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The Paediatric Regulation: Are Children Still Missing Out On Potentially Life-Saving Treatments?

Study for the ENVI Committee

The Paediatric Regulation: Are Children Still Missing Out on Potentially Life-Saving Treatments?

DIRECTORATE GENERAL FOR INTERNAL POLICIES
POLICY DEPARTMENT A: ECONOMIC AND SCIENTIFIC POLICY

WORKSHOP

The Paediatric Regulation: Are Children Still Missing Out on Potentially Life-Saving Treatments?

Brussels, 16 June 2015

PROCEEDINGS

Abstract

This report summarises the presentations and discussions of the Workshop on "The Paediatric Regulation: Are children still missing out on potentially life-saving treatments?" held at the European Parliament in Brussels, on Tuesday 16 June 2015. The aim of the workshop was to discuss the main challenges and future perspectives related to the treatment of children in Europe in view of a potential future revision of the Paediatric Regulation.

The first part of the workshop discussed the state of play of the implementation of the Paediatric Regulation. The European Commission presented an overview of the findings of the 2013 Commission progress report on the Paediatric Regulation highlighting the remaining challenges. Some key problems, such as the difficulty to recruit quickly and to find a sufficient number of children patients to conduct clinical trials, were also presented from the industry perspective. The second part of the workshop focused on practical experiences and policy options for improved medicines for children. Still too often, children die from diseases which could be cured with the right treatments. All participants agreed that the Regulation provides a good basis, but that it needs further improvements and fine-tuning to ensure that children are not missing out on life-saving treatments.

This workshop and the respective document were prepared by the Policy Department A at the request of the Committee on Environment, Public Health and Food Safety.

This document was requested by the European Parliament's Committee on Environment, Public Health and Food Safety.

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LIST OF ABBREVIATIONS

DG SANTE	Directorate General for Health and Food Safety
DG RESEARCH	Directorate General for Research and Innovation
EC	European Commission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
ENVI	Committee on the Environment, Public Health and Food and Safety of the European Parliament
EP	European Parliament
EU	European Union
MEP	Member of the European Parliament
PDCO	Paediatric Committee
PIP	Paediatric Investigation Plan
PUMA	Paediatric-use marketing authorisation
Regulation	Paediatric Regulation
SIOPE	European Society of Paediatric Oncology
US	United States

EXECUTIVE SUMMARY

On 16 June 2015, the Committee on the Environment, Public Health and Food Safety (ENVI) of the European Parliament held a workshop on "The Paediatric Regulation: Are children still missing out on potentially life-saving treatments?". The workshop was hosted by Ms Glenis WILLMOT (MEP) and Mr Alojz PETERLE (MEP), co-chairs of the Health Working Group within the ENVI Committee.

In her introduction to the first part of the workshop, Ms WILLMOT briefly presented the Paediatric Regulation and expressed her concern over the fact that children are still too often provided with medicines that have not been properly tested; many of them receive experimental treatments instead, with few safeguards. She stated that the workshop was a great occasion to discuss what needs to be done to change this situation. Mr PETERLE continued the introduction by pointing out that there are still challenging issues surrounding the Paediatric Regulation and we need to make sure that good quality medicines are available for children.

Ms Olga SOLOMON (DG SANTE, EC) provided an overview of the findings of the 2013 Commission progress report on the Paediatric Regulation and presented the roadmap towards the 2017 report. She emphasised that we cannot treat children like adults and that we need medicines that are specifically aimed at them. She then explained that the implementation of the Regulation has been quite successful by listing some major achievements up to 2014, namely: the existence of more data from neglected age-groups, an increase in the number of completed Paediatric Investigation Plans, and a rise in the participation rate of children in clinical trials. On the other hand, she also acknowledged that there is a need for more authorised products, an equal cover of all therapeutic areas, and more research capacities in Europe. In addition, waivers, issued to protect children from irrelevant studies, are often criticized as they may prevent research in certain fields. Finally, the Commission identified some important issues that will be considered for the report of 2017, such as an in depth economic analysis on the rewards and incentives, an assessment of the estimated public health impacts attributable to the implementation of the Regulation, as well as practical experiences from all stakeholders.

Ms Magda CHLEBUS, who represented the European Federation of Pharmaceutical Industries and Associations (EFPIA), outlined the industry's perspective on paediatric drug development. She started by highlighting the main challenges for the industry, for example, the ability to recruit quickly and the difficulty in finding a sufficient number of child patients to conduct clinical trials as well as the lack of prioritisation in the regulatory framework. Nevertheless, Ms CHLEBUS was optimistic about the future of the Regulation given the greater awareness on the topic and the stronger interest from the industry to collaborate with different stakeholders for the development of a robust regulatory and research framework, building on the positive examples of the Innovative Medicines Initiatives.

The second part of the workshop focused on practical experiences and policy options for improved medicines for children. A parents' view on paediatric drug development was given by Ms Karen and Mr Kevin CAPEL from the Christopher's Smile Organisation, a charity that strives to make a difference for children with cancer. Ms CAPEL talked about their personal experience with their son Christopher who passed away at the age of five from medulloblastoma due to the lack of specific and effective treatments. She explained that current treatments for children are outdated and have unacceptable side effects, with the survival rates remaining stable over the last 10 years. Mr CAPEL took over the presentation and highlighted the urgent need for safe and effective treatments in

children. He argued, in particular, that the practice of issuing waivers for oncology drugs in paediatric use, as established by the Regulation, should be changed to enable faster exploration of new and effective paediatric medicines. Ms and Mr CAPEL concluded their presentation with some concrete action points for the improvement of the Regulation, including a full review of the clause of waivers list.

The last speaker, Professor Andrea BIONDI (Department of Health Sciences, the University of Milano Bicocca), presented the lessons learnt and future options for paediatric clinical trials. He started by stating that cancer is still the leading cause of death by disease in children. Scientific investigations demonstrated that children and adolescents treated outside paediatric trials often do not survive and it is therefore essential to have children enrolled in clinical studies. Without underestimating the great impact the Paediatric Regulation has had in Europe since 2007, Prof BIONDI, recognised that the level of implementation is still far from addressing the needs: children and adolescents are still denied treatments and only 1 in 10 children in the EU will be cured from cancer. To tackle this challenge, he encouraged the pharmaceutical industry to work together with paediatric clinicians, academic experts and regulatory authorities. Moreover, he proposed to strengthen the focus of the Horizon 2020 work programme by also including specific objectives on paediatric oncology in the future, e.g. develop innovative treatments and precision medicine and increase biological knowledge and equal access across Europe to standard care.

During the general discussion, the topic was heavily debated by the public and the panel; Mr PETERLE called it “one of the most engaged workshops of the Working Group he had ever attended”. Participants agreed that the Regulation provides a good basis, but that it needs further improvements and fine-tuning to ensure that children are not missing out on life-saving treatments, which is currently still the case. Both co-chairs committed to take some immediate actions before the preparation of the 2017 Commission progress report, in particular with regard to the current practice of granting waivers. More specifically, the concrete action points brought forward by Mr and Ms CAPEL will be presented to other members of the ENVI Committee. Additionally, Ms WILLMOT promised to contact the Commissioner for Health & Food Safety, Mr Vytenis ANDRIUKAITIS, to highlight this matter of urgency.

In her closing remarks, Ms WILLMOT emphasised that the development of paediatric medicines should be a priority for EU action. Issuing incentives and waivers are important aspects of the Regulation, but specific measures need to be taken to modify the current implementation practices. Finally, Mr PETERLE concluded that this workshop provided information on the most important questions and challenges that should be addressed in a potential revision of the Paediatric Regulation.

1. LEGAL AND POLICY BACKGROUND

Prior to the introduction of European legislation on paediatrics, more than half of the medicines used in Europe to treat diseases in children had never actually been tested and studied on this population but only on adults¹. Wrong prescriptions of medicines, lack of paediatric formulations and unclear labels on medicines resulted in unnecessary injuries and even deaths in children. Since 1997, the EU has therefore stimulated research and policy development concerning medicines for children, leading to an increased use of authorised medicines for all ages².

In January 2007 the Paediatric Regulation^{3,4} (the Regulation) entered into force, which has been a large step forward in the improvement of paediatric medicines. Its objective is to improve the health of children aged 0-17 years by facilitating the development and availability of high quality medicines that have been ethically researched and authorised appropriately, and to ensure the availability of information on the use of medicines for children. It aims to achieve this without subjecting children to any unnecessary trials or delaying the authorisation of medicines for use in adults.

The Regulation also established the Paediatric Committee⁵ (PDCO) at the European Medicines Agency (EMA), which is responsible for assessing and providing opinions on the development of medicines for use on children. As part of this process, the PDCO reviews paediatric investigation plans (PIP) submitted by pharmaceutical companies at an early stage of product development. These plans describe how a medicine should be studied and adapted to children, covering the needs of all age groups and defining the timing of studies in children compared to adults. In September 2014, the Commission published a new guideline⁶ on the application of PIPs under the Paediatric Regulation. Moreover, the EMA has put together a paediatric research network: Enpr-EMA⁷, bringing together patients' associations, academia and the pharmaceutical industry from within and outside the EU.

Five years after the Regulation entered into force, the European Commission (EC) published a progress report on the experience acquired⁸ as a result of its application. The

¹ Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane AR, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ*. 2000;320:79–82, available at: <http://www.bmj.com/content/bmj/320/7227/79.full.pdf>.

² European Medicines Agency, The European paediatric initiative: History of the Paediatric Regulation, EMEA/17967/04 Rev 1, London, 11 July 2007, available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2009/09/WC500003693.pdf.

³ Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, Official Journal of the European Union, L378/1, 27.12.2006, available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf.

⁴ Regulation (EC) No 1902/2006 amending Regulation 1901/2006 on medicinal products for paediatric use, Official Journal of the European Union, L378/20, 27.12.2006, available at: http://ec.europa.eu/health/files/eudralex/vol-1/reg_2006_1902/reg_2006_1902_en.pdf.

⁵ European Medicines Agency, Paediatric Committee (PDCO), webpage, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000265.jsp.

⁶ Guideline on the format and content of applications for agreement or modification of a paediatric investigation plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies (2014/C 338/01), Official Journal of the European Union, C338/1, 27.9.2014, available at: http://ec.europa.eu/health/files/eudralex/vol-1/2014_c338_01/2014_c338_01_en.pdf.

⁷ European Medicines Agency, European Network of Paediatric Research at the European Medicines Agency (Enpr-EMA), webpage, available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp.

⁸ European Commission, Better Medicines for Children From Concept to Reality, Progress report on the Paediatric Regulation (EC) No 1901/2006, COM (2013) 443 final, 2013, available at: [http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com\(2013\)443_en.pdf](http://ec.europa.eu/health/files/paediatrics/2013_com443/paediatric_report-com(2013)443_en.pdf).

report concluded that paediatric development has become a more integral part of the development of medicinal products in the EU, with the Regulation working as a major catalyst to improve the situation for young patients. A number of new products with paediatric indications and age-appropriate pharmaceutical forms have been authorised and made available to patients.

Nevertheless, some challenges regarding the implementation of the Paediatric Regulation still exist, as also highlighted by the EMA. These include a lack of available paediatric medicines and relevant information for children, as well as an administrative burden for pharmaceutical companies in the application of PIPs and difficulties regarding monitoring and reporting data. Furthermore, the uptake by industry and academic networks of paediatric-use marketing authorisation (PUMA) - which was introduced as a new part of marketing authorisation by the Paediatric Regulation - is still low and needs to be improved. In 2017, the implementation of the Regulation and its impact on the health of children will be evaluated again by the European Commission.

2. PROCEEDINGS OF THE WORKSHOP

2.1. Introduction

Ms Glenis WILLMOTT (MEP) welcomed all the participants. She briefly introduced the Paediatric Regulation and the reasons why it had been adopted. She then acknowledged that there is still a lack of safe and effective paediatric medicines and that clinical trials in children are often expensive. However, there is still a strong need for more clinical trials involving children in order to increase the number of medicines specifically authorized for children. She mentioned that the Regulation will be reviewed before 2017 but there is no time to lose and children need treatments now. She highlighted that the aim of the workshop was to discover the successes of the Regulation and, most importantly, to find out where changes need to be made.

Mr Alojz PETERLE (MEP) continued by recognising that the availability of paediatric medicines for children is a very challenging issue that should be high on the political agenda. He was happy that the topic was debated at a conference on cancer organised in Slovenia a week before this workshop, to which he participated, where researchers presented their results on best possible treatments for children with cancer. He then gave the floor to the European Commission representative for the first presentation.

2.2. Part I: State Of Play of the Implementation of The Paediatrics Regulation

2.2.1. Better Medicines for Children from Concept to Reality: follow up to the General Report on experience acquired as a result of the application of Regulation (EC) n° 1901/2006 on medicinal products for paediatric use

Ms Olga SOLOMON, Deputy Head of Medicinal products – authorisations and relations with EMA Unit, European Commission

In her presentation, Ms SOLOMON started by saying that children are an important part of the European population (21% of the population are children) and should not be treated like adults. Before the introduction of the Regulation, due to economical and ethical factors, children were treated with medicines not specifically authorised for them. The situation has changed thanks to the Regulation and children are now more and more involved in clinical trials.

Ms Solomon then presented the milestones for the adoption of the Regulation and emphasised that the process from the proposal stage in 2005 to its adoption in 2007 took quite some time. Since 2007, some achievements have been observed ascribed to the implementation of the Regulation and in 2009 the first authorised medicine based on a completed PIP was developed. On the other hand, PUMAs have not been very successful as, until today, only two new authorised medicines have been developed.

Ms Solomon then described the key features of the Regulation. She listed the main obligations for the industry, such as the development of a PIP for every new medicine that is applying for a line-extension of their own patented medicines; and the types of incentives which are given in order to support research and develop indications for children. The different benefits granted to companies after the completion of a PIP were also mentioned, for example a six month extension of the supplementary protection certificate, a market exclusivity extension for two more years after the original ten years, and eight years of data protection and market protection.

Waivers are also a key feature of the Regulation. They are issued to protect children from unnecessary research, i.e. on medicines that will not give any benefit to them. However, they are also critically reviewed because they may prevent research in specific areas.

After talking about the supporting elements such as EU funding for scientific advice, operational costs and research, Ms Solomon presented the findings from the 2013 report. Overall it showed that the Regulation has been quite successful as it has put in place the system and structure needed for the development of authorised paediatric medicines, making paediatric development an integral part of product development for industries. To demonstrate this success, she mentioned some figures, for example 30% of PIPs have been studied with neonates and children, and 30% of new authorised medicines now have a paediatric indication, 72 medicines have an indication for children and 26 formulations specifically for children exist.

Furthermore, the report states that articles 45 and 46 of the Regulation, on the obligation for the industry to provide data on old medicines and on all information gathered from studies on children, resulted in 18,000 study reports about children which led to changes in product information for 12 medicines, and the availability of more data of neonates.

Since 2013, other promising developments have been observed such as the increase in PIPs from 600 in 2013 to more than 800 today; the increasing number of trials that include children; and the creation of 18 paediatric research networks. Nevertheless, Ms Solomon also admitted that the completion of PIPs remains difficult due to problems with the recruitment of children, and the small number of clinical trials including children. Ms Solomon also underlined that the fact that not all paediatric diseases are equally covered in product development by the industry is an issue.

Ms Solomon ended her presentation by setting out those elements that will feed into the review report of 2017, namely an economic analysis on rewards and incentives stated in the Regulation, an analysis of the estimated consequences for public health as a result of the implementation of the Regulation, a stakeholder consultation to learn about their experiences, and a comparison of the EU and United States' paediatric medicine development systems.

2.2.2. Strategies for paediatric drug development from an industry perspective

Ms Magda CHLEBUS, Director Science Policy, European Federation of Pharmaceutical Industries and Associations Director (EFPIA)

Ms CHLEBUS started her presentation by identifying some challenges the industry has to face in paediatric drug development. Since the paediatric population group is very diverse in age and development patterns, the research needs for paediatric treatments are more complex than those for adult treatments. For instance, it is estimated that it takes 7 to 8 paediatric studies to see whether an adult medicine is also effective for children. This proves to be more time consuming and very costly for the industry. Another problem is the difficulty to recruit a sufficient number of children to start and finish a clinical trial. This is difficult to attain due to a variety of reasons, such as: the fragmented population (i.e. infants and children's needs are different from adolescents' needs), the lack of a decent infrastructure and capability (i.e. there are not enough research centres and networks), as well as a lack of awareness among parents and those who subscribe to trials.

Ms Chlebus then moved to describing the opportunities that can reverse the current situation. She noticed that many stakeholders are willing to work together to achieve

common solutions and that many collaborative initiatives already exist. Furthermore, she highlighted the improvements in scientific knowledge observed in the past few years that could further facilitate the development of paediatric medicines.

She then offered some recommendations to tackle these challenges and seize opportunities for the upgrading of the regulatory framework and more effective implementation. First, she argued that a change has to be made from the focus on products, regulations, and adults to a real focus on paediatric medicines that address children's needs. More concretely, she suggested that the PIPs should be modified in order to speed up the development of medicines and more harmonised requirements should be promoted to help faster development of products for the industry operating in a global environment. Finally, enhanced education and information is needed for parents and patients in order to understand what clinical trials are and new models of collaborations and better coordination among all stakeholders should be ensured.

To conclude her presentation, Ms Chlebus mentioned the positive examples of the orphan medicines⁹ and the Innovative Medicine Initiative¹⁰. Under these two initiatives, cooperation between industry and other stakeholders has brought positive results for the development of better and safer medicines for patients. She therefore suggested that a similar approach should be followed for the development of paediatric medicines.

2.2.3. Questions and Answers

Mr PETERLE welcomed Mr Peter LIESE (MEP), coordinator for health within the ENVI Committee, and Mr Matthias GROOTE (MEP), former chair of the ENVI Committee. He then gave the floor to the audience.

Prof Gilles VASSAL, president of the European Society of Paediatric Oncology (SIOPE), expressed his gratitude to the European Parliament and the European Commission for the adoption of the Paediatric Regulation in 2007. He recognised that it clearly changed the landscape for developing new medicines for children and adolescents with cancer. Today in Europe, 15 new drugs are under development for children, however, currently only fewer than 10% of children and adolescents with cancer have access to innovative compounds. He therefore advocated for a revision of the Regulation.

SIOPE is a multi-stakeholder paediatric oncology platform¹¹ founded two years ago that has brought together a wide range of stakeholders in fighting cancer in children: academia, clinicians and researchers, parents, patients and survivors, industry, regulatory authorities and policy makers. Cooperation among all stakeholders is absolutely key and SIOPE is ready to work with the European institutions to make the Regulation better and ultimately speed up the development of new innovative compounds for children and adolescents with cancer.

Mr Liese said that while the adoption of the Regulation was a great step forward in the field of paediatric medicines, there is still a lot to be improved. He argued that market exclusivity is a stimulation for the industry, however, since the market for children is not large, the timeframes for this exclusivity should be prolonged. Further, more public support for research in paediatric medicines should be subsidised through Horizon 2020

⁹ EMA orphan medicines webpage, available at:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000029.jsp.

¹⁰ IMI website, available at: <http://www.imi.europa.eu/>.

¹¹ Vassal G, Rousseau R, Blanc P, Moreno L, Bode G, Schwoch S, Schrappe M, Skolnik J, Bergman L, Bradley-Garelik MB, Saha V, Pearson A, Zwierzina H, Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer, *Eur J Cancer*, 2015 Jan;51(2):218-24. doi: 10.1016/j.ejca.2014.10.029. Epub 2014 Nov 27.

research programme¹². For example, more emphasis could be given to clinical trials that result in a disapproval of a drug, and on research on limited use of medicines for children with cancer. Mr Liese therefore asked if and how the Commission is planning to prioritise these research needs.

In her reply to Mr Liese's first remark on market exclusivity Ms Solomon welcomed positively the idea that incentives and market exclusivity could stimulate the development of medicines, as it did for orphan medicines. However, further reflections should take place on whether incentives in the case of paediatric medicines really improve results and increase development. With regard to Horizon 2020, she agreed with Mr Liese on the fact that more attention could be given to paediatric medicine research and she promised to take the point of prioritisation within Horizon 2020 to her colleagues at DG RESEARCH.

Ms Patricia BLANC, from 'Imagine for Margo-children without cancer'¹³, a member organisation of the SIOPE platform, intervened in the discussion. She explained that the working group on incentives she chairs has investigated on different types of incentives that could be put in place to develop some specific drugs for children and adolescents with cancer. She also mentioned the 'Creating Hope Act' in the US, which introduced a specific incentive for the industry to develop new drugs, as an example that could be adopted in the EU.

2.3. Part II: Improved Medicines for Children: Practical Experience and Policy Options

2.3.1. Introduction by MEP Ms Glenis WILLMOTT

Ms WILLMOTT opened the second part of the workshop. Before giving the floor to Karen and Kevin CAPEL, she expressed the importance of involving patients or patients' parents in the discussion because it is much more effective to listen to personal experiences, draw conclusions and propose policy action from them.

2.3.2. Improving early access to new, potentially life-saving treatments: paediatric regulatory issues from a patient's perspective

Karen and Kevin CAPEL, Christopher's Smile Organisation, UK

Ms Karen CAPEL opened her presentation by telling the very personal story of their son Christopher who was diagnosed with cancer at the age of four. Due to the use of very aggressive drugs, and limited availability of more appropriate drugs, he died few months after the diagnosis. Their and many other parents' experiences show that it is difficult for parents to make firm decisions due to the heavy side-effects of the available drugs and treatments in paediatric oncology, e.g. weakened immune system, hearing loss, brain damage, heart and kidney problems.

Ms Capel then continued by explaining what has changed after the adoption of the Regulation. Science and technology have progressed at a fast rate and adult drugs come from the pipeline to the fore for use. However this is still not the case for paediatric medicines. Headlines in the news show an increase in adult cancer survival rates, whereas the rates for children have been stable for more than ten years now. Although progress has been seen in the most common children cancers such as leukaemia, in

¹² Information on Horizon 2020 work programme is available at the following website: <http://ec.europa.eu/programmes/horizon2020/en/what-work-programme>.

¹³ Association website: <http://imagineformargo.org/origine/>.

many cancers no progress has been made. The main problem is that children do not only die from the disease, they die from the treatments too.

The parent community is extremely disappointed for the slow rate in the introduction of new drugs and the Regulation has shown very little progress in that sense. The scientific community is in the position to change the situation thanks to more knowledge and drugs available; however, policy makers and industry must be willing to act as quickly as possible to provide new, safe and effective treatments for children.

Mr Kevin Capel continued and expressed his worries regarding the granting of waivers which are not complementary to the objectives of the Regulation. Once a waiver for a drug in the paediatric population is granted, there is no obligation for the drug manufacturer to further research the drug for paediatric care, so the full potential use in children is not explored.

He also presented and commented on the EMA document "Policy on the determination of the condition(s) for a PIP/waiver"¹⁴ from 2012. The document shows that the scope of the evaluation of the potential paediatric use does not go beyond the initial condition for which it is tested for. This condition, i.e. the potential adverse reaction to the drug that will be tested, is determined before the start of the research and is based on an international hierarchical classification system from the Medical Dictionary for Regulatory Activities (MedDRA¹⁵). Within this system, broad terms for diseases are listed at the top of the hierarchy, while more specific terms for diseases or health conditions related to the more general terms follow along the hierarchy. This rule is problematic as it limits the scope of the evaluation of the potential of the use of a paediatric drug¹⁶. Moreover, the use of such a hierarchy has also implications for the granting of waivers. For example, when a waiver is granted for a condition that is high in the hierarchy, this waiver automatically will cover all conditions falling under it. As a result, specific health conditions (low in the hierarchy) that potentially could be treated with the drug, are not being explored.

Mr Capel also highlighted his concerns about contradictions in the existing inventories of therapeutic drugs for children. Article 43 of the Regulation states that an inventory of therapeutic needs for children needs to be established. The EMA has created an inventory of drugs, mainly old ones and highly cytotoxic drugs, for which waivers are granted¹⁷. However, six drugs included in this inventory of waivers are also listed in another inventory of drugs that can be used in everyday paediatric use¹⁸. Mr Capel therefore argued that the current inventory list is outdated and needs to be changed to reflect current scientific advances and avoid contradictions.

¹⁴ EMA (2012), Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver). Available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf.

¹⁵ MedDRA data retrieval and presentation, available at:

http://www.meddra.org/sites/default/files/guidance/file/9610-1800_datretptc_r3_9_mar2015.pdf.

¹⁶ For example, a general term at the top of the hierarchy is *cardiac arrhythmias* and the more specific terms listed down in the hierarchy for this term are *cardiac conduction disorders* and *rate and rhythm disorder*. According to the EMA guidelines, when the applicant determines a condition(s) for the evaluation of a potential paediatric drug (e.g. cardiac conduction disorders and rate and rhythm disorder), it can only take into account adverse health conditions that are listed below this determined condition in the hierarchy. Whereas conditions that are listed at a higher level in the hierarchy (e.g. cardiac arrhythmias) are ignored during the evaluation, thus limiting the scope of the evaluation of the potential of the use of a paediatric drug.

¹⁷ Paediatric Committee (PDCO) Minutes of the 05-07 December 2012 meeting, available at:

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

¹⁸ Draft inventory of paediatric therapeutic needs Paediatric oncology, available at:

http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/10/WC500175064.pdf.

Mr Capel continued with a slide that showed the results of a research project funded by Christophers' Smile organisation that looked at the relation between specific genes and drug sensitivity¹⁹. The data shows that 60% of the researched children with abnormalities could have benefited from current drugs that are in current adult trials. To avoid denying children access to potentially lifesaving drugs, article 11 of the Regulation on waivers should be changed to enable subsequent data to be taken into account by the EMA.

Ms Capel concluded the presentation by proposing some action points for the future. In particular, she encouraged the EC to instruct the EMA and the Paediatric Committee to implement article 11b, and to issue waivers based on specific conditions, where conditions are defined by biological or genetic abnormality; she also recommended to conduct a full review of the clause waiver list and removal of all diseases where biologic or genetic mutation occur in the paediatric oncology population; finally she called upon all MEPs to work closely with the Commission to make sure that these necessary changes are made at the earliest opportunity.

2.3.3. Paediatric clinical trials: lessons learnt and political options based on scientific and clinical daily practice

Prof Andrea BIONDI, Department of Health Sciences, University of Milano Bicocca, IT

Prof BIONDI presented the lessons learnt and future options for paediatric clinical trials. He started by stating that cancer is still the leading cause of death by disease in children.

He strongly advocated the importance to have children with cancer to take part in clinical trials as it has been demonstrated by the success rate of treatments of paediatric cancers where children have been involved in trials. To illustrate the situation more practically, Prof Biondi presented some figures from a study on survival rates from cancer in Germany and Austria where more than 90% of paediatric cancer patients are enrolled into nationwide disease-specific first-line clinical trials²⁰. The study results show an increase of five-year overall survival rate. This has been confirmed by other studies showing increasing death rates for children and adolescents treated outside paediatric trials²¹. Despite this discovery, adolescents and young adults are however still widely underrepresented in clinical trials²².

After mentioning the key issues for clinical trials, i.e. the difficulty to recruit a sufficient number of children, the large differences of survival rates within Europe, Prof Biondi proposed three areas of action for the future. First, the new EU Regulation on Clinical Trials that will be implemented next year will enhance harmonisation of clinical trials practices and of availability of treatments across Europe, and thus facilitate the possibility to deal with clinical trials in Europe.

¹⁹ Garnett et al. (2012), Systematic identification of genomic markers of drug sensitivity in cancer cells. Available at: http://www.nature.com/nature/journal/v483/n7391/full/nature11005.html%3FWT.ec_id%3DNATURE-20120329.

²⁰ Rossig C., Juergens H., Schrappe M., Moericke A., Henze G., von Stackelberg A., Reinhardt D., Burkhardt B., Woessmann W., Zimmerman M., Gadner H., Mann G., Schellong G., Mauz-Koerholz C., Dirksen U., Bielsack S., Berthold F., Graf N., Rutkowski S., Calaminus G., Kaatsch P. & Creutzig Y. (2013). Effective Childhood Cancer Treatment: The Impact of Large Scale Clinical Trials in Germany and Austria. *Paediatr Blood Cancer* 60, pp 1574-1581. Available at: <http://onlinelibrary.wiley.com/doi/10.1002/pbc.24598/epdf>.

²¹ Bleyer A., Siegel S., Coccia P., Stock W. & Seibel N. (2012). Children, adolescents and young adults with leukemia: the empty half of the glass is growing. *Journal of Clinical Oncology* 30 (32), pp 4037-4047. Available at: <http://jco.ascopubs.org/content/30/32/4037.full.pdf>.

²² Bleyer A. (2007). Young adult oncology: the patients and their survival challenges. *Cancer J Clin* 57, pp 242-255. Available at: <http://onlinelibrary.wiley.com/doi/10.3322/canjclin.57.4.242/epdf>.

Second, the Paediatric Regulation itself needs to be changed. The majority of children still have no access to potentially lifesaving drugs in Europe and only less than 1 in 10 children will be cured. Network initiatives such as SIOPE are already in place and increase the capability to reach the sufficient number of children enrolled in trials on different types of diseases. However, the cooperation between networks and pharmaceutical companies should be improved to achieve even better results.

Finally, Prof Biondi recommended that paediatric oncology is prioritised under Horizon 2020 and mentioned possible research objectives that can be included in the next work programme, *inter alia*: introduce new innovative treatments in multidisciplinary standard care; increase the biological knowledge on paediatric tumours; address the specific needs of teenagers and young adults jointly with adult oncology; improve the quality of survivorship; and understand the causes of paediatric cancers and set up prevention where possible.

2.3.4. General Discussion

Ms WILLMOTT also recognised the advantages of the new EU Regulation on Clinical Trials that will enter into force next year and will make trials faster, cheaper and more transparent. She then gave the floor to Françoise GROSSETÊTE (MEP), rapporteur of the Paediatric Regulation, who commented in particular on the presentation of the Capel's.

Ms Grossetête expressed her thankfulness for the presentation, not only because of the personal experiences they shared, but also because it pointed out the shortcomings of the Regulation. She greatly valued parent associations and had involved them significantly when developing the Regulation. Ms Grossetête also mentioned her regular contact with paediatric hospitals who are pleased with the existence of the Regulation, but have not seen any progress. She stated that not only cosmetic changes should be made to the Regulation, but that there are some real weaknesses that must be tackled as quickly as possible.

Ms SOLOMON agreed that strong points were made with regard to the implementation of the Regulation and promised to take them into account in the 2017 report. In her reply to Ms Grossetête's remarks, she acknowledged that the Regulation did not solve all problems and that paediatric oncology is indeed a complex and challenging field. She came back to the point on waivers and said that the Paediatric Committee is already looking into the waiver clause and will review it in light of the issues raised during the workshop discussion. However, some implementation issues cannot be dealt with by the PDCO or with specific guidelines, for example, the EC cannot force companies to prepare a PIP for certain medicines.

Mr CAPEL responded to Ms Grossetête's previous comments by comparing the Regulation with the EMA document "Policy on the determination of the condition(s) for a PIP and waiver"²³. In his view, the Regulation does not need to be changed in the short-term. On the contrary, he stressed that the EMA policy document needs immediate revision to ensure that exploring the potential of drugs for specific health conditions in children is not ignored and children suffering from a very specific disease have the opportunity to use potential lifesaving drugs that might be available.

Ms Willmott proposed that she will refer this information quickly to the ENVI Committee and ask them to scrutinise what actions can be taken for improvement.

²³ EMA (2012), Policy on the determination of the condition(s) for a Paediatric Investigation Plan/Waiver (scope of the PIP/waiver). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/09/WC500133065.pdf.

Prof VASSAL asked Ms Solomon whether the modification of the EMA policy document can be done before 2017 and what changes can be done in the short term.

Ms Solomon responded that changes in the EMA policy document can be done before 2017 as long as they do not contradict the Regulation. A full revision of the Regulation will be considered depending on the results of the 2017 report.

Prof Vassal continued by showing his concern that some stakeholders might push against the revision of the Regulation in 2017 or even that the revision will result in a weakened Regulation. On the contrary, he strongly advocated for a better Regulation setting the basis for faster medicine developments and better incentives for the industry.

Ms Willmott assured that it is absolutely not in the interest of the Parliament to weaken the Regulation. In agreement, Ms Grossetête stated that the Parliament is very determined to face the pharmaceutical industry and to demand, pressurise, and oblige them to move in the right direction. A close cooperation between the Parliament and Commission will be ensured in the revision process.

On behalf of the industry, Ms CHLEBUS intervened and promised to take into account the discussion points. She also repeated that the industry is really keen to work together with the various stakeholders and to achieve progress.

2.3.5. Conclusions

In her closing remarks, Ms WILMOTT summarized the main points of discussion. She highlighted that there should be prioritisation for the development of paediatric medicines compared to adult medicines, particularly for those paediatric diseases that are either urgent or that have not received much attention until now. Furthermore, there is a need for better incentives for the industry to trigger investments in the development of specific paediatric drugs. Moreover, the issuing of waivers should be examined to avoid that certain diseases are underrepresented in trials. Ms Willmott also committed herself to take on board the action points presented by Ms and Mr Capel. Additionally, Ms Willmott promised to contact the Commissioner for Health & Food Safety, Mr Vytenis ANDRIUKAITIS, to highlight this matter of urgency.

Mr PETERLE finished by appreciating that it was a very engaged workshop with clear messages in an inclusive format. The workshop revealed new and pressing reasons to act for a change. Further, he highlighted that the number of cancers today is growing, also in children, and this is the driver to speed up and address this growing challenge for Europe with full responsibility and the best possible cooperation.

ANNEX 1: PROGRAMME

WORKSHOP

The Paediatric Regulation: Are children still missing out on potentially life-saving treatments?

16 June 2015 from 10.30 to 12.30
European Parliament, A1G-2, Brussels

**Organised by the Policy Department A-Economy & Science
for the Committee on the Environment, Public Health and Food Safety (ENVI)**

AGENDA

10.30 - 10.40

Welcome and opening by MEP Glenis WILLMOTT and MEP Alojz PETERLE, co-Chairs of the Health Working Group, ENVI Committee.

Part 1

State of play of of the implementation of the Paediatrics Regulation

Chair: Mr Alojz PETERLE

10.40-10.50

Better Medicines for Children from Concept to Reality: follow up to the General Report on experience acquired as a result of the application of Regulation (EC) n° 1901/2006 on medicinal products for paediatric use

Ms Olga SOLOMON, Deputy Head of Medicinal products – authorisations and relations with EMA Unit, European Commission

10.50 - 11.00

Strategies for paediatric drug development from an industry perspective

Ms Magda CHLEBUS, Director Science Policy, European Federation of Pharmaceutical Industries and Associations Director (EFPIA)

11.00-11.30

Q&A

Part 2

Improved medicines for children: practical experience and policy options

Chair: Ms Glenis WILLMOTT

11.30 – 11.40

Improving early access to new, potentially life-saving treatments: paediatric regulatory issues from a patient's perspective

Karen and Kevin CAPEL, Christopher's Smile Organisation, UK

11.40-11.50

Paediatric clinical trials: lessons learnt and political options based on scientific and clinical daily practice

Professor Andrea BIONDI, Department of Health Sciences, University of Milano Bicocca, IT

11.50-12.20

General Discussion

12.205 - 12.30

Conclusions by MEPs, Ms Glenis WILLMOTT and Mr Alojz PETERLE

ANNEX 2: SHORT BIOGRAPHIES OF EXPERTS

Ms Olga SOLOMON

BSc in Chemistry, MSc in Food Science

European Commission, Deputy Head of Medicinal products – authorisations and relations with EMA Unit

- Current position: Deputy Head of Unit
- Previous position/Career highlight:

Olga Solomon studied Chemistry at the Aristotle University of Thessaloniki, Greece and holds an MSc in Food Science from the Gothenburg University, Sweden. Before joining the European Commission she worked for 5 years for a beverage producing company in Greece.

She joined DG SANCO in 2000 and worked for 10 years in the field of Food Safety in particular dealing with legislation on Food Contact Materials, Food Additives and Enzymes. In 2010, she moved to the Directorate 'Health Systems and Products' where she worked in the field of human origin before taking up a post in the pharmaceutical sector in 2011. She is currently Deputy of Head of the SANCO Unit responsible for medicinal products – authorisations and relations with EMA.

Ms Magda CHLEBUS

Magda Chlebus is Director Science Policy at the European Federation of Pharmaceutical Industries and Associations (EFPIA). She is in charge of policy and legislative debates which shape research environment in Europe. This includes public private collaborations (incl. the Innovative Medicines Initiative) and enabling and sensitive technologies.

After a Master Degree in Applied Linguistics at University of Warsaw in 1992 and a career as translator and teacher, in 1995 she joined EFPIA, the representative voice of R&D-based pharmaceutical industry in Europe. Her experience covers public and government affairs with focus on Brussels Village, including designing and implementing advocacy campaigns on EU legislation as well as implementation of the pharmaceutical legislation in new Member States.

Ms Karen and Mr Kevin CAPEL

Karen and Kevin Capel are the Founders of UK based charity Christopher's Smile. The organisation was set up in October 2008 following the death of Karen and Kevin's only child Christopher, 9 days before his 6th birthday.

Karen started her career as a modern languages teacher. This was followed by a move to the airline industry to work in customer services, training, management of executive training programmes and training consultancy. Kevin's career began as an aeronautical engineer with a move to airline IT. Following Christopher's death to Medulloblastoma the Capels decided to use their diverse skills to set up a charity to fund the development of innovative treatments for childhood cancers so others need not suffer.

Four UK research projects have thus far been successfully funded with approximately 1.5 million euros raised. Achievements include enabling 11 new trials commenced in 2014; children's tumour sequencing at diagnosis which will become standard process at The

Royal Marsden specialist hospital from June 2015 with a roll out programme planned across all UK centres.

Christopher's Smile has actively participated in former BDA (now CDDF) conferences both in London and Paris, SIOPE Conference in Brussels in early 2015 and is an invited parent representative of the Biological Studies Steering Committee within the UK based CCLG. The charity is also a UK National Cancer Research Institute non-clinical partner. Karen and Kevin have met with UK parliamentarians and have appeared on UK national radio and TV. They work together with other UK and European parent led organisations with the aim of introducing safe and effective targeted treatments to save children's lives from cancer.

The learning curve in paediatric oncology research, commercial practice, processes and treatments has been both steep and enlightening with discoveries seldom positive. Christopher's Smile actively campaigns for positive change in the areas it feels it can make the biggest impact and where the needs are greatest.

Prof Andrea BIONDI

Andrea Biondi, M.D., is the Director of the Department and the School of Paediatrics, University of Milano-Bicocca, San Gerardo Hospital, Monza (MI), Italy.

He is Full Professor of Paediatrics at the Faculty of Medicine and Surgery, University of Milano-Bicocca, Italy. He is also head of the "M.Tettamanti" Research Center and "S. Verri" Cellular and Gene Therapy Laboratory, San Gerardo Hospital, Monza (MI), Italy.

Since 2006 he is Scientific Director of the Fondazione M. Tettamanti M. De Marchi Onlus, and President of the Human Molecular Genetic Consortium, Monza (MI), Italy, and since 2007 he is Coordinator of the Ph.D. Program in Translational and Molecular Medicine – University of Milano-Bicocca, Milan, Italy (www.dimet.org). Previously, from 2004-08 he has been President of SIOP Europe, European Society of Paediatric Oncology. More recently, since November 2012, he has been elected President of the Italian Society of Pediatric Hematology and Oncology (AIEOP) and, since August 2013, Pro-Rector for International Affairs of the University of Milano-Bicocca, Italy.

Moreover, Professor Biondi is member of the following Societies: the Italian Society of Experimental Hematology, the American Society of Hematology, the Italian Society of Pediatric Hematology and Oncology (AIEOP), the International Society of Pediatric Oncology (SIOP), the European Society of Hematology (EHA).

He is actively involved in the site visit and funding programmes of the following international organisations/agencies: Cancer Research,UK; Children Oncology Group, USA; Leukemia Research Fund, UK; National Cancer Institute/National Institute of Health, USA; OncoSuisse; CH; Swiss Federation Against Cancer, CH; Stichting Kindergeneeskunde Kankeronderzoek (SKK), NL; International Union Against Cancer (UICC), CH.

His scientific research activity, mainly focussed in the field of molecular genetics of childhood leukaemia and immuno and cell therapy of leukaemia, has resulted in 423 publications on international peer reviewed journals.

ANNEX 3: PRESENTATIONS

Presentation by Ms Olga Solomon





European Commission


The Paediatric Regulation

Milestones

- 1997: Discussion process started
- 2002: Consultation paper
- 2004: Commission legal proposal
- 2006: Adoption of Regulation (EC) No 1901/2006
- 2007: First meeting PDCO
- 2009: The first marketing authorisation based on a completed PIP
- 2011: The first PUMA
- 2013: The first Commission report
- 2014: Review of Commission guideline
- 2017: The 2nd Commission report









European Commission

The detailed features

Paediatrics	
Aim	<ul style="list-style-type: none"> •Ensure high-quality research into developments of medicines for children •Ensure that over time majority of medicines used for children are authorised for such use •Ensure availability of high-quality information about medicines used by children
Scope	<ul style="list-style-type: none"> •New products or •Line extension of a patent-protected product •PUMA (Paediatric Use Marketing Authorisation)
Procedure	<ul style="list-style-type: none"> •Paediatric Investigation Plan •Waiver/Deferral •Authorisation
Actors	Industry/Paediatric committee at EMA/National competent authorities
Incentives	<ul style="list-style-type: none"> •6-month SPC prolongation •Scientific advice/Protocol assistance •EU-funded research





European Commission

The supporting elements

- **No fees**
- **Scientific advice and operational costs of the Paediatric Regulation are covered by the EU budget (more than EUR 50 million since 2007)**
- **Member States' authorities contribute resources in kind for the assessment of individual PIPs**
- **EU funding of research into off-patent medicinal products (21 projects received EU funding – EUR 108 million)**


ANNEX III
List of funded projects


List of projects as off-patent medicines funded by the European Commission through the EU Framework Programme Health area 4.2 adults, off-patent medicines (calls 2, 3, 4 and 5):

- HEALTH2007-42-1 Adapting off-patent medicines to the specific needs of paediatric populations
- HEALTH2009-42-1 Adapting off-patent medicines to the specific needs of paediatric populations
- HEALTH2010-42-2 Off-patent medicines for Children FP7-HEALTH 2010 1st stage
- HEALTH2010-42-2 2 International paediatric reference medicines of Good Quality
- HEALTH2011-42-3 Investigator chosen clinical trials on off-patent medicines for children

Table 15:
Funded off-patent medicines projects (launched up to 31 January 2012) and agreed PIPs, if available

No.	Acronym	Year started	Description	Agreed PIP
1	400000	2011	To develop an innovative, age-appropriate, flexible and safe paediatric formulation of abacavir for the treatment of children with HIV infection	NA
2	MEDEC	2011	To provide safety and efficacy data for abacavir, to perform general studies, to identify the categories of children and to adjust a formulation for paediatric use	EMA-001262-PPV3-12
3	3AM	2011	To develop a novel formulation of hydrocortisone for the treatment of congenital and acquired adrenal insufficiency and to study its efficacy, safety and quality	EMA-001383-PPV3-12
4	6000	2011	To explore a new formulation route to stabilize and facilitate the development and safe use of insulin in children	NA
5	0010	2011	To evaluate Pharmacokinetics (PK) & Pharmacodynamics (PD) of abacavir in a 2- to 10-year old children to enable to produce an optimal paediatric formulation suitable for respiratory infections	EMA-001126-PPV3-10
6	7000	2011	To evaluate PK & PD of abacavir against amoxicillin in acute Otitis media	EMA-001298-PPV3-12
7	001000	2010	To evaluate the efficacy, safety, PK, PD of abacavir and dependence in the management of tropical leishmaniasis in high endemicity for children and adult & formulate a new Marketing Authorisation	NA / EMA-001100-PPV3-10

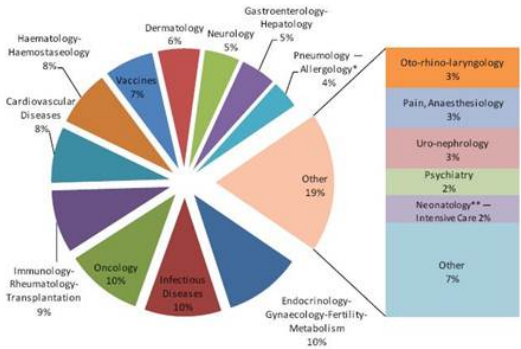





European Commission

The 2013 report

- **The implementation of the legislation**
- **Optimised framework**
- **Paediatric development integral part of product development**
- **The promising product pipeline**
- **The Article 45/46 worksharing**
- **More data in previously neglected age groups (neonates)**
- **More age-appropriate forms**







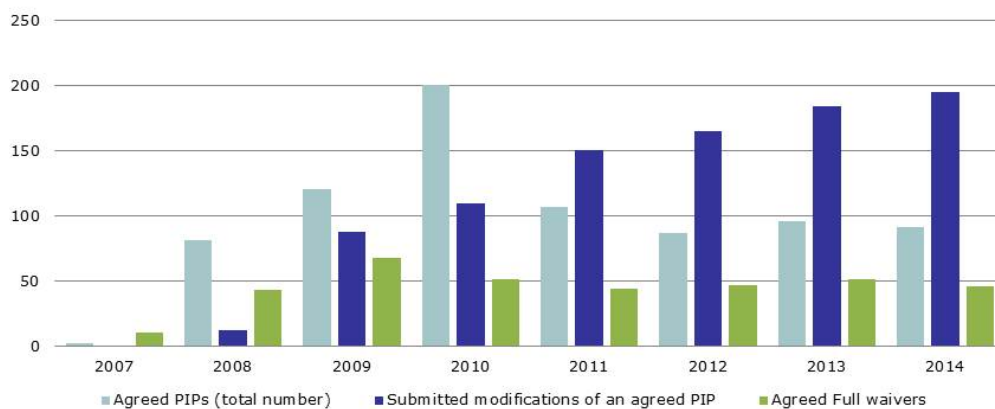
The 2013 report - conclusions

- Promising signs, but further experience needed:
 - More than **600 Paediatric Investigation Plans in 2013 (now more than 800)**
 - Around **350-400 clinical trials per year including children (0-18 years)**
 - Proportion of clinical trials including children has increased, to approximately **10%**
 - Increase in the PIP studies of neonates and infants ; currently, **30%** of the paediatric investigation plans include studies with neonates
 - Enpr-EMA - Network of paediatric research networks has been created by the EMA (**18 research networks**)
 - Mixed picture in the field of paediatric oncology

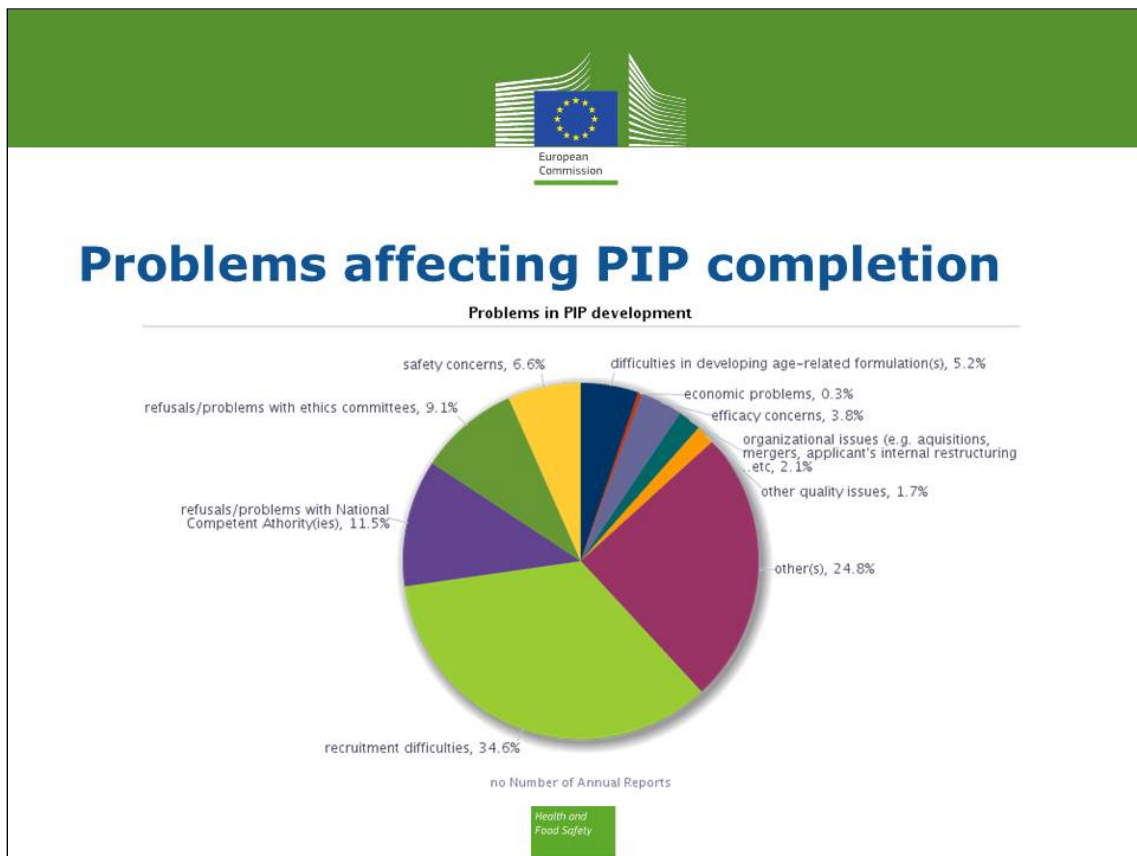
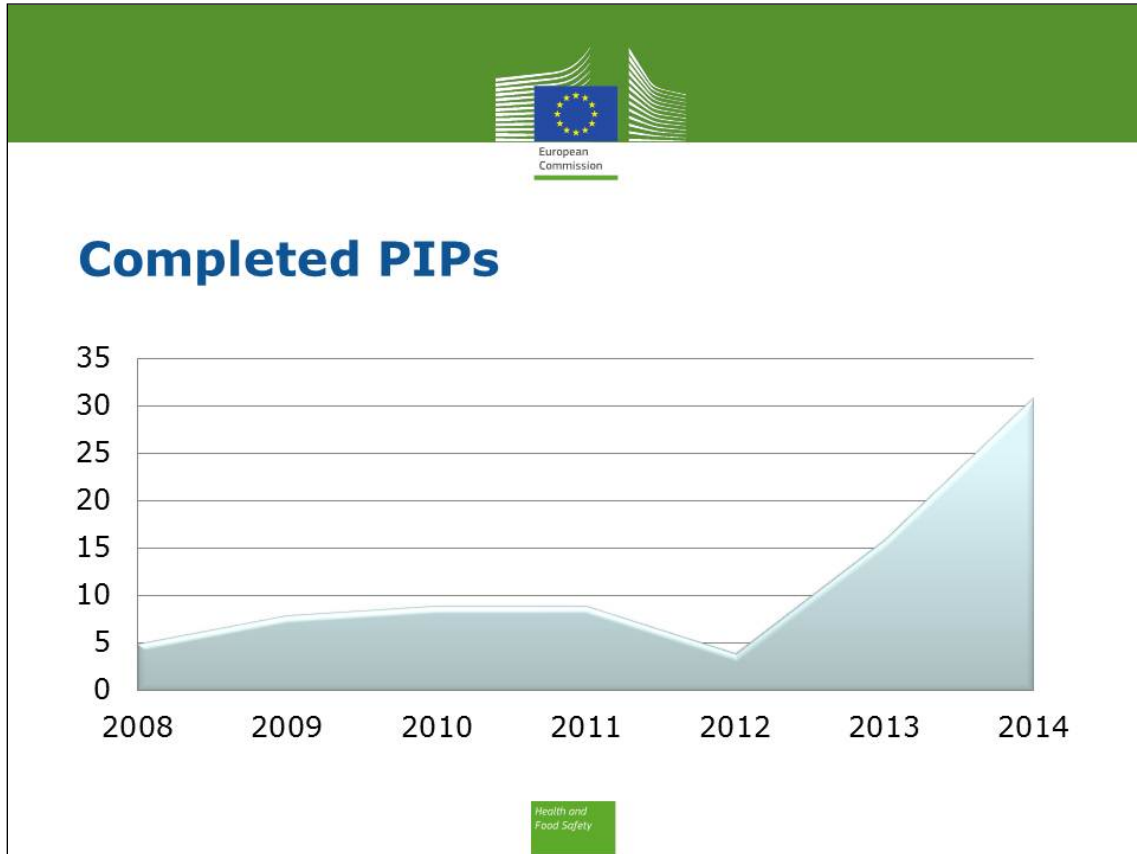
Health and Food Safety




Current experience - PIPs



Health and Food Safety





Paediatric clinical trials

Number of subjects	2006	2007	2008	2009	2010	2011	2012	2013	2014
Preterm newborns	0	0	0	327	82	2522	1552	3724	4331
Newborns	0	98	5	184	169	1348	2283	1496	1948
Infants and toddlers	530	119	20	54715	2212	13313	62224	13414	39615
Children	2683	706	270	5783	2721	21654	30826	23230	62979
Adolescents	435	36458	285	5801	4831	20206	22680	17300	42353
Sum of above	3648	37381	580	66810	10015	59043	119565	59164	151226
Reference: number of paediatric trials	340	362	342	406	392	372	401	337	432

Health and Food Safety



The things to watch

- **Number of authorised products**
- **All therapeutic areas equally covered (e.g. progress in oncology)**
- **High number of modifications**
- **The PUMA concept**
- **Research capacities in the EU**
- **Clinical trials with children**
- **Impact on adult development**
- **Cost/benefit ratio**

6. Outlook — A fairy-tale ending ahead?

Better Medicines for Children — From Concept to Reality is the title of this report. Readers may suggest that, based on the evaluation referred to above, it would be more appropriate to add a question mark. It is evident that it is too early still to make a firm statement. Despite more than five years of experience, the true impact of the Regulation on the health of children will only become apparent over time as experience is accumulated in the longer term.

There are encouraging signs though. Paediatric development has become a more integral part of the overall development of medicinal products in the EU. A number of new products with paediatric indications and age-appropriate pharmaceutical forms have been authorised and made available to patients. A high number of agreed paediatric investigation plans indicates that further products are in the pipeline.

However, it needs to be pointed out that it would be wrong to expect the Regulation to be able to solve all problems. Indeed, it is a major catalyst to improve the situation.

question mark should be added to the title of the report, but on whether it should be an exclamation mark instead



Health and Food Safety



The 2017 report

Article 50(3) of Regulation 1901/2006

"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."

Health and
Food Safety

13



The road to 2017

- Economic analysis
 - Public health impact
 - Stakeholder experience
 - Views of regulators
 - EU and US system in comparison
- => Feed into the report

Health and
Food Safety

European Commission
Public Health information:
http://ec.europa.eu/health/index_en.htm



Presentation by Ms Magda Chlebus




Strategies for paediatric drug development from an industry perspective


Magda Chlebus, Director Science Policy
European Parliament, 16 June 2015

European Federation of Pharmaceutical Industries and Associations
www.efpia.eu

The “journey”



Before 2007 Post-Paediatric Regulation Once upon a time?
How to get there?



STRATEGIES FOR PAEDIATRIC DRUG DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE * 2

Challenges

- * Diverse population: from 0 (premature babies and neonates) to 18 years
 - * 1 adult indication – 7-8 paediatric studies

- * Ability to recruit fast and sufficient numbers of patients
 - * Fragmentation – many trials, some would never end...
 - * Infrastructure and capability
 - * Awareness

- * Regulatory framework
 - * Based on adult development
 - * Focused on products/regulatory compliance
 - * No prioritisation



STRATEGIES FOR PAEDIATRIC DRUG DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE * 3

Opportunities

- * Momentum
 - * Experience with the Regulation in Europe and similar legislation elsewhere
 - * Paediatric community mobilised and willing to break the silos

- * Science and regulatory science
 - * Adaptive pathways, pragmatic trial design based on wealth of historical and real life data, modelling and simulation ...

- * Collaborative initiatives – such as the Innovative Medicines Initiative
 - * Infrastructure, Business models, Pathways



STRATEGIES FOR PAEDIATRIC DRUG DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE * 4

The vision: collective intelligence

- * Real focus on development of paediatric medicines addressing children's conditions – regulation that focuses on needs rather than on products?
- * Prioritisation and coordination: define what most urgent needs are & set clusters of excellence
- * Regulation: facilitate seamless integration into development pipelines (time of submission of PIP) and global convergence of requirements
- * Build capacity: Paediatric clinical trials infrastructure through IMI building on EnprEMA network
- * Information and education: make it easier for parents and children
- * De-silo: "safe harbour" to develop and test new operational and business models



STRATEGIES FOR PAEDIATRIC DRUG DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE 5

Learning from antimicrobial resistance and orphan medicines?



Home Find medicine Human regulatory Veterinary regulatory Committees N

Pre-authorisation
Post-opinion
Post-authorisation
Product information
Scientific advice and protocol assistance
Scientific guidelines
Innovation Task Force
SME office
Paediatric medicine
Geriatric medicine

Home > Human regulatory > Orphan designation

Orphan designation

This section provides guidance and procedural information designation for medicines for rare diseases in the European Union, including information on what happens after a designation, including the incentives available for sponsors developing

Orphan designation

To qualify for orphan designation, a medicine must meet a number of criteria:

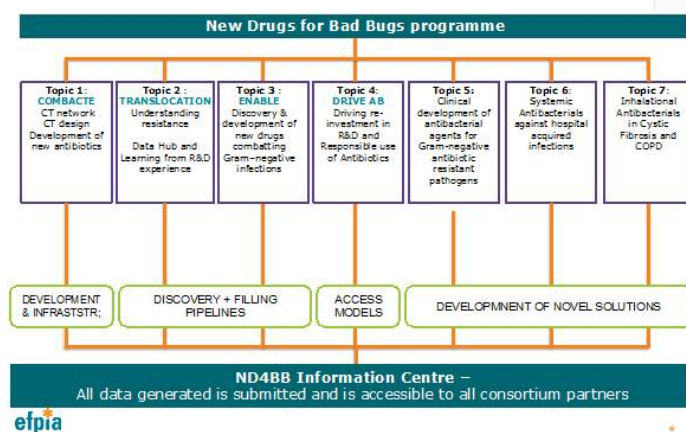
- > it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating;
- > the prevalence of the condition in the EU must not be more than one in 10,000 people;
- > no satisfactory method of diagnosis, prevention or treatment of the disease can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.



STRATEGIES FOR PAEDIATRIC DRUG DEVELOPMENT FROM AN INDUSTRY PERSPECTIVE 6

Learning from antimicrobial resistance and orphan medicines?

Joining forces in IMI



Learning from antimicrobial resistance and orphan medicines?

- * Difficult science
 - * Inadequate regulation
 - * Fragmentation
 - * Lack of infrastructure
 - * Silo thinking
- = Empty pipelines + Disinvestment



Presentation by Ms Karen and Mr Kevin Capel

Karen and Kevin Capel (Parents and Research Funders) Christopher's Smile

European Parliament Workshop

"Paediatric Regulation: are children still missing out on potentially life-saving treatments?"

16th June 2015



Christopher

- Diagnosed with medulloblastoma at 4^{1/4}
- Treated with chemotherapy/high dose chemotherapy with stem cell rescue
- Immediate post therapy prognosis good
- Relapse 4 months post therapy
- Died 21 months after diagnosis



Paediatric Oncology Current Treatments

First line treatment options: surgery, and/or cytotoxic chemotherapy and/or radiotherapy

- Surgery: Neurosurgery – high risk, amputated limbs do not grow back
- Chemotherapy: vast majority is used ‘off label’ and often leaves a legacy of issues
- Radiotherapy: devastates a developing brain



Commonly used drugs to treat children with cancer:

- include known carcinogens
- are not approved for use on children and have an average age of 40-50 years



Is this the best that is available in 2015 after 8 years of the Paediatric Regulation?



Current Treatments – Legacy of Issues

- Survival plateaued in last 10 years
- Children still dying from decades old toxic treatments
- Unacceptable side effects
- Ongoing late effects
- Cost burden of survival
- 7 years since Christopher's death, 8 years of the Paediatric Regulation – **what has changed?**



What parents want

New safe and effective treatments - **NOW**



New treatments for children - Challenges

- Pharma focus their R&D on adult conditions
- Too easy for Pharma to obtain a waiver for potential new life saving treatments for children
- Years may pass between initial adult trial and agent availability for paediatric pre clinical testing



Current Implementation of the Paediatric Regulation - Oncology

- More waivers are issued for oncology drugs than any other clinical area despite cancer being the principal cause of death by disease in children in Europe
- In the implementation of Article 43 for Oncology drugs, the EMA have drawn up an inventory which includes highly cytotoxic agents decades old and drugs for which the EMA have granted waivers



Can anyone explain this?



Contains the following drugs that **ALL** have a waiver

Axitinib
Bortezomib
Cabazitaxel

Crizotinib
Ruxolinitib
Sorafenib



VI Discussion on the applicability of class waiver

Active substance	Proposed indication	Condition	Outcome	Potential paediatric interest of this medicine suggested by PDCO
¹⁷⁷ Lu-DOTA ⁰ -Tyr ³ -Octreotate	Treatment of metastatic or unresectable, well differentiated, midgut neuroendocrine tumours, which overexpress somatostatin receptors	Treatment of gastroenteropancreatic neuroendocrine tumours (excluding neuroblastoma, neuroganglioblastoma, pheochromocytoma)	Positive	Neuroblastomas, Medulloblastomas and Ewing sarcomas
Ramucirumab	<ul style="list-style-type: none"> Cyramza in combination with paclitaxel is indicated for the treatment of adult patients with advanced gastric cancer or gastro-oesophageal junction adenocarcinoma with disease progression after prior platinum and fluoropyrimidine chemotherapy; Cyramza monotherapy is indicated for the 	<ul style="list-style-type: none"> Treatment of lung carcinoma (small and non-small cell carcinoma); Treatment of liver and intrahepatic bile duct carcinoma (excluding hepatoblastoma); Treatment of gastric adenocarcinoma; Treatment of adenocarcinoma of the colon and rectum; Treatment of ureter and bladder carcinoma. 	Positive	Paediatric solid tumours



Figure 4: Ewing's sarcoma cell lines are sensitive to PARP inhibition.

From
Systematic identification of genomic markers of drug sensitivity in cancer cells
 Mathew J. Garnett, Elena J. Edelman, Sonja J. Heidorn, Chris D. Greenman, Anahita Dastur, King Wai Lau, Patricia Greninger, I. Richard Thompson, Xi Luo, Jorge Soares, Qingsong Liu, Francesco Iorio, Didier Surdez, Li Chen, Randy J. Milano, Graham R. Bignell, Ah T. Tam, Helen Davies, Jesse A. Stevenson, Syd Barhorpe, Stephen R. Lutz, Fiona Kogera, Karl Lawrence, Anne McLaren-Douglas, Xeni Mitropoulos, et al.
 Nature 483, 570–575 (29 March 2012) | doi:10.1038/nature11005

b

Relative viability

Concentration of olaparib (µM)

Ewing's
 MHH-ES-1
 ES1
 ES7
 ES8
 BRCA2
 DoTc2-4510
 CAPAN-1
 Osteosarcoma
 HuO-3N1
 HOS
 U-2-OS
 SJSA-1
 Soft tissue
 HT-1080
 SW982
 RD
 AZ04
 Epithelial
 OVCAR-4
 SW1710
 HeLaSF

0-575 (29 March 2012) | doi:

Christopher's Smile
 coz kids get cancer too

EUROPEAN MEDICINES AGENCY
 SCIENCE MEDICINES HEALTH

09 January 2012
 EMA/636304/2008
 Human Medicines Development and Evaluation

Paediatric Committee (PDCO)
 Minutes of the 05-07 December 2012 meeting

Class waiver number	Active substance	Proposed indication	Condition	Outcome (confirmed / not confirmed)
EMA-62-2012	Olaparib (AZD2281, KU-0059436)	Maintenance monotherapy for the treatment of patients with gBRCA mutation positive Platinum Sensitive Relapse (PSR) ovarian cancer who have responded (complete response or partial response) to platinum-based chemotherapy	Treatment of ovarian carcinoma	Confirmed
		Maintenance monotherapy for the treatment of patients with gBRCA mutation positive first line ovarian cancer who have responded (complete response or partial response) to first-line platinum-based chemotherapy.		

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Paediatric Regulation Chapter 2 Article 11

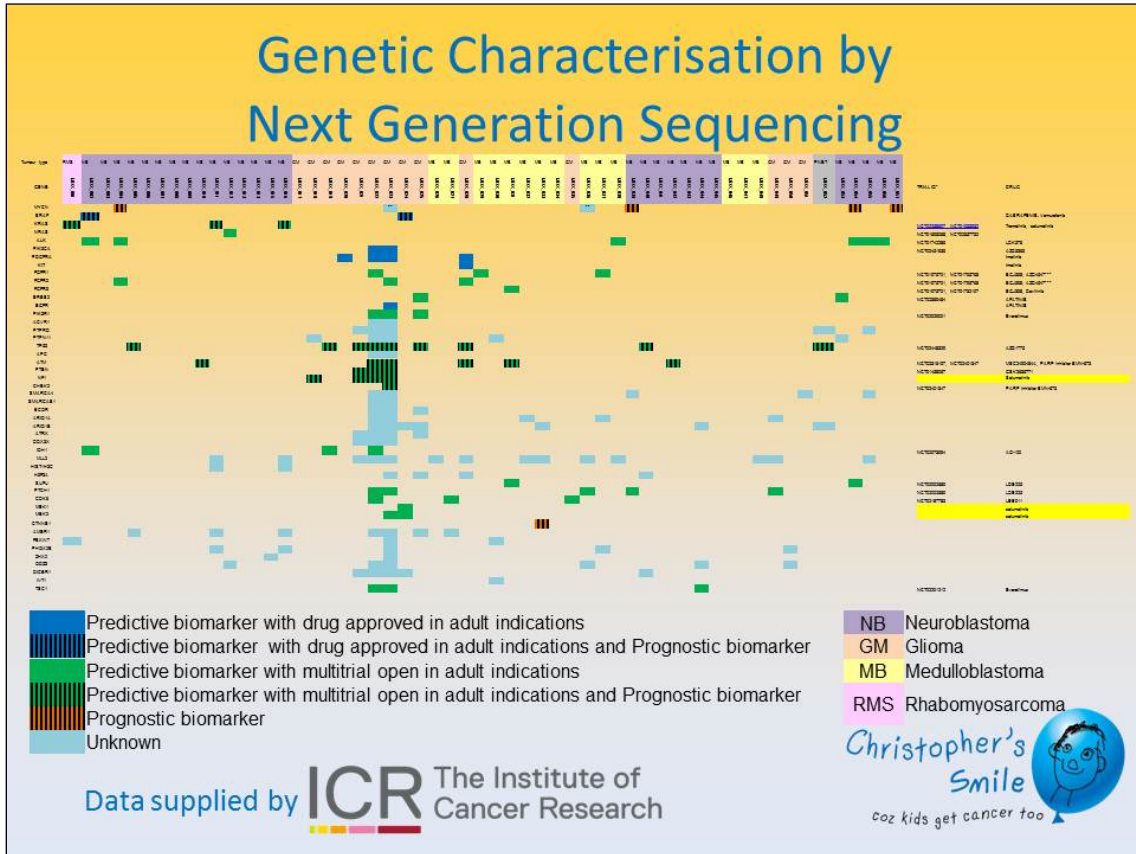
1. Production of the information referred to in point (a) of Article 7(1) shall be waived for specific medicinal products or for classes of medicinal products, if there is evidence showing any of the following:
 - (a) that the specific medicinal product or class of medicinal products is likely to be ineffective or unsafe in part or all of the paediatric population;
 - (b) that the **disease or condition** for which the specific medicinal product or class is intended occurs only in adult populations;
 - (c) that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients.



What needs to change


- The original objectives of the Paediatric Regulation need to be implemented for the area of oncology.
- The current implementation of Article 11(b) for oncology drugs is failing children with cancer (MedDRA HLT vs PT)





Genetic Characterisation by Next Generation Sequencing

From 57 patients 35 (~60%) could potentially be eligible for novel trials using target specific therapies, either as predictive biomarkers into clinical practice or prognostic biomarkers for treatment decision.


 Christopher's Smile
 coz kids get cancer too

Genetic mutations “talked about” in the media



Women like Angelina Jolie who carry the BRCA1 gene are less likely to die from breast cancer if they have their OVARIES removed

- Carriers of BRCA1 gene mutation who are diagnosed with breast cancer are less likely to die if they have their ovaries removed, study found
- But the theory does not apply for those with BRCA2 gene mutation
- Having the BRCA1 or BRCA2 genes increase risk of breast cancer by 70%



Ovarian cancer drug row: 'Breakthrough' treatment won't be available on the NHS because it's deemed too expensive

- Olaparib is designed for women who carry the BRCA gene
- HER2-positive is responsible for 13,000 new cases in the UK each year



Paediatric Regulation Recital (13)

(13) In order to ensure that research in the paediatric population is only conducted to meet their therapeutic needs, there is a need to establish procedures for the Agency to waive the requirement referred to in Recital (11) for specific products or for classes or part of classes of medicinal products, these waivers being then made public by the Agency. **As knowledge of science and medicine evolves over time, provision should be made for the lists of waivers to be amended.** However, if a waiver is revoked, that requirement should not apply for a given period in order to allow time for at least a paediatric investigation plan to be agreed and studies in the paediatric population to be initiated before an application for marketing authorisation is submitted.



Actions – not just talk



- What & Who

- EC to instruct EMA Paediatric Committee to implement Article 11(b) to issue waivers based upon 'Condition' where 'Condition' is defined by a biological or genetic abnormality (change to MedDRA PT-level)
- For oncology, EMA should review class list and remove all diseases where biological or genetic mutation occurs in the paediatric population.
- MEPs to work with the Commission to ensure necessary changes are implemented with all speed.

- When

- Agree timescales *at this meeting*

**Children with cancer do not have time
on their side**



Presentation by Prof Andrea Biondi



Paediatrics Regulations: are children still missing out on potentially Live-saving treatments?
European Parliament, 16th June, 2015

Paediatric clinical trials: lessons learnt and political options based on scientific and daily practice



Andrea Biondi

Clinica Pediatrica and Centro Tettamanti
Università Milano-Bicocca, Monza, Italy



abiondi.unimib@gmail.com

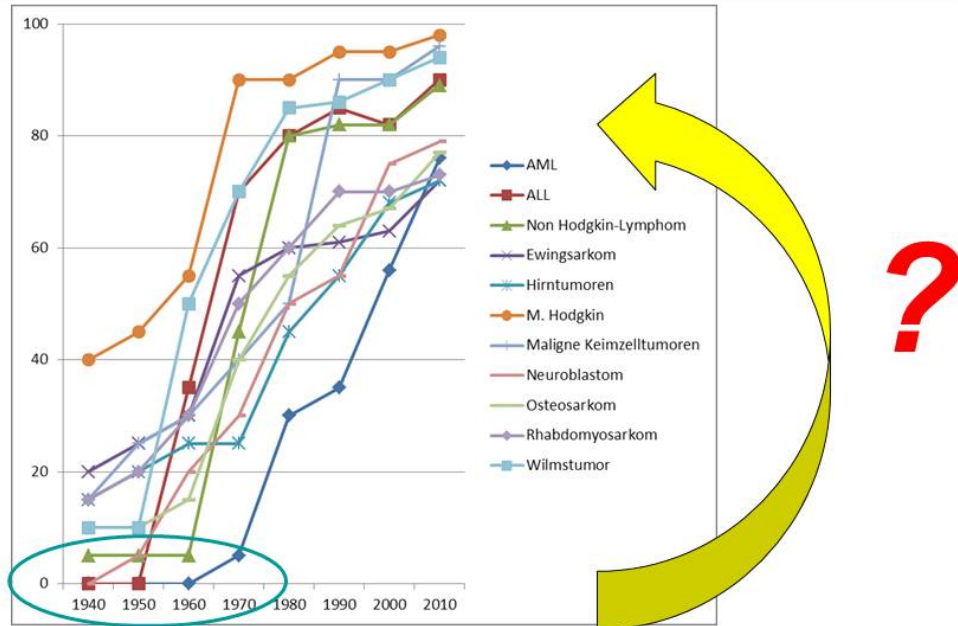
Landscape of Cancer in Children and Adolescents in Europe

- 15,000 new cases each year
- 80% can be cured with multidisciplinary treatments
- 3,000 will die
- *More than 60 different diseases from newborns to teenagers (even more when biomarkers are considered)*
- *≈ 250 EU public specialised treatment centres*
- *Networked since 1970's for clinical research*
 - *40% of patients treated within trials (phase I to III)*
 - *40% of patients treated according to standard within prospective studies*
 - *Less than 5% of pharma-sponsored trials*
- *Many high-level research teams dedicated to paediatric tumour biology*



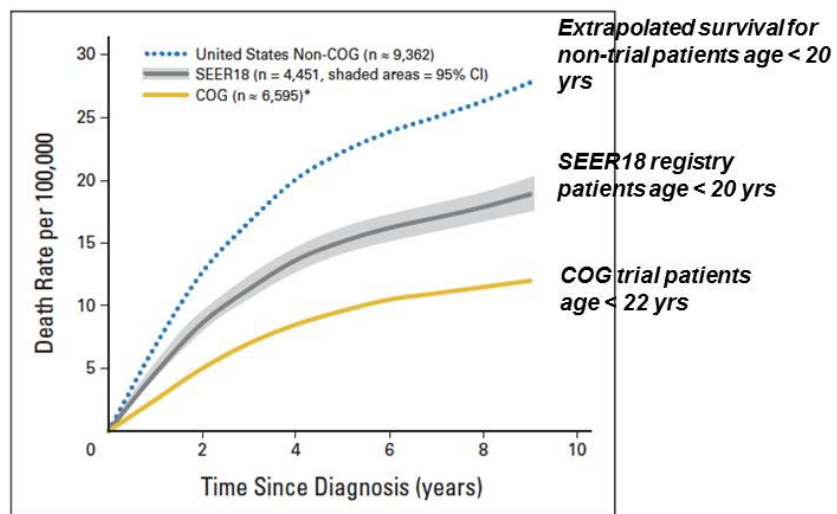
KPJ, 2013

Where are we ?



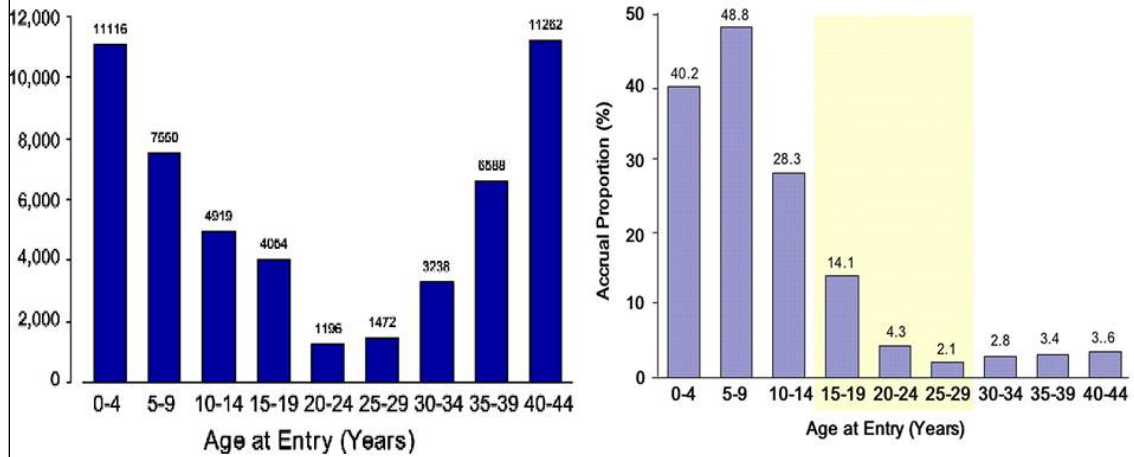
Rossig C et al. Ped Blood Cancer 2013

Outcomes for non-trial patients



Bleyer A et al, JCO (Nov 2012) 30:4037-8, letter to editor
Annual death rate in USA from ALL, 2000-2005

TYA are under-represented in clinical trials

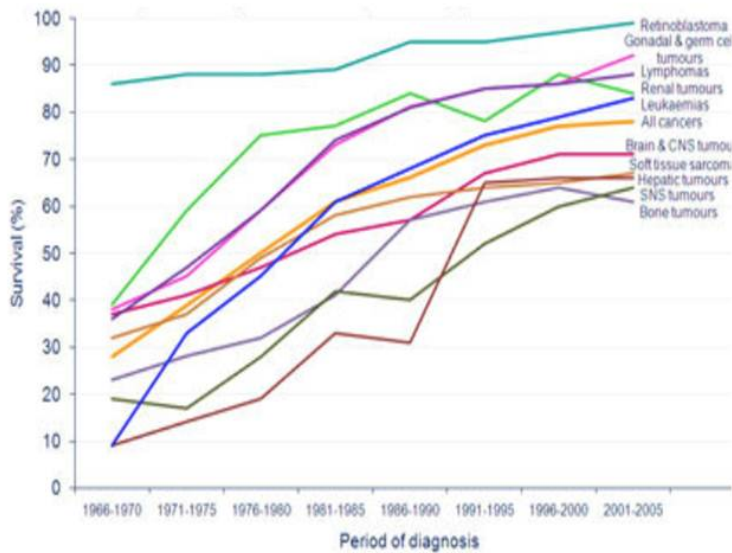


Estimated Proportion of Newly Diagnosed Cancer Patients Accrued to National Treatment Trials by Patient Age at Study Entry, 1997 to 2003. Clinical trial data courtesy of Montello M, Budd T, Cancer Treatment Evaluation Program, US National Cancer Institute. Population data from the US Bureau of Census. The yellow background zone designates the 15- to 29-year-old age range. Data from SEER



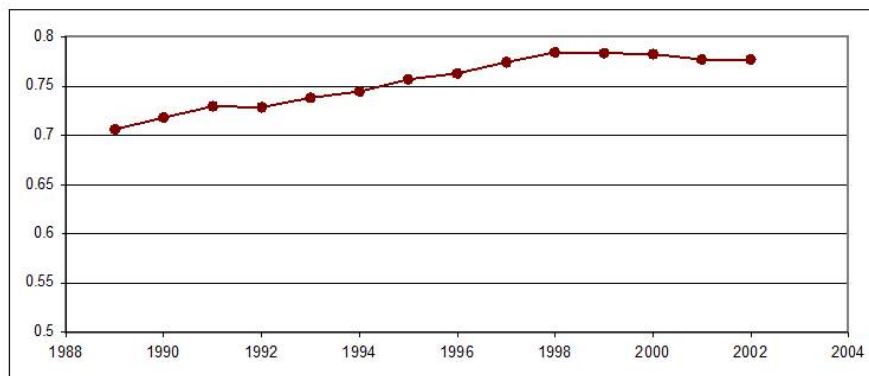
Bleyer CA Cancer J Clin 2007; 57:242-255

Improved population-based overall survival from childhood cancers in the UK has mirrored results achieved in the contemporaneous clinical trials



Charles Stiller, National Childhood Tumour Registry, Childhood Cancer Research Group, Oxford

Improvement in OS has slowed

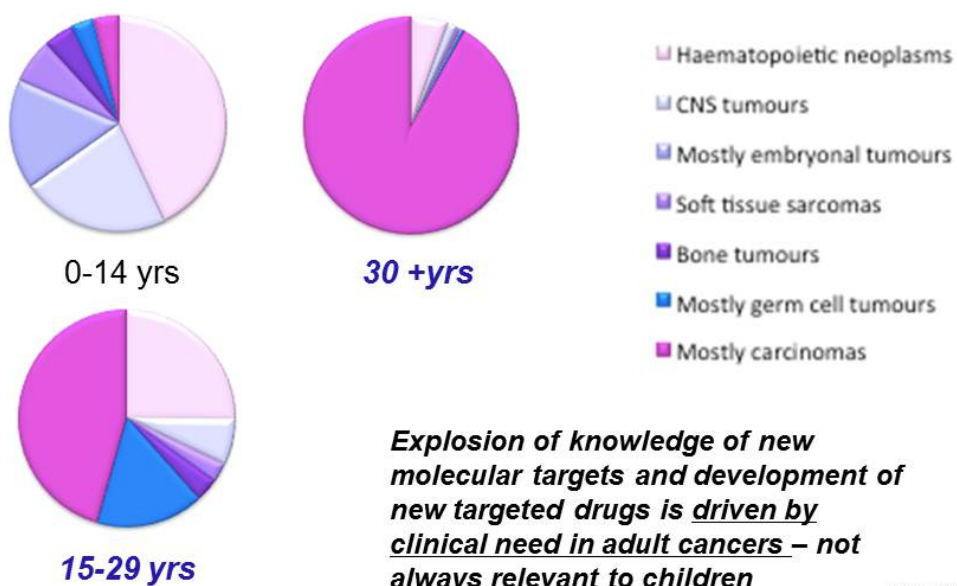


5 year overall survival, all cancer, Europe
EUROCARE 4 (1995-2002) Gatta G et al, EJC 2009

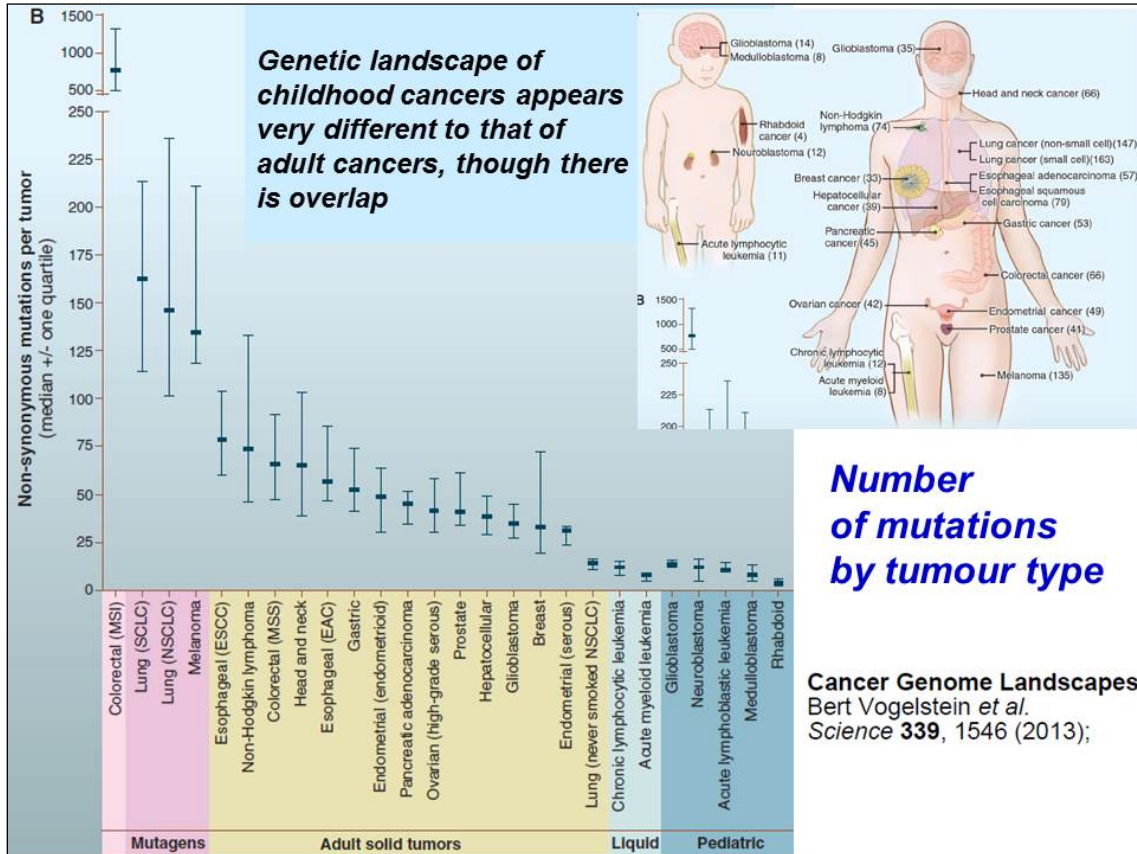


KPJ, 2013

Spectrum of childhood cancers compared to adult cancers



KPJ, 2013



Paediatric Oncology in Europe

Work with clinical trial groups and parents and survivors:

- to define the most important questions that can be addressed
- to refine the datasets and link with cancer registration/health record information in each countries.

Key issues form the clinical daily practice

- ✓ How to get children still enroll in prospective clinical trials as front-line standard of care;
- ✓ How to increase the number of adolescents and young adults up to age of 18 yrs, enrolled in clinical trials;
- ✓ How to get access to new drugs for relapsing/resistant patients;
- ✓ How to face with number when targeted therapies will further narrow defined subgroups of patients;
- ✓ How to face with the need of combination of agents (different companies!) to assess effective therapy.



Within the CTR definitions (article 2)

Clinical Study

any investigation in relation to humans intended

(a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products

(b) to identify any adverse reactions to one or more medicinal products; or

(c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining their safety or efficacy.

Clinical Trial

a clinical study which fulfils **any** of the following conditions:

- the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned;
- the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study;
- diagnostic or monitoring procedures in addition to normal clinical practice are applied

'Non-interventional study': a clinical study other than a clinical trial;

Kearns P, 2015

Implementation of the CTR what should/can we still influence?

1. Definition of the Low Intervention Trials

- Defined close to our requested definition

2. Co-sponsorship implementation

- *Well defined in New Regulation*

3. Clinical Trials Insurance

- *No National indemnity scheme*
- *Still will be a major issue*
- *An area we need to continue to lobby*

4. Proportionate Safety Reporting

- *'off label' use of standard licensed drugs still requires annual safety reporting*
- *Unlikely to be able to change in the near future*

Kearns P, 2015

Low intervention trial They should be subject to less stringent rules

'Low-intervention clinical trial': a clinical trial which fulfils **all** of the following conditions:

- (a) the investigational medicinal products, **excluding placebos**, are authorised;
- (b) according to the protocol of the clinical trial,
 - the investigational medicinal products are used in accordance with the terms of the marketing authorisation or
 - **the use of the investigational medicinal products is evidence based and supported by published scientific evidence on safety and efficacy** in any of the Member States concerned
- (c) the additional diagnostic or monitoring procedures do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

Kearns P, 2015

low intervention trial

They should be subject to less stringent rules

'Low-intervention clinical trial': a clinical trial which fulfils **all** of the following conditions:

- (a) the investigator and sponsor are authorised;
- (b) according to the terms of the agreement with the sponsor:
 - the investigator must ensure the safety of the subjects
 - **the base and**
- (c) the additional burden to the safety of the subjects compared to normal clinical practice in any Member State concerned

Sponsoring institutions and Investigators need to have a uniform approach to risk assessments of SIOPE clinical trials

PROPOSAL

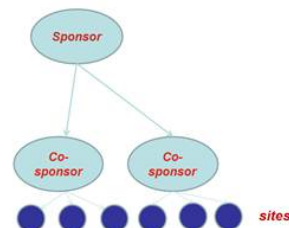
*Develop a guideline using examples
Seek support of guidelines from regulatory authorities*

Sponsors and Co-Sponsors

(42) In order to ensure clear responsibilities the **concept of a 'sponsor'** of a clinical trial, in line with international guidelines, was introduced with Directive 2001/20/EC. This concept **should be upheld**.

(43) In practice, there may be loose, informal networks of researchers or research institutions which run jointly a clinical trial. **Those networks should be able to be co-sponsors of a clinical trial**. In order not to weaken the concept of responsibility in a clinical trial, where a clinical trial has several sponsors, they should all be subject to the obligations of a sponsor under this Regulation. **However, the co-sponsors should be able to split up the responsibilities of the sponsor by contractual agreement**.

Possible guidelines on shared responsibilities and implementation of co-sponsorship agreements ?



Kearns P, 2015



Damage Compensation Article 72

1. Member States shall ensure that systems for compensation for any damage suffered by a subject resulting from participation in a clinical trial conducted on their territory are in place in the form of insurance or a guarantee or a similar arrangement that is equivalent as regards its purpose and which is appropriate to the nature and the extent of the risk.
2. The sponsor and the investigator shall make use of the system referred to in paragraph 1 in the form appropriate for the Member State concerned where the clinical trial is conducted
3. Member States shall not require any additional use of the system referred to in paragraph 1 from the sponsor for low-intervention clinical trials if any possible damage that could be suffered by a subject resulting from the use of the investigational medicinal product in accordance with the protocol of that specific clinical trial on the territory of that Member State is covered by the applicable compensation system already in place.

Kearns P, 2015

Compensation/damages does it apply to low intervention trials ???

Where, in the course of a clinical trial, **damage caused to the subject leads to the civil or criminal liability of the investigator or the sponsor**, the conditions for liability in such cases, including issues of causality and the level of damages and sanctions, should **remain governed by national legislation**.

(46) In clinical trials with non-authorized investigational medicinal products, or where the intervention poses more than an insignificant risk to subject safety, compensation should be ensured for damages successfully claimed in accordance with the applicable laws. **Therefore Member States should ensure that systems for compensation for damages suffered by a subject are in place which are appropriate to the nature and the extent of the risk.**

Kearns P, 2015

Compensation/damages does it apply to low intervention trials ???

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ACTION

Understand how this will be interpreted nationally

Understand how it will be implemented nationally

Engagement at National Level and with Regulatory Authorities

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Kearns P, 2015

Actions: some proposals

- **SHORT-TERM OUTPUT:**
 - SIOP-E position paper on the implementation of the CTR
- **MEDIUM TERM PROPOSALS:**
 - Co-sponsorship agreements
 - guidelines on shared responsibilities and implementation of co-sponsorship agreements : ITCC Sponsors Consortium already initiated
 - Low intervention trials:
 - SIOP-E risk assessment guidelines to define low intervention trials
 - Insurance
 - Engage in a process of working with regulatory authorities in how Article 72 will be interpreted
- **LONGER TERM PROPOSAL**
 - Safety reporting:
 - Review the use of current safety data from SIOP-E multi-agent, multi-arm trials using authorised but off-label drugs
 - Output as a publication ahead of the next revision?

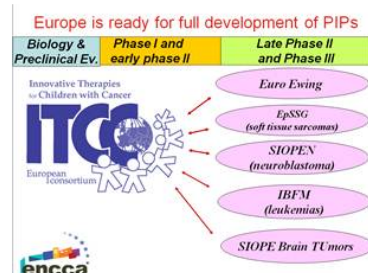
Kearns P, 2015

Questions and challenges

- Low interventional trial, if cleared, could potentially solve the issues of the treatment of standard pediatric patients with cancer;
- Still it remains the question of costs and insurance;
- Patients with features that can benefit to be enrolled in RCT will be the real challenge: how to integrate new drugs after phase I/II (pharma interest?) and who is going to support the study;
- We need to have at EU levels a coordinating effort to have Pharma, regulatory authorities and pediatric "voice" (SIOPe) to implement the introduction of new compounds (NCI-CTEP-COG in USA)
- As formal RCT, the cost of the trial in terms of management, additional diagnostic, insurance, will make it unaffordable.

European pediatric oncology centers are ready for new drugs!

- **ITCO:** Innovative Therapies for Children with Cancer European Consortium
 - Created on March 25th, 2003
 - 40 clinical centers and 9 labs
 - 4000 new patients/year and ≈ 900 with a relapse
 - in 7 member states: France, UK, the Netherlands, Italy, Germany, Austria, Spain
 - A Non-for-Profit organisation in 2011
 - "to conduct a comprehensive preclinical and clinical early drug development program (Phase 1 and 2) taking into account the unique ethical dimension of investigating new treatments in children with life-threatening disease".
- **ENCCA:** The European Network for Cancer research in Children and Adolescents



NOTES

DIRECTORATE-GENERAL FOR INTERNAL POLICIES

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