Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: **Unite2Cure**

Transparency Register ID number (for organisations): **487418022922-47**

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

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A citizen

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A non-governmental organisation (NGO)

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A patient group√

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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

(You may choose not to reply to every consultation items)

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?

We support the view of the *European Consortium for Innovative Therapies for Children with Cancer* (ITCC) that legislation is necessary because of the widespread use of unlicensed and off-label medicine with children in Europe.

> In the EU, fifty per-cent or more of medicines used in children have never been investigated in this population, but only in adults and not necessarily for the same indication (or the same disease).[1]

A significant factor in the lack of new drug development for children with cancer has been commercial considerations.

> In paediatric oncology, access to innovative therapies *developed by pharmaceutical companies* has so far been extremely limited for children in Europe, one reason being that paediatric oncology does not represent a large and hence financially attractive area for drug marketing. Of 25 authorised products (1995-2002) for the diagnosis or treatment of a malignancy or cancer-related condition, only two of them were evaluated in children prior to submission.[(ibid)]

It was in this context that the introduction of the PMR in 2007 was considered so important and we believe it is vital that this piece of legislation is now reformed to make it properly effective.

The Commission's report states that 'figures show that the Paediatric Regulation has had a substantial impact on the development of paediatric medicines in the EU.' However, according to the *European Society for Paediatric Oncology* (SIOPE), this has resulted in very few new medicines for children with cancer. Their analysis is that, within oncology, only 2 medicines with innovative mechanisms of action, Votubia (Everolimus) and Unituxin (Dunituximab), have been approved through a Paediatric Investigation Plan.[2]

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?

We accept the Commission's view that under current legislation 'progress in paediatric medicines is dependent… on advances in the therapeutic areas and conditions in which there is a need or a market in the adult population.' This results in a desperately unfair situation where there is no provision for the 'considerable number of diseases that are biologically different in adults and children… or that only exist in children.' The most obvious example of these is, of course, cancer.

[1] ITCC (2016) *Why is a New Regulation Necessary*?
Accessed 26 / 11/ 16 at: http://www.itcc-consortium.org/new-regulation-necessary.php

[2] Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin.

We strongly disagree with the Commission's conclusion that this is 'partly dependant on factors that can hardly be influenced by legislation.' The effectiveness of the Regulation in other areas of paediatric illness has already been acknowledged. We simply advocate that this success is extended to young people with cancer. Proposals for legislative changes that would make this practical are set out in Section 1.17.

Paediatric oncology does indeed need a regulatory turnaround to improve the situation of children with cancer. 6000 children die of cancer each year (about 20% of children diagnosed with cancer). In addition, two thirds of the survivors suffer long term effects from their treatment and beyond 5 years from diagnosis, disease-free survivors have higher mortality rates than their non-affected peers.[3] By 2020, there will be half a million childhood cancer survivors [ibid]. The severe impact of long term effects of the current treatments on our children's daily life cannot be underestimated.

Raphael

One of our members from Belgium reports:

'Our son was diagnosed with an alveolar Rhabdomyosarcoma at the age of eight in 2013.

His tumour was located in his right foot and, despite very intensive treatment, the tumour had not sufficiently shrunk to avoid a partial foot amputation.

Our son has done a fantastic job at adapting to the situation but it remains a challenge for him to go out for long walks and perform some sports, such as running, swimming or skiing, all of which he used to enjoy immensely. He also needs to attend weekly physiotherapy sessions in order to avoid growth issues with his tendons. Many activities that seem trivial to anyone have become complicated… buying shoes, putting pants on (we had to customize them all with a zipper along his right leg)… Physical activities also need to be planned well in advance to make sure they will be feasible for him and, most of the time, we need to have the regular sports gear adapted to his specific condition.'

Margo

Another member from France reports that after a few doses of cisplatine, her 14 year old daughter's hearing was impaired, and after one week of radiotherapy sessions, she had lost all sensitivity on the left side of her body.

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?

There has not been a substantial increase in paediatric medicines for cancer (see section 1.1). There is a broad consensus, within the children's cancer community, that this is largely a result of the 'loophole' of waivers that the Regulation offers for adult illnesses that do not exist in children. The failure to recognise that the mechanism of action of a drug should be the crucial factor in establishing a PIP has resulted in numerous lost opportunities.

[3] The SIOPE Strategic Plan, 2015, p. 8

According to minutes of the EMA Paediatric Committee[4], from 2012 - 2014:

- 214 class waivers were discussed,
- 72% for an oncology drug, from which 95% were granted waivers (i.e. 147 drugs)
- 63% of those drugs waived were relevant to paediatric malignancies

Thus, investigations into significant numbers of drugs relevant to childhood cancers were revoked without scientific grounds.

Bethany
My daughter Bethany sadly lost her fight with Wilm's tumour after 4 years and 2 relapses. Her initial diagnosis was favourable; however it soon became apparent that this would not be the case. After the second relapse we were left in the position with no further treatment options which would guarantee a cure or even prolong life. She was failed by the fact that we had nothing left to even try. Development into new treatments for children that do not respond as hoped is vital, especially in diseases that are perceived as 'curable'.

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?

We note the Commission's view that costs 'are reasonable and that they lead to only a limited increase in the total costs of medicine development.' Although costs may be sustainable by big pharmaceutical companies, they may, however, be a burden for smaller biotechs, where important innovation often takes place.

In section 1.17, we propose changes to the reward system that would create greater incentives for the industry and produce better outcomes for children with cancer.

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?

In our view, the balance between the cost of an oncology PIP and the potential reward is not sufficiently motivating for Pharma. Delays are a disincentive as a reward is often only available after 10 years' clinical research. We are concerned that the failure of a drug to show positive results in an adult cancer leads to the corresponding PIP also being cancelled. Although there may be evidence of the potential for benefit for children, the reward is withdrawn in these circumstances.

[4] PDCO minutes from June 2012 to June 2015 plus Literature search then blinded panel of 16 ITCC experts. Source: Vassal G. (2016). Accelerating new oncology drug development for children and adolescents: challenges and the European Strategy. Unpublished paper presented at 48th Congress of Paediatric Oncology, 19 - 22 October, Dublin.

Laura

'When my daughter had a sudden relapse with Ewing's Sarcoma in 2009 and we were told her condition was terminal, we immediately enquired about clinical trials, specifically mentioning IGF-1R inhibitors, which we had heard about at a conference. In the following year leading to her death, not a single relevant trial was available. It was only some years after her death that I understood some of the background to this.

> 'IGF-1R inhibitors have shown efficacy in Ewings sarcoma, one of the commonest childhood and adolescent sarcomas and have provided significant benefit to a small proportion of patients (approximately 10%). The development of most IGF-1R inhibitors has been discontinued because of failure in randomised phase III trials in [adult] lung cancer. No Paediatric Investigation Plans (PIPs) have been delivered in this area.' [5]

I have also since learnt of the potential that has been demonstrated of PARP inhibitors for Ewing's.[6] Here a PIP was granted a waiver[7] because the adult investigation was into ovarian cancer, a disease not experienced in children.

I am not suggesting that had such trials gone forward that this would necessarily have made a difference for my own daughter. However, seven years on, there are virtually no opportunities for children to take part in such trials or to benefit from them and families, a number of them our supporters, continue to lose their children to illnesses like Ewing's Sarcoma. '

Incentives are necessary that are proportionate to the costs of investment, that offer these rewards sooner and which stimulate paediatric investigations uncoupled to those for adult cancers. This should include those malignancies that only exist in children and for which there is no connection with an adult cancer even by the mechanism of action.

See recommendations in Section 1.17.

2.6. The orphan reward

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

We accept Orphan Drug Legislation provides incentives for drug development for other childhood conditions. However, these incentives are not effective with paediatric cancer drugs as treatment times are generally shorter and, also, they are unlikely to be given a premium price if the same drug is used in more common, adult cancers[8]

[5] ITCC. (2012.) General report on experience acquired as a result of the application of the Paediatric Regulation. Viewed 18/07/15 at: http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/31-itcc.pdf

[6] Vormoor B, Curtin NJ. (2014) Poly(ADP-ribose) polymerase inhibitors in Ewing sarcoma. Current Opinion in Oncology, 26(4), 428-433.

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

[8] Unite2Cure. A letter to the Commissioner. 2016. Available at: https://unite2cure.org/2016/02/29/a-letter-to-the-commissioner/ [Accessed 2 April 2016]

We accept the view of the Institute for Cancer Research:

> 'The ICR believes that orphan drug designation has not proved effective at providing financial incentives for companies to develop drugs solely for paediatric cancers. No cancer drugs have gone through this process purely for childhood cancers, indicating that companies do not regard it as financially attractive. Instead, we believe that an improved PIP process should be the main route for developing paediatric medicines.'[9]

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?

One example of progress that is often given is the revision in 2015 of some *class waivers*. It should be emphasized that these measures, however, will not come into force until 2018. Removal of some of the broad *class waivers* should engender more research. However, companies can still apply for *product specific waivers.* We were signatories to a letter to Lancet Oncology which emphasised that this change was, therefore, of minor significance:

> ' If the company decides to request a waiver because the illness does not exist in children, even though the drug's mechanism of action is relevant for paediatric malignancies, EMA cannot force the company to assess a drug in children.'[10]

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?

The EMA acknowledge in their 10 year report the importance of the Mechanism of Action principle.

> Paediatric oncology has been identified as a neglected therapeutic area as little progress has been made with new and better treatments for childhood cancers, and this was attributed in part to the difference in clinical conditions between adults and children. Cancers that concern children are biologically different from those concerning adults, and therefore any medicine's mechanism of action needs to be used to guide investigating treatments of the paediatric malignancies and to address the unmet therapeutic needs in paediatric oncology. Consequently, the development should be driven by the potential paediatric use, i.e. by the data (existing or to be generated as part of a PIP) on the mechanism of action, or on the target of the anti-cancer medicine where the anti-cancer adult indication is under development.

[9] CR (2014) Early-stage clinical trials of cancer drugs for children
Accessed 26 / 11/ 16 at: http://www.icr.ac.uk/about-us/policy-and-factsheets/early-stage-clinical-trials-of-cancer-drugs-for-children

[10] Vassal, Gilles et al. (2015) Will the revised class waiver list make it? The Lancet Oncology , Volume 16 , Issue 9 , e425 - e42

We support this view and that of Pearson et al, members of the ACCELERATE Working Group, who point out:

> Whilst the Regulation has brought positive change and advances, the waiver mechanism means that with over 60% of 89 potentially valuable anti-cancer drugs granted a waiver, there are still few paediatric trials and only between 9% and 15% of all oncology agents have ongoing paediatric studies.[11]

They go on to clarify the extent of this lost opportunity.

> 'It is critically important to realise that the average number of non-synonymous coding mutations in childhood tumours is on average about a hundred-fold lower than in adult malignancies. This means that the likelihood of correctly identifying the Achilles' heel' of the tumour for targeted therapies is much higher, thus, comprising a much more promising and clean target population for Mechanism of Action based drugs to actually work.[(ibid.)]

Crizotinib is an example of how opportunities have been missed under the current system. This drug is now authorised in Europe for the treatment of non-small cell lung cancer (NSCLC). Research on crizotinib began as recently as 2007, but its development in children was waived in 2010 on the grounds that "NSCLC does not exist in children". This was despite the fact that the drug was known to be active *at a molecular level* in a number of childhood cancers, including lymphoma, something that has been confirmed since in trials conducted in the United States.[12]

The Commission suggest that 'some companies decided not to apply the waiver and to carry out paediatric research on a voluntary basis and based on the 'mechanism of action' principle.' In section 1.10, we present evidence that voluntary paediatric research of this kind has been insignificant.

2.9. Deferrals

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

We agree with the Commission that 'there is no evidence that the paediatric requirements have delayed the processing of adult applications.'

However, delays with paediatric plans are an issue, particularly those for oncology, which are unlikely to be submitted at end of the phase 1 trial in adults, though this is a legal requirement and which are granted deferrals in many cases. The result is that drug development is significantly delayed compared to that for adults.

As parents, we testify to the *frustration* the report mentions where the treatment 'for a life-threatening disease will only be available to children years after the adult authorisation.'

We also share the concern of the EMA, in their 10 year report, that deferrals may ultimately lead to PIPs becoming unenforceable.

11 Pearson et al. (2016) Implementation of mechanism of action biology-driven early drug development for children with cancer, European Journal of Cancer, Volume 62, July 2016, Pages 124–131. Accessed 2.01.17 at: http://www.sciencedirect.com/science/article/pii/S0959804916320597

12 ITCC. (2012.) General report on experience acquired as a result of the application of the Paediatric Regulation. Viewed 18/07/15 at: http://ec.europa.eu/health/files/paediatrics/2013_pc_paediatrics/31-itcc.pdf

> In spite of that success, once the marketing authorisation for adults is granted, deferred paediatric studies may be delayed or not initiated. This is due to the fact that once the product becomes authorised, the most significant deterrent of the Regulation, non-validation of the marketing authorisation application, is not applicable. This leaves the regulatory network without the means to enforce the PIP completion once the product is authorised. Additionally, once the medicine is authorised in adults and thus available for off-label use in children, it becomes more difficult to recruit children into clinical trials.

We are concerned that there is no penalty for submitting a PIP late.

In the absence of tighter requirements for timely submission and completion of PIPs, we propose in section 1.17 incentives to meet deadlines.

2.10. Voluntary paediatric investigation plans

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

Herold of the European Medicines Agency relates how encouragement for voluntary engagement on both sides of the Atlantic has proved unsuccessful.[13]

The 10 year report by the EMA confirms this situation:

> "Experience from the EU, the US and other regions conclusively shows that a system based exclusively or primarily on voluntary initiatives from developers, or solely on incentives, does not result in development of medicines that address satisfactorily the public health needs of children….
>
> Between 2011 and 2014, the Agency confirmed the applicability of the class waiver in 73 cases and identified a potential paediatric interest for 50 of them (68%). Unfortunately, the suggestion to submit a PIP application to cover a new paediatric development was accepted only in a single case, suggesting that rewards without obligations have some limitations in fostering the development of paediatric medicines".

Moreover, there is a point of principle here. Our children's lives should not depend on the goodwill of members of the pharmaceutical industry, a 'privilege' that can very easily be withdrawn. Adequate research into childhood cancers should be a requirement in any society that considers itself part of the developed world.

For this reason, the ACCELERATE Position Statement[14] (see section 1.17) advocates an *obligation* to undertake a Paediatric Investigation Plan, though complemented with more attractive incentives.

[13] Saint-Raymond, A. and Herold, R., (2012). Medicines for paediatric oncology: can we overcome the failure to deliver? *Expert Reviews. Clinical Pharmacology*. 5(5), 493-495. Viewed 18/07/15 at: http://www.researchgate.net/publication/232809972_Medicines_for_pediatric_oncology_Can_we_overcome_the_failure_to_deliver

[14] SIOPE. (2016). Paediatric Cancer Medicines - Urgent need to speed up life-saving innovation. Position Statement. Available at: https://drive.google.com/file/d/0BzKY_XqYJN-SejdiaFkwZXZzcFBRYWkyaC1NMktKS1phZmhz/view [Accessed: 14.01.17]

2.11. Biosimilars

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

Biosimilars are generic versions of biological agents. As there are few biological agents developed for children, we should not expect Biosimilars to have an impact on childhood cancer treatment.

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?

PUMA is a disappointment because it is a weak incentive. A clinical study may be granted a PUMA but the product would then have to compete with off-label use of the generic drug. From the commercial point of view, this is unlikely to be profitable. The key challenge is to develop a paediatric-specific formulation that can offset off-label use.

Specific areas in which research on off-patent anti-cancer drugs could be beneficial include:

- age appropriate formulation of oral anticancer drugs
- dosing of chemotherapy below one year of age
- long term toxicity in childhood cancer survivors

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 support the approach of *Nuffield Bio-ethics* to research with children:

> Central to the report is the idea that from a young age, children have a role in determining their own lives and should be seen as active participants in research. The assumption that all children are necessarily vulnerable may prevent worthwhile research from going ahead. The risk of children being placed in vulnerable situations can be minimised by ensuring that researchers engage with children's and parents' views and experiences in the prioritisation, design and review of research and that research is subject to appropriate scrutiny and governance. Children and parents should be confident that an invitation to take part in research is a 'fair offer' where the value of the research and its risks and benefits, have been independently assessed.[15]

Furthermore, members of this group feel that clinical trials are not limited to just influencing survival odds or testing of new drugs, but also reviewing and evaluating the efficacy of current treatments in order to minimize toxicity. In this regard, ethically speaking, it is essential to increase research and clinical trials on children.

Elliot
"When my son was put on a clinical trial for stage 4 Wilm's Tumour, we were told that the

[15] Nuffield Council on Bioethics (2015) Children and clinical research: ethical issues. Accessed on 2.01.17 at: http://nuffieldbioethics.org/wp-content/uploads/Children-and-clinical-research-full-report.pdf

purpose was to determine whether certain cases of his type of cancer could still be cured using fewer toxic drugs. He was given the heavier protocol, and we have no regrets since he is still in remission 4 years later. But it is interesting to know that we participated in a trial which later proved that children like him can have fewer drugs and still have the same odds of survival. Two thirds of children who survive cancer will have long term side effects, many of them serious. It is imperative that research be put into how to minimize these."

The ethical question about clinical trials should be balanced with the current situation where 50% or more of the drugs given to children are off-label. Should we accept that the vast majority of children with cancer are given off label drugs, i.e., drugs that were neither developed, nor specifically authorised for a paediatric indication? Is this "more ethical" than involving children in properly framed clinical trials? We need more drugs, earlier and for more children.

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?

We have no comment on this question.

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?

There appears to be a consensus that the PMR has had an impact in terms of 'mindset,' i.e. attitudes and awareness within the industry and amongst academic researchers, and in the establishment of collaborative networks, ACCELERATE being only one example. However, this has not been reflected in actual results for childhood cancers.

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?

Emerging developments, such as individualised medicine, are compatible with the mechanism of action approach we advocate. Both involve matching a drug with a molecular target, though with individualised medicine, this involves a particular patient rather than a disease category. Molecular profiling is becoming an increasingly standard practice through programmes such as MAPPYACTS and COMET and this approach, in turn, is being used to match individuals to the particular arm of a trial, such as in ESMART. Making mechanism of action intrinsic to the requirements of the Regulation would add a welcome impetus to these exciting new developments.

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?

One issue we would also like to be considered is access to trials for adolescents. Trials specifically for teenagers and young adults are less common even than for children.[16] Adolescents tend to be grouped with children and thus are excluded from adult trials. This is despite the fact that adolescents have a similar tolerance to toxicity as adults. We contend that inclusion in trials should be based on medical need rather than arbitrary age limits.

We support the recommendations in the Position Statement[17] by SIOPE, Unite2Cure and Cancer Research UK:

1. Ensure that the *obligation* to undertake a Paediatric Investigation Plan is based on how a drug works and its capacity to address an unmet medical need in children - rather than the type of disease in adults for which it is first introduced.

2. Set up a mechanism to choose the best potential drugs and prioritise, among drugs developed by different companies, in relation to the real needs of children affected by rare cancers.

3. Reduce delays in paediatric medicines reaching children by enabling Paediatric Investigation Plans to be submitted not later than the start of pivotal trials in adults, if paediatric biological, preclinical and preliminary clinical data are available to better evaluate the potential therapeutic benefit in the paediatric population.

4. Add provisions for more effective and flexible rewards for companies undertaking early and timely Paediatric Investigation Plans and those researching therapies specifically for cancers which only
occur in children

To this, we would add a further item:

5. Introduce flexible ages of entry to adult trials based on considerations of biology and safety

We stress the need for the Commission to respond to childhood cancer with a great sense of urgency. Cancer is and remains the most common cause of death by disease for children in Europe – the equivalent of 160 school bus crashes every year without any survivors. This is a crisis that demands a swift and proportionate response. The time for action is NOW.

[16] Whelan, J., &Fern, L. (2008) Poor accrual of teenagers and young adults into clinical trials in the UK. The Lancet Oncology.
Vol. 9. Available from: http://oncology.thelancet.com [Accessed 14.01.17]

[17] SIOPE. (2016). Paediatric Cancer Medicines - Urgent need to speed up life-saving innovation. Position Statement. Available at:
https://drive.google.com/file/d/0BzKY_XqYJN-SejdiaFkwZXZzcFBRYWkyaC1NMktKS1phZmhz/view

[Accessed: 14.01.17]