART paediatric trial, a pan European stratified medicine trial currently in progress, uses Olaparib as one of the component drugs. Therefore, a paediatric trial is going ahead with a drug that has an active waiver granted by the EMA!

https://clinicaltrials.gov/ct2/show/NCT02813135?term=NCT02813135&rank=1

This situation then begs the question:- "If Olaparib is being provided by Astra Zeneca for the eSMART trial, is one of the conditions of supply that of access to trial data? If so, Astra Zeneca could amass some or all of the required data for a voluntary PIP at no addition to the cost of the supplied Olaparib. The charities and other funding bodies who are funding eSMART would then be subsidising the PIP process for Astra Zeneca who in turn would then reap the benefits of a 6 month SPC for Olaparib."

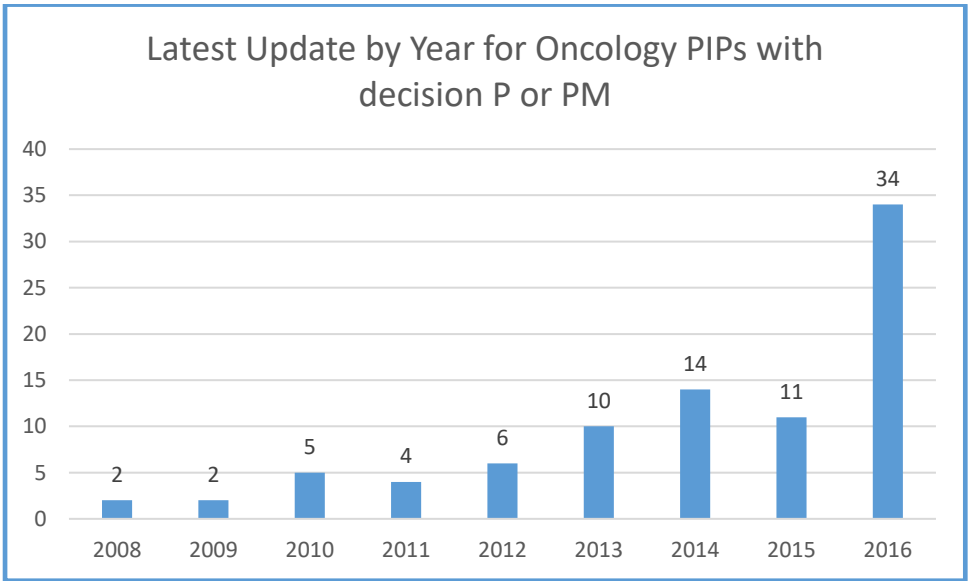
If this turned out to be true, the question above in Consultation Question 5 "and that early, strategic planning will usually ensure that a company receives a reward" would be remarkably appropriate.

2.9. Deferrals

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

We see deferrals as a necessary tool for PIP completion in realistic time frames. Due to the very small number of paediatric patients, data cannot be amassed within the original time estimates of the PIP and therefore ongoing deferrals are the only answer. In the 2015 EMA annual report to the European Commission (https://ec.europa.eu/health/sites/health/files/files/paediatrics/2015_annual_report.pdf) , recruitment difficulties was the reason given for a quarter of all PIP deferrals. However, we believe that deferrals need to be managed carefully and a fine line exists between repetitively deferring the completion of a PIP and no intention of ever completing the PIP. PIPs are deferred for a number of reasons but realistic timescales must be set and a plan must be included in the PIP stating what course of action is to be taken if timescales cannot be met.

To give an idea of PIP management, a search on the Opinions and Decisions on Paediatric Investigation Plans web page using the therapeutic area of "Oncology" yielded 88 entries with the category P or PM (P = decision agreeing on a Paediatric investigation plan, with or without partial waiver(s) and or deferral(s), PM = decision on the application for modification of an agreed PIP)



This shows that 61% of PIPs with a decision of P or PM did not receive an update during 2016.
Is this indicative of the management of deferrals?

2.10. Voluntary paediatric investigation plans

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

The opportunity of conducting a voluntary PIP provides a useful vehicle for companies to obtain a 6 month SPC when an agent has already been granted a class or product specific waiver. While it is the objective of the Paediatric Regulation to have as many drugs used in children approved for paediatric use through the PIP process, the voluntary PIP process does allow companies access to rewards after obtaining a waiver.

We return to the comments in the EMA 5-year report above which describes the take up of voluntary PIPs by the pharmaceutical industry.

2.11. Biosimilars

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

We have no comment to make on Biosimilars.

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?

The PUMA concept has been a disaster and the incentives for developing off patent medicines needs urgent review. Currently there is no reward to justify the development costs of off label medicine development. To encourage off patent medicine development, there needs to be a significant change in the rewards legislation.

As paediatric oncology patient numbers can be extremely small the rewards for repurposing an existing off patent drug must significantly exceed the trial and PIP costs as ongoing profits would be small due to a tiny market.

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?

We view clinical trials in children as an absolute necessity if new drugs are to be introduced into the paediatric oncology arena. Trials must be valid and realistic and trial design must take into account the potential number of patient participants versus the data requirements. There is little point in making a PIP dependant on data from a trial that will need over 500 participants if the incidence of the disease is only 20 per year in the EU.

We have long advocated that paediatric oncology trials need to bring the children to the trial, not the trial to the children. Currently there are few opportunities for children in some EU counties to participate in innovative trials as the costs for treating children in a centre in another EU country are not included in the trial budget. We see this as unethical as it means that some children will always be excluded from trials due purely to geography.

If we change the criteria for waivers to be based upon a drug's mechanism of action, we must also ensure that participants in trials are chosen by specific abnormalities in their tumour. If blind trials are to continue, then clinicians must ensure that those children with a given genetic abnormality in their tumour have a chance of survival or significant life extension with conventional therapies and not deny half the trial participants the chance of a lifesaving new agent simply because the trial protocol stated that a 'control' statistic was needed.

We would also like to see more clarity surrounding clinical trials for teenagers. Teenagers aged 15 to 17 years of age fall between children (up to and including 14 year olds) and adults (18 years old and above). Teenagers fall between these 2 categories and more trials need to include teenagers within their scope.

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?

Our view on this subject is that if the European Legislators want approved medicines for children and are offering incentives for companies who undertake a PIP for one of their products then introducing additional fees would be counterproductive.
The current system has been in use for 10 years. There are much larger issues with the Paediatric regulation than fees for PIPs.

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?

The biggest obstacle to paediatric research has been the availability of new agents.
If you view this from a purely business perspective – a company spends hundreds of millions of pounds developing a drug for a huge adult market e.g. lung or breast cancer. The opportunity for profits are huge. The company wants to get the drug through adult trials as soon as possible as once marketing approval has been granted, the drug can be a revenue earner.
If the company offers the drug at the earliest stage, i.e. before adult stage 1 trials, to paediatric researchers who find in preclinical trials that the drug has huge potential in a children's cancer, and an excellent case for a PIP is put before the PDCO, what chance is there of a successful PIP waiver application?
By offering the drug to paediatric researchers, the company is 'letting the genie out of the bottle'. The company would have to embark on paediatric trials in parallel to adult trials in the period before marketing approval is gained. This would make the project to bring the drug to market costlier, more complex and with added risks. Who would want to do that? The safer option would be to delay the supply of the drug to paediatric researchers until the latest possible moment and certainly after a class or product specific waiver has been granted. (see 2.3 above)
This may appear to be a cynical view but why do paediatric trials lag behind adult trials by so many years?
Unless something is done to make new drugs available to paediatric researchers at the earliest opportunity, paediatric research will continue to be hampered.
We as a charity have had one of our projects not reach its intended objectives simply because drugs that were available to researchers into adult cancers were not made available to our funded paediatric researchers.

Until the process for granting waivers is overhauled and incentives are offered for the supply of new drugs at the earliest responsible moment and certainly no later than adult phase one trials, paediatric research will continue to be hampered.

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?

In 2007 when the paediatric regulation was first introduced, DNA sequencing was a research tool that was expensive and took a lot of time. With the ever increasing pace of development in technology, DNA sequencing has become both low cost and quick and is now starting to become a trusted clinical diagnostic tool.

To introduce waivers based on mechanism of action, the data must be produced to give the Paediatric Committee the information as to which are valid paediatric drug targets and which are not. Data from the sequencing of paediatric tumours can provide this data. Our charity funded the development of a paediatric focused Next Generation Sequencing panel. The panel identifies abnormalities in 93 known genes (v2 of the paediatric panel which identifies abnormalities in 93 genes is about to go live at the time of writing) that occur in paediatric cancers. The panel is being further developed to include more genes as and when research progresses. The NGS panel is in use at the Royal Marsden Hospital in the UK and despite an attempt to invite the EMA to meet with the researchers and view the output data, the EMA showed very little visible interest and certainly were not interested in an offer of the researchers from the Institute of Cancer Research in the UK to present their work at the EMA offices in London.

This technology is also key to selecting the most appropriate paediatric candidates for trials of targeted drugs and must be introduced across Europe in the clinical setting as soon as practicably possible.

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?

Since the first results of our funded work to develop a Paediatric Next Generation Sequencing Panel, we have always thought that the data could be used to define a 'condition' as defined in the EMA document - Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver)
http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf
This policy document was produced by the EMA with no consultation with other stakeholders and it appears to document the process for defining PIPs and the granting of waivers. Our argument is that whereas currently waivers are defined at the HLT level on the MedRA hierarchical system, the PT level should be used to define whether a waiver is granted. We proposed that the output from the sequencing work be overlaid on the MedRA hierarchical system to utilise the latest information available but this was rejected by the EMA as the Next Generation Sequencing technology was still in its infancy (even though it is in common use in adults).
We would like to see Article 11 – 1(b) of the regulation overhauled as quickly as possible and use the mechanism of action of a drug to determine the granting of a waiver. Furthermore, we would recommend that the EMA hold a reference list of paediatric drug targets that is under constant review and updated from sequencing data obtained from accredited laboratories across the European Union.

Article 50 - 3 of the Paediatric Regulation clearly states:
By 26 January 2017, the Commission shall present a report to the European Parliament and the Council on the experience acquired as a result of the application of Articles 36, 37 and 38. The report shall include an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health of this Regulation, with a view to proposing any necessary amendments.

With the consultation not starting until November 2016 and closing by 20thFebruary 2017 the date defined in legislation cannot be met. Moreover, the messages on the EMA website and the EC Public Health website state 'the report will be delivered in 2017'. Why has the date specified (26th January 2017) been omitted and seemingly ignored?

This is not acceptable.

Who gave the European Commission the authority to disregard the dates that have been enshrined in legislation? What confidence can we have in the European Commission when it flagrantly flouts its own laws?
We mention above that mechanism of action was conveniently omitted from the 5-year report. What confidence can we have that the 10-year report will convey the comments of all stakeholders and not just those whose comments the European Commission see as acceptable?
We see the above as the responsibility of Commissioner Andriukaitis. We would like him to take the lead in finding out why the European Commission is disregarding EU law and take appropriate action in order to restore public confidence in the activities of the European Commission.
The dates in Article 50 have been in place for 10 years. The European Commission should not be able to pick and choose which pieces of the Paediatric Regulation legislation can be changed or disregarded. If the legislation can be "changed" with such ease and impunity, then surely Article 11 – 1(b), where there would be distinct benefits, could be disregarded and mechanism of action introduced as the deciding factor for a waiver?