

## Consultation in relation to the Paediatric Report

### *Ref. PCPM/16 – Paediatric Report*

Response from The Institute of Cancer Research, London and The Royal Marsden NHS Foundation Trust

#### **Consultation item No 1: More medicines for children**

Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

It is essential to be able to run clinical trials in paediatric cancers internationally if we are to improve children's survival and quality of life.

The EU Paediatric Regulation has delivered a common Europe framework as a means of promoting paediatric development and international collaboration and increasing the number of trials that are run. We support the aims of the Regulation and believe it has delivered some progress in increasing the number of cancer drugs evaluated in children.

However, we are concerned that it is outdated and by not keeping up with advances in science it is delaying children access to the latest cancer drugs. It now needs to be revised to deliver further benefits.

#### **Consultation item No 2: Mirroring paediatric needs**

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?

#### *Unmet need in paediatric cancers*

We believe that paediatric oncology is still an area of significant unmet need.

Too many children continue to die from cancer, and some survivors suffer lifelong adverse effects from treatment. To meet the needs of children, we need to see a major expansion in the number of medicines available for children with cancer, with treatments rationally selected based on the mechanism of action of the drug.

While we have seen some additional trials of cancer medicines for children in recent years, the EU Paediatric Regulation has not been successful at delivering the scale of increase required.

In 2012, the EMA specifically highlighted paediatric oncology as a neglected therapeutic area in need of improvement in its five-year report to the European Commission<sup>1</sup>. It stated that '*further*

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<sup>1</sup> European Medical Agency. *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\\_pediatic\\_report-annex1-2\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2012-09_pediatic_report-annex1-2_en.pdf)

*steps are considered necessary to achieve the main objectives of the Paediatric Regulation for paediatric therapeutic areas such as paediatric oncology where little progress has been made’.*

In its 10-year report<sup>2</sup>, the EMA recognised that there is still much ongoing debate in this area. While there has been some increase in paediatric developments, it acknowledges that *“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”*. It specifically highlights *“the gap between paediatric oncology research and development and the medicines that reach the regulatory networks”*.

We would agree with this assessment that while a small number of drugs have been licenced for children, and have made available through trials in recent years, this is happening at nothing like the rate that drugs are developed for adults.

In its 10-year report, the EMA list 11 drugs which have been approved for paediatric oncology since 2008 – when almost 50 cancer drugs were approved for adult cancers over the same time period. Of the 11 drugs only six were newly authorised treatments which included a paediatric authorisation alongside an adult drug. Five of the 11 were drugs that were already authorised for adult use – with some such as daunorubicin, etoposide and idarubicin approved for adults as long ago as 2001, 1996 and 1990 respectively.

Children therefore continue to benefit from new cancer treatments at a much slower rate than adults. The Regulation has not delivered sufficient progress because it has not kept pace with the science. Modern cancer drugs are often designed against specific molecular mechanisms, rather than for a particular cancer type. As a result, there are instances where potentially important cancer drugs are given a waiver from testing in children, even though the drugs could be effective against children’s cancers. Revising the waiver system for paediatric medicine could bring new types of drugs to the clinic for children and make a huge difference to survival rates in childhood cancers. We discuss this further in our response to later questions.

#### *Inventory of paediatric needs*

In 2014, the EMA launched a call for evidence to update the inventory of paediatric need for cancer medicines, as outlined in the Regulation, identifying priority areas of need for children with cancer and relevant medicinal products for paediatric use. The inventory contains a list of active substances that do not hold a paediatric market authorisation but for which some data support the relevance of their mechanism(s) of action. The ICR submitted a response recommending 14 additional drugs for inclusion on this list. To our knowledge, the final version of this list has not been published by the EMA yet. We would welcome an update to this list as a key way to recognise the gaps in paediatric oncology.

#### *Age limits on trials*

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<sup>2</sup> European Medical Agency. *10-year Report to the European Commission*  
[https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016\\_pc\\_report\\_2017/ema\\_10\\_year\\_report\\_for\\_consultation.pdf](https://ec.europa.eu/health/sites/health/files/files/paediatrics/2016_pc_report_2017/ema_10_year_report_for_consultation.pdf)

We would like to see a cultural change to phase I trial design to lower the age limit of eligibility for adult trials where appropriate to help ensure that patients with cancer are able to access relevant trials.

Adult phase I trials have a fixed lower age limit of 18 years and the ICR and The Royal Marsden believe that this age limit should be lowered to safely include adolescents in a staggered fashion. Once an adult phase I study has shown an appropriate safety profile in adults, if the target is appropriate and if the drug has a relevant mechanism of action, adolescents should have the option of being included in the adult trial without waiting for a subsequent paediatric phase I trial. In certain cases this could be as low as 12 years old, if cared for by medical professionals experienced in running early phase studies in this age group.

We also recommend more flexibility to increase the age limit for paediatric trials to allow options to involve young adults who have paediatric-type cancers but find themselves too old to take part in paediatric trials. For example many sarcomas will affect both children and young adults. Decisions on inclusion in trials should be rationally made, based on mechanism of action of the drug and whether a target is present in the patient, rather than the age of the patient.

While financial incentives may not be appropriate to encourage this, some sort of incentive such as an accelerated review for drugs where adolescents had been allowed on the trials might help encourage this.

### *Factors outside the Regulation*

The consultation document suggests that the Paediatric Regulation may be an important enabler to redirect private investment towards neglected areas, but that its effects are partly dependant on factors that can't be influenced by the Regulation itself. We would concede that the Paediatric Regulation cannot necessarily regulate every aspect of the R+D ecosystem, but believe there is much more that can be done within the framework of the Regulation to drive research in neglected areas such as paediatric oncology. Changes to the Regulation detailed below would have lasting benefits for children with cancer.

### **Consultation item No 3: Availability of paediatric medicines in the EU**

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

As discussed above, while we have seen some increase in the number of trials running for children with cancer in recent years, there have been very few authorisations of new medicines for children, and very few cases where standard therapy has been replaced by an innovative new treatment.

The Regulation states that, where the product is already authorised, the authorisation holder should be obliged to place the product on the market for paediatrics within two years of the date of approval of the indication. We feel that this is an unduly long time, particularly where a product is already marketed for other indications.

In the United States, under the terms of the Creating Hope Act, the FDA may revoke rewards to a company if a paediatric product is not marketed in the US within a year, actively incentivising shorter

time periods to bring a drug to market. We recommend similar routes to speed up access to paediatric medicines are explored here in Europe.

#### **Consultation item No 4: Reasonable costs**

Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

The consultation document suggests the average cost of filing and carrying out a paediatric investigation plan is in the region of €20 million, which it states to be a reasonable cost, and only a limited increase on the total cost of a medicine's development. The report also states that in most cases, the value of the reward a company gains from carrying out a paediatric investigation plan is likely to surpass the compliance costs, although we know that many in the pharmaceutical industry state that the costs likely exceed the return.

We recognise that developing drugs for small patient populations can be financially challenging and we believe we need to see a reduction in costs of running trials across the board for cancer drug development. We need to look at how altering trial design can bring costs down by using biomarkers to stratify patients into the most appropriate trials, where they are likely to receive the most benefit. Particularly where a medicine has a predictive biomarker, we hope this will be a particular incentive for companies working on treatments for smaller populations, as there is higher chance of patients responding to a drug and of a treatments eventual authorisation.

We note that in recent years there has been a move toward pre-competitive collaborative research in the sector, which we welcome as a way to ensure that research is prioritised in the most viable paediatric targets. Non-traditional funding models including partnerships may be needed to support these collaborations.

#### **Consultation item No 5: Functioning reward system**

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 believe the key to ensuring more paediatric cancer trials are run is a system that balances the regulatory requirement for drugs to be evaluated in children with appropriate rewards for companies.

Companies are currently given an additional six-months market exclusivity for submitting a new marketing authorisation application based on data from a completed PIP. However, this system of reward is only effective if a company is likely to gain marketing authorisation for the new product in adults. If the drug is unlikely to be licensed in adults, there is less incentive for the company to complete a PIP. The ICR and The Royal Marsden feel strongly that early clinical evaluation of drugs in children should not be stopped just because a company is unable to gain market authorisation for a drug in adults.

We would recommend that further schemes are explored to incentivise paediatric drug development. The European Society for Paediatric Oncology (SIOPE) has called for more flexible rewards to be introduced to encourage companies to begin PIPs earlier on in the development of a

drug, providing incentives even where drug development is discontinued for adults<sup>3</sup>. We welcome this suggestion and believe rewards could be provided at the start of preclinical work, development of a paediatric formulation of the drug and phase I clinical trials.

We also believe pharmaceutical companies need stronger financial incentives to develop and trial drugs which are purely for paediatric use. Developing drugs for small patient populations is financially challenging and there is currently little commercial incentive for companies to develop drugs designed only for paediatric cancers. Incentives such as extra protection of market exclusivity or R&D tax credits, or ways of 'weighting' existing R&D tax credits to favour paediatric R&D might help to persuade companies to complete trials in children.

In the US, the Creating Hope Act awards vouchers giving rights to faster FDA review for a subsequent product to companies that complete paediatric drug development. It is particularly innovative in that these vouchers are fully transferable to another product or can even be sold to another company, meaning that a drug does not have to have a large market for it to be financially beneficial to develop it for children. We would welcome the exploration of similar innovative routes to incentivise the development of paediatric medicines.

Lengthy and uncertain processes for drug reimbursement and pricing approval in European countries may further disincentivise companies from developing paediatric treatments. While marketing approval can be granted at a European level, these decisions are carried out at the national level, with Member States forming their own decisions to different timelines. Accelerated approval for products with paediatric indication may act as further incentive for companies to develop drugs for children. A reward transferable to other products could be even more attractive to companies.

#### **Consultation item No 6: The orphan reward**

How do you judge the importance of the orphan reward compared with the SPC reward?

The ICR and The Royal Marsden believe that orphan drug designation has not proved effective at providing incentives for companies to develop drugs solely for paediatric cancers.

In the report 'Better Medicines for Children – From Concept to Reality', the European Commission pointed to mechanisms to encourage the development of new drugs specifically for childhood cancers, such as the Orphan Regulation.

Data analysis by the ICR and others<sup>4</sup> shows that as of June 2013, none of the 25 approved orphan medicinal products for oncology were registered for children in a different indication to adults, indicating that companies are not using this route for developing new drugs solely for paediatric cancers. We believe that an improved PIP process should be the main route for developing paediatric medicines.

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<sup>3</sup> [https://coalition4acure.files.wordpress.com/2016/12/paediatric\\_reg\\_position\\_paper\\_final\\_draft.pdf](https://coalition4acure.files.wordpress.com/2016/12/paediatric_reg_position_paper_final_draft.pdf)

<sup>4</sup> Vassal *et al.* (2013) *Need for change in implementation of paediatric regulation*  
[http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045\(13\)70467-4.pdf](http://www.thelancet.com/pdfs/journals/lanonc/PIIS1470-2045(13)70467-4.pdf)

**Consultation item No 7: Improved implementation**

Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

We welcome the fact that the EMA has made efforts to address the class waiver system in the period before the Regulation itself can be updated.

The changes to the 'class waiver' system, announced by the EMA in 2015, make it harder for companies to gain a waiver for an adult cancer drug that has a relevant mechanism of action simply because the precise condition it was developed for doesn't occur in children. Under revised qualification criteria, many drugs will no longer be eligible for class waivers.

However, these drugs will still be eligible for 'product specific waivers'. This process continues to allow waivers for drugs on the grounds that an adult cancer does not occur in children, although it does require in-depth discussion with the EMA's Paediatric Committee to ensure decision making is evidence based. Until these changes come into force in 2018 it is difficult to know the extent of the impact, and whether the more in-depth process will lead to an increase in voluntary PIPs.

While the waiver system has been reformed in part, the changes are not so radical as to ensure that all potentially valuable cancer drugs are likely to be trialled in children as well as adults. Changes to the Paediatric Regulation itself are needed to make sure that children benefit just as much from the new wave of targeted cancer treatments as adults.

**Consultation item No 8: Waivers and the 'mechanism of action' principle**

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 ICR and The Royal Marsden believe the EU's system of waivers for paediatric investigational plans (PIPs) needs to be revised to ensure cancer drugs developed for adults are also tested in children whenever their mechanism of action suggests they could be effective.

Increasingly what matters most in determining relevant treatment for cancers is not the site of origin of a tumour, but the particular combination of mutations that drive the cancer's development. Medicine has moved on from simply categorising cancers as 'breast cancer' or 'lung cancer'. It is increasingly common to look at specific molecular defects in an individual's cancer, and use medicines specifically targeted at the particular genetic features of that tumour. These genetic features may occur in a subset of patients across a number of cancers, rather than a single tumour type.

Companies are able to gain a waiver from having to prepare and carry out a PIP, if the disease the drug is active against does not occur in children. However, many adult cancers do not have direct equivalents in children, even though they may be caused by similar combinations of mutations.

As a result companies have often been granted waivers exempting them from testing their drugs in children – even though many have mechanisms of action that could be effective against other types of children's cancer.

In a recent study from 2016<sup>5</sup>, Pearson *et al.* cite that 60 per cent of 89 potentially valuable cancer drugs were waived, suggesting that the situation has not improved in this time.

In similar analysis in its 10-year report to the European Commission, the EMA cites that 27 out of 48 (56%) adult cancer medicines approved during the time frame they looked at received a waiver during initial marketing authorisation, although the EMA highlights that for 11 of these drugs, companies proposed voluntary PIPs.

We support replacing the waiver system with one that looks at the mechanism of action of the drug and argue that this one change would have the greatest single impact on increasing access to clinical trials for children and adolescents.

We welcomed the EMA's interim solution to incorporate a drug's mechanism of action into class waivers, ensuring that more drugs will need to be reviewed through the more involved product-specific waiver route.

However, until Article 11 of the Paediatric Regulation itself is revised companies will continue to be able to be granted waivers for drugs which could be effective in children. The Regulation itself must be updated in order to have the full impact.

#### **Consultation item No 9: Deferrals**

Do you agree with the above assessment of deferrals?

We agree that long delays in gaining access to potentially life-saving treatments can cause immense frustration for patients, parents and clinicians. In some cases drugs are only being made available for children years after marketing authorisation in adults. We welcome initiatives to accelerate the development of innovative new medicines for children.

We believe that trials themselves could be adapted and modernised to speed up the development of innovative new medicines for children. For example, the starting dose for a paediatric trial is typically around 75-80% of the starting dose for a phase I adult trial (adjusted for body size). It takes time to then escalate the dose during trials – to what in some cases can finally result in an even higher dose in children as they can have a greater ability to tolerate toxic therapy. Many paediatric clinicians now consider 100% of the adult dose to be a safe starting dose for paediatric trials (where the dose is adjusted for the size) in children over three years old. A few recent trials across Europe have already implemented this approach. We recommend this becomes standard for rationally designed clinical trials where patients are preselected by genomic testing, and the trials include appropriate biomarkers of response.

There are also some situations where it may be appropriate to carry out phase I paediatric trials in children before studies have been conducted in adults in certain high-priority targets for children's cancers, providing the trial is rationally driven with patients preselected by genomic or other testing and the trials are biomarker rich, and animal studies have found no strong indication of likely developmental consequences.

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<sup>5</sup> Pearson *et al.* (2016) *Implementation of mechanism of action biology-driven early drug development for children with cancer*

<http://www.sciencedirect.com/science/article/pii/S0959804916320597>

**Consultation item No 10: Voluntary paediatric investigation plans**

Do you have any comments on the above

We welcome the fact that some companies have submitted and carried out voluntary paediatric investigation plans in cases where they would have been eligible for class waivers. In its 10-year report to the Commission, the EMA lists 14 cases of voluntary PIPs that have been agreed since 2008, with majority of these in the last four years.

However, these 14 drugs represent only a small proportion of the total number with relevant mechanisms of action for children's cancers. It is not enough to rely on voluntary PIPs. The Regulation itself must be updated in order to address the number of drugs waived when they have a relevant mechanism of action that justifies testing in children.

We know that any change to the Regulation is likely to be a slow process taking several years to implement, so in the meantime we welcome voluntary PIPs as a way to deliver trials of relevant medicines for children with cancer.

**Consultation item No 11: Biosimilars**

Do you have any comments on the above?

**Consultation item No 12: PUMA — Paediatric-use marketing authorisation**

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 document suggests that PUMAs have not appeared to stimulate interest in developing off-patent treatments for paediatric use. As we understand it, companies may feel that the return does not justify the investment.

We feel that academic organisations may be able to play a role in making this a more attractive route for companies. Academic organisations, who have a greater tolerance of financial risk, can push forward high-risk, innovative projects to proof of concept by molecularly characterising patients and conducting preclinical studies using large-scale mouse models. This would reduce the amount of early investment for companies.

**Consultation item No 13: Scientifically valid and ethically sound — Clinical trials with children**

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 do believe that the Regulation has fostered expert discussion about the optimal design of paediatric trials, and we welcome the developments that we have seen in recent years.

Programmes like the UK's Stratified Medicine for Paediatrics allow us to sequence all paediatric patients, allowing clinicians to maximise the chance of selecting a relevant trial for the child. We recommend it becomes standard practice to sequence patients in trials across the NHS.

We are seeing an increase in combined phase I/II paediatric clinical trials. These can avoid much of the delay that might otherwise occur between one trial ending and the next beginning.

There has also been a move towards multi-arm trials testing multiple drugs from different companies at once. Basket studies such as the E-SMART trial - which has nine arms with drugs from two or three different companies, including combination therapies - are particularly innovative. We recommend more paediatric trials are conducted in this way in future.

#### *Prioritising clinical studies*

In oncology, multiple drugs can be developed by different companies against the same target. We agree that it would be unnecessary and unfeasible to carry out a paediatric research programme for each individual 'me too' drug against the same target as this would lead to trials competing for the same patients.

We note that the paediatric oncology community is already trialling new models to address this. The ACCELERATE platform has coordinated a meeting with the EMA soon, bringing together pharmaceutical companies and academic clinicians to prioritise the paediatric development of ALK inhibitors, based on side-effects and potency of the drugs. This is a brand new model and so guidance will be needed from the EMA on exactly how these decisions should be made and how the resulting trials will be funded.

We would like to highlight several ways that we believe that drugs should be prioritised for paediatric clinical trials.

Preclinical research is vital for selecting the best drugs to take forward into clinical trials for children. For example IMI2 is an innovative pan-European project, in collaboration between academic organisations and the pharmaceutical industry. Academic hospital partners take tissue samples from paediatric patients for analysis. Half of each sample will be intensively sequenced to help identify new childhood cancer targets and half will be used to make mouse models to test medicines which have potential for paediatric use. This will make preclinical testing much more efficient, lowering the hurdle for companies developing drugs in these systems, and allowing us to prioritise the most promising drugs to take forward into trials for children sooner, increasing the speed of development of new drugs for children.

Drugs that have relevant pharmacodynamic biomarkers should also be prioritised for taking into clinical trials for children.

#### **Consultation item No 14: The question of financial sustainability**

Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

## **Consultation item No 15: Positive impact on paediatric research in Europe**

How do you judge the effects of the Paediatric Regulation on paediatric research?

In recent years, a culture change around designing paediatric trials has begun, with more research beginning to incorporate the advances seen in some modern adult trials. By studying the mechanism of action of a drug we can identify the most important targets to study for paediatric cancers. Preclinical studies such as IMI2 are helping to prioritise which drugs to take forward into clinical trials for children, and the incorporation of biomarkers and sequencing into paediatric trials is helping to make sure we select the right patients to take into the trials.

### *Networks*

It is hard to know to what degree advances in paediatric research over the period of the Regulation can be attributed to the Regulation itself. The consultation document highlights the importance of networks in driving forwards paediatric research which we support, and many of the advances seen are in most part due to these strong networks working together to drive change. Strong links are vital to enable collaboration, particularly in research studies for rare cancers with smaller populations such as paediatric studies, where multi-centre trials are always needed.

We'd like to highlight pan-European networks such as the Innovative Therapies for Children with Cancer (ITCC) Consortium, Cancer Drug Development Forum (CDDF), European Network for Cancer Research in Children and Adolescents (ENCCA), and SIOPE, as well as disease specific networks such as SIOPE-N for neuroblastoma, and collaborations with adult networks such as the Euro Ewing consortium.

We welcome the fact that we've seen an increase in collaboration between academic and industry, with multi-stakeholder groups like the Paediatric Oncology Platform involving industry, academia, parents and regulators. This has played a large role in bringing the culture change that we are currently seeing.

### *Infrastructure underpinning paediatric drug development*

While we welcome these advances, we believe that further infrastructure support is needed.

The consultation document highlights the need for additional basic research in order to facilitate and inform appropriate paediatric development, stressing that it requires additional efforts and funding from public and private sources as research infrastructure needed to conduct paediatric trials did not develop at the pace needed.

We agree with this analysis and suggest that additional infrastructure is needed to further support paediatric research.

While in some centres of excellence, infrastructure is being put in place – such as the pilot of Stratified Medicine for Paediatrics as a national sequencing programme in the UK. The Royal Marsden is the first UK hospital to establish a Molecular Tumour Board to discuss the sequence of every paediatric patient, an initiative we believe should be rolled out across the NHS, and the model could also be used for other rare adult cancers as well. However, despite these advances, core infrastructure – such as data managers, trial coordinators, nurses, tissue sample collectors etc – is often not covered by the research funding that we receive to conduct paediatric trials, leaving a funding gap. Funding the infrastructure to support pharmacodynamic biomarker testing for paediatric trials (which is crucial to confirm treatments are inhibiting the relevant target) is also very

challenging as it is often considered an ‘exploratory endpoint’ by funders rather than a crucial trial endpoint, and so isn’t covered in trial funds.

We also believe that additional measures are needed to support the basic scientific research which underpins the delivery of novel drugs and treatments for children to the clinic. We believe early research into paediatric drug targets is currently underfunded and we need new collaborative models of funding involving Government, academic, charities and industry.

One barrier to conducting basic and preclinical animal studies into children’s cancers is access to drugs of potential interest for childhood illnesses. We strongly encourage pharmaceutical and biotechnology companies to provide academic researchers with easier access to their drugs to support early-stage pre-clinical paediatric studies, and welcome those that are already doing so.

The costs of accessing these drugs can be prohibitively expensive. We welcome the involvement of companies in the IMI2 programme, providing academic researchers with access to compounds for preclinical research.

**Consultation item No 16: “Mirror, mirror on the wall” – Emerging trends and the future of paediatric medicine**

Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

We welcome the fact that the Commission is consulting on future trends in paediatric medicine, to ensure that children can benefit from future advances in modern science. To date, the Regulation has not kept pace with advances in science, with the class waiver system a vestige of a time when what mattered most was the anatomical location and histology of a cancer, and not the molecular changes such as mutations that drive it. We welcome the fact that the Commission is thinking about how to future proof the Regulation.

*Personalised medicine and sequencing*

The consultation document highlights personalised, precision medicines as an emerging development that we need to ensure children can fully benefit from.

In adult oncology, the use of predictive biomarkers is becoming more routine on clinical trials, which has helped to accelerate the development of personalised treatments and improve the success of trials. We believe that the pilot of the Stratified Medicine for Paediatrics programme could act as a model for precision medicine for paediatrics and should be rolled out further.

However, we have learnt from personalised medicines that cancers often respond initially to treatment only to become drug resistant – and we now know that this happens because tumours are extremely genetically diverse, and can evolve dynamically over time. Tumour diversity, evolution and drug resistance are major challenges to targeted therapy, indeed Darwinian evolution of cancer is one of the biggest challenges we face.

Tumours now need to be sequenced and re-sequenced throughout treatment, often using liquid biopsies. Adult cancer drugs that may not previously have been considered to have relevant mechanisms of action may start to look relevant if mutations are picked up during a cancer’s later development and spread. This strengthens the argument for having access to a broad range of

potential drugs with a wide range of mechanisms of action to be used in combination, as described below.

As we begin to understand the complexities of cancer in more detail and bring further personalised treatments into the clinic for patients, we will likely move beyond stratified medicines towards an era of truly personalised medicine, where decisions are made on the basis of an individual's genome and other characteristics. This will bring challenges in itself, particularly when looking at rare mutations.

For childhood cancers, which are already rare diseases, we will end up with some mutations that seen very rarely in patients, making the clinical study of drugs against these targets incredibly difficult. For the very rarest mutations, the classical approach of trialling targeted agents may not be applicable.

We need to be thinking of mechanisms to allow children to access drugs where there has not been a large enough patient population for full clinical studies of drugs - this may need more flexible forms of licensing. One potential approach would be to form a global registry to bring together world-wide expertise from both academia and industry to collect and share all relevant data.

### *Combination therapies*

Combination treatments use several drugs at the same time or in close sequence, using rational combinations of drugs to hit different cancer pathways at once, for example knocking out all the tumour sub-populations. With this approach, tumours are less likely to be able to escape the effects of the drugs. It will be vital to use rational combinations of drugs against several pathways at once in order to address tumour heterogeneity and evolution, just as we seen in combination treatment for HIV.

### *Pharmacodynamic biomarkers*

The use of pharmacodynamic biomarkers to measure a drug action in tumour and surrogate tissues has allowed investigators to more accurately discern the impact of drug treatments. By monitoring biomarkers of drug response we can make informed decisions about drug development without having to wait years to see the final results of large clinical trials.

### *Immunotherapies*

Immunotherapies are transforming adult cancer drug development and have the potential to be effective in treating children too. As they are particularly effective in specific subsets of patients it will be particularly important to have biomarkers to help predict those who will benefit. Immunotherapies may take longer to show a clinical impact, and then go on to have a longer, more sustained impact and so we need to ensure that there are appropriate immune response assessment criteria.

### **Consultation item No 17: Other**

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?

