



## CDDF-ITCC-ENCCA-SIOPE 3<sup>rd</sup> Conference

### Prioritisation in paediatric oncology drug development: Vienna, Austria 5-6 February 2015

Summary by CDDF-ITCC-ENCCA-SIOPE of presentations, discussions and proposals for the future

*Conference Chair:* Gilles Vassal

*Present:* See attached list of participants

**Abbreviations:** ALCL: anaplastic large cell lymphoma; ALK: anaplastic lymphoma kinase; BPCA: Biologics Price Competition & Innovation; CDDF: Cancer Drug Development Forum; COG: Children's Oncology Group; EFPIA: European Federation of Pharmaceutical Industries and Associations; EMA: European Medicines Agency; ENCCA: European Network for Cancer Research in Children and Adolescents; ENPR-EMA: European Network of Paediatric Research at the EMA; e-SMART: European Proof of Concept Therapeutic Stratification Trial of Molecular Anomalies in Relapsed or Refractory Tumours in children; FDA: Federal Drug Agency; ICR: The Institute of Cancer Research, UK; IMI: Innovative Medicine Initiative; IST: Investigator Sponsored Trials; ITCC: Innovative Therapies for Children with Cancer; LTFU: long-term follow-up; MA: marketing authorisation; MB: medulloblastoma; MATCH: Molecular Analysis for Therapy Choice; MoA: Mechanism of Action; NB: neuroblastoma; NCI: National Cancer Institute, US; PCM: molecular characterisation program; PDCO: the Paediatric Committee [of the EMA]; PIP: Paediatric Investigation Plan; PoC: proof of concept; PPTP: Paediatric Preclinical Testing Program; PREA: Pediatric Research Equity Act; RMB: rhabdomyosarcoma; RoW: Rest of World; RP2D: recommended Phase II dose; SIOPE: European Society for Paediatric Oncology; SME: small and medium enterprises; SPC: supplementary protection certificate; US: United States [of America]; WHO: World Health Organization; WG: Working Group; WR: written requests.

**This document summarises the presentations given at the meeting: it also includes the question and discussion sessions after presentations, all of which were recorded. NOTES are important items of information that arose during the presentations and discussions. Discussions, consisting of Comments (C), Questions (Q) and Answers (A), arising out of the presentations were partly what informed the Overall Conclusions Comments, Questions and Answers reflect the personal views of the participants, not the opinion of their organization (industry, PDCO, EMA or academia).**

### Introduction

This third CDDF-ITCC-ENCCA-SIOPE paediatric conference aimed to examine and share the work of the 4 Paediatric Platform Working Groups (WGs) established in 2013; define and fine tune future plans; identify ways for cooperation between Europe and the US; develop the Platform further with a focus on communication and dissemination; and the academic stakeholders aimed to work towards the revision of the European Paediatric Regulation in 2017.

Table 1: Working Groups

|            | Remit  | Chair(s)   |
|------------|--|--|
| <b>WG1</b> | MoA biology-driven drug development within the current regulations                                     | Andy Pearson: Institute for Cancer Research, UK and ITCC                           |
| <b>WG2</b> | Compound prioritisation across industry; a forum to discuss individual drugs in Europe                 | Raphael Rousseau, Genentech, USA   |
| <b>WG3</b> | Innovative design and methodology for drug development to include better extrapolation from adult data | Ralf Herold, EMA, UK and Koen Norga, Antwerp University Hospital, Belgium and PDCO |
| <b>WG4</b> | New incentives for specific paediatric drugs and drug repositioning                                    | Patricia Blanc, Imagine for Margo, France  |

The sessions were divided into four main areas:

- Strategic outlook;
- Biology and mechanism of action driven drug development;
- Cross pharmaceutical company developments and cooperation;
- Innovative European regulatory initiatives.

## Strategic outlook

**Strategic outlook and prioritisation in the US and Europe** (presented by Gilles Vassal)

In the United States (US) there are 3 sets of paediatric regulations and incentives that work through the Federal Drug Agency (FDA): the Best Pharmaceuticals for Children Act, the Pediatric Research Equity Act, and the Creating Hope Act, and in Europe the Paediatric Investigation Plan (PIP) run by the European Medicines Agency (EMA); all are designed to help develop drugs for children with cancer. In addition, the Orphan Drug regulation addresses the needs of rare diseases, each paediatric malignancy being a rare or very rare disease. Within these parameters two perspectives predominate: the patient/disease centric held by academia and funders and the drug centric held by industry and regulators, and these two differing viewpoints cause difficulties when it comes to prioritisation. For success in paediatric oncology drug development, partnership between academia, industry and regulators is critical. Input from academia, regulators and industry is essential to decide which trials should be conducted. Furthermore, the current regulations and incentives need to change to optimise the decision making process.

**The US academic perspective** (presented by Peter Adamson)

A number of paediatric trial designs were presented: Phase I paediatric dose finding, Phase I/II efficacy testing with expansion cohorts, Phase II multi-strata efficacy trials, and randomised Phase II trials with 2 targeted drugs interrogating different targets. A number of examples in anaplastic large

cell lymphoma (ALCL) and rhabdomyosarcoma (RMB) were presented to show the advantages of using adult data to inform paediatric trials and of 2-arm trials for gathering data to show the way forward. A 2-arm trial in newly diagnosed ALCL was also discussed showing that mixed company involvement is achievable, and provides data to all.

Major new initiatives in paediatric oncology were described: 1) the Children's Oncology Group (COG) ([www.childrensoncologygroup.org](http://www.childrensoncologygroup.org)) through which 90% of children with cancer in the US are cared for in one of ~200 COG research sites and which also works with collaborative sites in Europe, Australia, and New Zealand; 2) The COG Everychild Project in which molecular tumour information will be generated for each child at diagnosis; 3) a National Cancer Institute-(NCI)-Molecular Analysis for Therapy Choice-(MATCH) scheme for study inclusion at Phase II which uses a Workflow and Turnover Time of the Assay System for detecting actionable mutations; this includes the Pediatric MATCH Trial, a multi-strata Phase II study where patient data will be accrued according to the molecular characterisation of their tumour.

***The European academic perspective (presented by Gilles Vassal)***

A strategic plan established by the European Society for Paediatric Oncology (SIOPE) within the FP7 - European Network for Cancer Research in Children and Adolescents (ENCCA) aims to increase cure rates in poor prognosis paediatric malignancies and the quality of life in survivors through a biology driven new drug development strategy. The initiative has a roadmap of objectives for 2020: innovative therapies across Europe; precision medicine; increased knowledge of tumour biology; provision of equal access to care, expertise and research for all; specific needs of teenagers and young adults; quality of survivorship; and identifying the causes of paediatric cancer.

Within this strategic plan, Innovative Therapies for Children with Cancer (ITCC) ([www.itcc-consortium.org](http://www.itcc-consortium.org)) works to bring positive change in European paediatric oncology drug development through early phase trials, prioritising and increasing evaluation of new drugs, improving access to trials, rethinking trial designs and methodology, and speeding up the introduction of new drugs before relapse. Part of this agenda requires enhanced evaluation of adult oncology drugs, identifying new therapeutic interventions and paediatric targets for new drug development, and developing MoA development plans for specific paediatric drugs. ITCC has set up a Mechanism of Action (MoA) paediatric oncology development plan to examine targeted compounds and biomarkers and to prioritise compounds to go forward for development.

They work through their molecular characterisation programmes (Precision Cancer Medicine [PCM] programme), investigator sponsored early phase clinical trials, and with industry, for example, in the Genentech Roche Matrix Trial; trial data feeds into a European Union (EU) clinico-biological database to generate new knowledge and new druggable pathways. The eSMART trial is an ITCC project that aims to explore 6 to 15 new anticancer drugs from several pharmaceutical companies in a phase I /II setting, as single agents or in combination, in order to match the molecular tumour alterations (through whole exome and RNA sequencing as well as immunophenotyping) that will be identified in the tumours of patients participating in the ITCC PCM programme.

In 2014, the ITCC created a Sponsor's committee, with sponsoring academic institutions from 4 European countries, to speed up the development and implementation of high-quality investigator-driven clinical trials in partnership with pharmaceutical companies..

***EMA and Paediatric Committee (PDCO) perspective on prioritisation (presented by Koen Norga)***

A brief view of the regulatory aspect examined what might be prioritised, what the purpose of prioritisation is, the unique contributions of stakeholders, and the challenges that must be tackled; for example, numbers of compounds and timelines, limited data, and ethical considerations of research in minors. And the big question is how to go forward and how to objectively compare and prioritise the different compounds and options available?

First methodology: 1) comparing data on available pipeline products and/or 2) extrapolating from various sources to predict therapeutic potential in children through proof of concept and safety data. There are also regulatory instruments and tools such as PIPs actively being used to contribute to this task, through, for example, early phase development and PIP modification.

Going forward, forums such as CDDF are important, enabling early consensus-seeking discussion between stakeholders and potential for precompetitive sharing of data and expertise. Interfaces between different groups aid communication and provide opportunity for interaction. Practical aims include bringing more trials to patients and improving trial methodology. The role of the European Network of Paediatric Research at the EMA (Enpr-EMA) ([www.ema.europa.eu/ema/index.jsp?curl=pages/partners\\_and\\_networks/general/general\\_content\\_000303.jsp](http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_000303.jsp)) was outlined: fostering high-quality research and stakeholder collaboration, disseminating trial information to parents and patients, raising awareness with and supporting Health Care Professionals, and contributing to ethics committees for clinical trials and relevant matters.

Regulators are willing to be involved early in decision-making on prioritisation; they have a unique perspective, and are prepared to facilitate innovative research methods to achieve this goal. Prioritisation is at the core of the EMA and PDCO mission.

***FDA perspective on prioritising new drugs for childhood cancers*** (presented by Greg Reaman)

The principles of US paediatric drug regulations and incentives through the Best Pharmaceuticals for Children Act (BPCA) (1997) and the Pediatric Research Equity Act (PREA) (2002) were outlined. FDA initiatives assist paediatric development generally and paediatric cancer therapy specifically. An FDA Advisory Committee published consensus (2003) outlined its specific policy. Though paediatric development was generally to be coordinated with adult development, there was already some suggestion that the adult and paediatric diseases might be different and that studies could be initiated case-by-case on the basis of type of agent, safety and MoA. Thus with scientific rationale and a paediatric oncology population with an unmet need, clinical studies could be initiated following Phase I adult trials. However, the FDA requires that studies provide labelling information and this must be considered in the design of early phase studies.

A new draft guidance is currently under review to consider Written Requests (WR), the mechanism by which the BPCA requests sponsors to consider developing a paediatric study, specifically the role of MoA and scientific rationale in the evaluation of a potential paediatric drug. Importantly, the new draft guidance provides the opportunity to align PIP and WR requirements, and expand the monthly dialogues between the EMA and FDA, and the Japanese, Australian and Canadian regulatory agencies. The need for greater academic and industry collaboration is recognised.

The role of the FDA in new drug prioritisation is supportive and facilitative towards stakeholders. It believes early and frequent communication is pivotal and that optimal leveraging of current legislative initiatives is essential. Regulatory flexibility exists but is limited; lack of labelling data, and benefit-risk analysis and information should be part of development plans and study designs.

**Discussion:** Q = question; A = answer; C = comment

**Q:** *What is most needed to speed up paediatric drug development in the next 5 years?*

**A:** All stakeholders across the US and EU, and the Rest of World (RoW) working together.

**A:** As soon as there is enough evidence for a potential new drug, paediatric Phase I trials should start and begin to collect data, even if Phase II/III are still unplanned.

**A:** A consensus on minimal data sets to enable comparison across companies and targets.

**A:** Defining the genetic characteristics of paediatric tumours.

**C:** *Are there any well-designed tissue/serum/bio banks that could be used for future biomarker identification? If not, setting one up, preferably within academia, would be a key achievement.*

**Q:** *With a novel Phase II design combination study how would academia bring two new agents and thus probably two companies together to enable successful collaboration?*

**A:** Academia can act as an honest broker and bring together two companies; regulators are also willing to work on this; e.g., the ITCC BIOMEDE programme with 3 compounds and 3 companies, but it took 2 years to organise. A fast-track industry-wide system would be good.

**Q:** *Is the level of evidence needed for Marketing Authorisation (MA) of targeted drugs for small patient populations changing and is there a concept of a post-marketing commitment to carry out efficacy studies?*

**A:** FDA has expedited approval processes, though not yet relevant for paediatric populations. The most recent is the 'breakthrough designation'. This requires clinical evidence of activity for a company to make a WR to the FDA to go forward with research.

**C:** *The EMA-PDCO proposed to gather all stakeholders together later this year to prioritise a number of medicines for studies in paediatric patients with a cancer such as lymphoma or another group of cancers.*

*Post-meeting note: This proposal has been taken up, with academic stakeholders working on types of medicines they would like to discuss, and a first multi-stakeholder prioritisation platform meeting hence is planned for 2016.*

**C:** PIPs that demand Phase III are a disincentive. We need to cut through red tape. Preclinical data exist in most compounds that we want to use in children. The problem is incentivising industry to give drugs to children early.

**C:** Industry recognises the need to go faster, but consensus is needed. Industry needs PIP approval for return on investment; legal issues around precompetitive collaboration need discussing. PIP approval currently takes too long – acceleration of the process would be great – but there has been progress and detailed Phase III plans are no longer necessary. A neutral ground to discuss PIP possibilities would be welcome.

## **Biology and MoA driven drug development**

### ***Lessons learnt from the Paediatric Preclinical Testing Program (PPTP) (presented by Malcolm Smith)***

The PPTP began in 2005 and completes its second 5-year funding period in 2015; the Program is systematically evaluating new agents against childhood solid tumours and leukaemia models (<http://gccri.uthscsa.edu/pptp/>). There are 6 working centres in the US. The Program is essentially an *in vivo* one with 60 xenograft lines and an *in vitro* panel with 27 cell lines. It is testing approximately 10 new agents per year against the PPTP childhood cancer panels and has collaborations with more than 50 companies.

*In vivo* testing examines therapeutic windows, questions whether concentrations in the active range are achievable in patients, and whether clinically relevant concentrations are affected by other parameters such as pharmacokinetics. A key question is how to define *in vivo* testing activity and whether this will translate to an active agent in patients. In paediatrics, cure is the objective, and requires complete response whereas PPTP defines *in vivo* high activity as regression.

A number of agents with little tumour regressing activity and some exceptional responders were described. The PPTP experience supports the premise that good responders are likely to have a



genomic basis related to the agent's MoA. PPTP is also testing combination models that are therapeutically significantly better than single agents and a number of these were described.

A new NCI-supported Pediatric Preclinical Testing Consortium will be funded from mid-2015. The research teams that will form the Consortium will be selected in a competitive peer-review process, and public announcements about the Consortium and its composition will be made in July 2015.

***Innovative preclinical models*** (presented by Louis Chesler)

Gene driven mouse models are now part of the accelerated MoA-based development of targeted therapeutics, thanks to new technology. The Institute of Cancer Research (ICR) has developed a rapid and flexible approach for modelling and targeting oncogenic mutations. It is specifically targeting MYCN and TP53 in medulloblastoma (MB), and MYCN and anaplastic lymphoma kinase (ALK) in neuroblastoma (NB), solid tumours that still have a bad outcome in children; modelling of NB, MB, glioma, RMS and retinoblastoma are ongoing. Three complementary *in vivo* models were described: xenografts for traditional drug development, Explants models – avatars for drug resistance trials, and GEM – gene engineered for MoA and oncogene function. This preclinical model for drug development is a valuable addition to MoA driven drug development.

GEM-modelling is ideal for some embryonal cancers: glioblastoma, MB, RMB, and NB. A number of modelling studies were presented including those for metastases, resistance, and optimised pre-clinical trial design. This approach is flexible and useful for studying oncogenic origin and function and is ideal for developmental biology studies of gene function. It can also be used to run drug screens and almost any preclinical trial treatment strategy. If used correctly and understood in its clinical context, it can provide data directly translatable to clinical trials. Examples from the ICR dataset were presented and the resulting MoA-driven drug development, for example, crizotinib/ temsirolimus in ALCL, and NB and second-generation ALK inhibitors for NB.

Disease-associated mutations are being rapidly identified in childhood cancers and a GEM mouse-modelling approach has been instrumental in moving targeted compounds to patients. These models are specifically useful for MoA-driven drug development and an effective/robust preclinical network would serve children in Europe well.

***The ITCC Precision Cancer Medicine Program*** (presented by Birgit Georger)

Recent European initiatives have shown the feasibility of generating a tumour's molecular portrait for children and adolescents at relapse in a timely fashion to allow treatment decisions that match identified molecular alterations.

In France, the MOSCATO-01: (MOlecular Screening for CANcer Treatment Optimization) was a single institution pilot trial at Gustave Roussy in 50 relapsed children: molecular profiling of fresh biopsies, examined by a tumour board for molecular changes, and suggested adaptive treatment – within a median of 21 days (2012-2015). This pilot study will be followed by a national and international molecular matching trial - MAPPYACTS: (MoleculAr Profiling for Pediatric and Young Adult Cancer Treatment Stratification), a proof of concept trial (from 2015) to screen as many relapsed or refractory paediatric patients as possible, and provide molecular profiling and treatment with matched innovative targeted agents if possible.

In Germany, the INFORM trial run by the German Cancer Research Center (DKFZ) and started in early 2015 carries out molecular profiling at relapse on archived material or fresh biopsy. A feasibility registry will run for the first 2 years followed by a clinical trial in Years 3-5. In the Netherlands, the iTHER project is run by the Amsterdam Medical Center. In the United Kingdom, COMET, a matching trial, is in preparation. The goal for ITCC is to integrate these national initiatives, merging data and building expertise in the field of interpretation of comprehensive molecular data for decision making.

A review was given of both ongoing targeted and non-targeted EU / ITCC Phase I/II clinical trials, further trials starting in 2015, the e-SMART, multi-agent, pluri-company, proof of concept trial, and the Genentech Roche Matrix trial. There is also ongoing work at the preclinical level to explore biomarkers, cancer evolution, and validation of oncogenic drivers.

***Proposals from WG1: Implementation of MoA biology-driven drug development for children***

WG1 led by Andy Pearson (ITCC, Institute of Cancer Research) is composed of 19 people representing the 4 stakeholder groups. Over the last 12 months, the group has worked together through several telephone conferences and a face-to-face meeting held on February the 4th 2015, ahead of the Paediatric Annual Conference. The original goals of WG1 were to define and develop a strategy for the implementation of MoA biology-driven drug development in order to deliver precision medicine through studies within the confines of the European Paediatric Regulation. Additionally, to define a process to obtain biological data within ITCC-ENCCA-SIOPE to enable the strategy to go forward.



A Workshop held on February 4<sup>th</sup> produced the following conclusions, proposals and action points (see attached summary for details):

### *Conclusions*

1. The proposed model of MoA biology-driven drug development would align an aggregated pipeline of drugs with an aggregated database of paediatric tumour targets and enable early-phase clinical trials to evaluate drug against targets and generate data in less than two years.
2. Key is that the process for prioritisation of drug evaluation should be systematically used by academics, funders, industry and regulatory bodies through PIPs. There is full support for paediatric early phase clinical studies starting at 100% of adult recommended Phase II dose (RP2D) corrected for body surface area, unless there is a good reason not to do so. Special attention is needed for potentially more severe toxicity in very young children (<2 years of age) with immature organ function.
3. A life-cycle approach in MoA biology-driven drug development PIPS is strongly supported and would have many advantages. It would be important especially when different companies generate a lot of data with difficulties in sharing data; it is not yet clear how to move forward with this in the current regulatory setting. A life-cycle approach should be across compounds of the same class as well as for a given disease.
4. A strategy is needed for the evaluation of multiple paediatric compounds of the same class where the number of children with tumours with the target is very limited.
5. Complex PIPs with double blind randomised parallel group studies are not believed to be feasible. This issue could be resolved through the life-cycle concept.
6. Teenagers ( $\geq 13$  years) should be included in adult, early phase clinical studies of rare cancers that occur in teenagers. This will avoid delay in developing new therapies for these patients.
7. Academia to establish an adequate healthcare organisation for patients with very rare tumours.
8. To progress, cross-pharma initiatives with pre-competitive collaboration between pharma and multi-company trials are required. This will benefit pharma, children with cancer and regulators.

### *Proposals and actions*

1. To publish this model of MoA biology driven drug development with prioritisation of drugs.  
**Action:** Manuscript to be drafted and circulated to WG 1 for comments.
2. To develop the aggregated database of paediatric tumour targets (already in progress). **Action:** To develop and then discuss with WG1 a detailed proposal for the aggregated database and to define the mechanism of access to the database.

3. To develop a “lifecycle-approach” – an iterative approach where the direction of drug development is continually reviewed especially after the conclusion of pivotal clinical trials.  
**Action:** Discussion at WG 1 and planning with the PDCO.
4. Publication of juvenile toxicity results with recent anti-cancer medicines. **Action:** Publication (not part of activities of this multi-stakeholder meeting).
5. To develop a strategy for the paediatric development of multiple compounds of the same class where the number of children with tumours expressing the target is very limited. **Action:** Further discussion by WG1 leading to strategy.
6. Inclusion of teenagers  $\geq 13$  years in adult early phase clinical studies. **Action:** Discussion in WG1 about best method of implementation, leading to publication and implementation.
7. Establishment of an adequate healthcare organisation for patients with extremely rare tumours.  
**Action:** Support of development of EXPeRT by SIOPE Europe.

**Discussion:** Q = question; A = answer; C = comment

**Q:** *How would you see implementation of MoA biology driven drug development?*

**A:** We are working with smaller and smaller sub-sets of patients and this becomes problematic when thinking about trial design. The initial focus should be on early studies done in 2 years to generate initial information, then to discuss the next steps and whether to go on to larger studies.

**Q:** *The lifecycle of the drug class will enable work across compounds. Has implementation of this been discussed with the regulators?*

**A:** We have begun to think about it. The opportunity to hold discussions with PDCO, as suggested, is very welcome, as that will potentially give the opportunity to address this problem.

**Q:** *Looking at the lifecycle of a PIP for any given drug and at a drug’s patent life, which is relatively short, if we are working on combination studies and combination PIPs, how will this work practically in terms of incentives for industry?*

**A:** The goal would be to avoid duplication of effort, to enable sponsors to focus on where they technically could deliver a clinical study at the end of the time limit.

**A:** Regarding the lifecycle proposal, firstly PDCO is offering an initial consultation with industry. Second, currently a PIP **can** be presented with detailed Phase I and or Phase II but with not Phase III, only an outline of a study synopsis. This is a more flexible approach. The idea of a progressive PIP cycle is to have a PIP with a first study detailed and then for industry to come back to PDCO to define the next step.

**C:** *This idea of lifecycle has come up at this meeting and everyone is in agreement with it. And this is what the Platform is about, to discuss new ideas. In 2017 the Commission will decide if it is going to amend the European Paediatric Regulation, so any things that are recognised here as being needed should be pushed forward.*

**Q:** *Could there be greater flexibility in the reward system for drug development because development times are very variable?*

**A:** This is being considered but it is a general problem and complicated; as yet there is no answer.

**Q:** *For smaller companies how do they deal with a MoA for a paediatric drug, when they are aiming*

*for an adult indication? Is this possible to do?*

**A:** It is possible with the current PR, but there is the question also of whether a MoA approach should be mandatory or not. This could be difficult for smaller companies with less resource and needs discussion.

**A:** From the regulatory perspective, the MoA is an evolving area, and there comes a decision point when available information is used to plan going forward. This seems naturally a point for feedback: what data are needed; it could even be part of the PIP. Flexibility and ability to discuss plans at different stages of a PIP is something that regulators are ready to do.

**C:** *There is no hindrance from the PR to go forward with MoA-based development, but the need to submit supplemental PIPs for every change, every new formulation, is what becomes the problem and will need addressing.*

**C:** *At Genentech we are encouraging our colleagues to enrol children as young as 12 in adult trials, where MoA and baseline data allow it.*

**C:** *Parents feel a great sense of frustration at the lack of pace. There has been progress but still we would like to know what we can do to accelerate the process.*

**C:** *Where are the media campaigns to take this forward. We hear the same conversations over and over, so what can we do NOW to stop children dying.*

**C:** *We see lots of progress and hard work, but we do not feel in all of that the sense of urgency that we feel as parents: "waiting is not an option". Can we get moving!*

### **Session 3: Cross-pharmaceutical companies development and cooperation**

#### ***Innovation in paediatric oncology drug development: the Matrix trial concept*** (presented by Maoxia Zheng)

Genentech/Roche have initiated a new approach in paediatric oncology drug development by consolidating relevant expertise within an internal single paediatric oncology group (iPODD) that is responsible for the strategy and execution of drug development within a portfolio-based development paradigm. Historically development has been along adult, reactive, obligatory lines but this is changing to a paediatric, proactive, deliberate approach based on the MoA of a drug.

MoA development is within both single and multiple molecule paradigms and with a gated approach. With a single molecule, Gates 1-3 feature after PK and safety data (1), initial response assessment (2), and additional response assessment (3), beyond Gate 3 drugs advance to a pivotal study based on disease and molecule-specific target treatment effect; these three Gates form the Phase I/II matrix. Eligible patients are identified by biomarker profile, and ongoing inclusion/exclusion criteria are based on re-evaluation of biomarkers as safety and efficacy data accrue. The multiple molecule paradigm has different allocation rules, so that treatment may be randomly assigned if a patient is eligible for more than one molecule, and for advancement beyond Gate 3, totality of data, level of unmet medical need and enrolment feasibility form the prioritisation strategy. Genentech/Roche has a good haematology and oncology drug pipeline and a MoA study design and Matrix framework that aims for patient centric drug development matching children with cancer to the most promising therapy.

### ***Proposals for WG2: Cross pharmaceutical company development and cooperation***

WG2 is led by Raphaël Rousseau (Genentech). A formal group has not been created. The feasibility and relevance of the MATRIX trial as a potential tool for cross-pharmaceutical company cooperation has been explored. During the last 12 months, common items between WG1 and WG2 have been identified.

The ultimate objective is improved patient care through updated product labelling. This involves a number of steps. The Matrix trial is classic science but it is new from the filing and regulatory standpoint, and brings efficiencies and rigour that lead to a label. It shows that there is a way to move things forward and get drugs to children earlier and is already bringing about collaborative work with other companies.

There are three projects forming the WG2 initiative:

**Project 1:** To build an **aggregated drug portfolio**, in an open and systematic way, so that it can be matched with the aggregated target validation, and this will include having an active list of prioritised compounds to go forward to the Matrix trial; to look at all available oncology molecules; to drive the prioritisation process along with academia; to question the development of multiple drugs for the same illness. There are academic groups that can do the work, and demonstrate Proof of Concept (PoC) of molecules, leading to a list of drugs with PoC, a regulatory strategy, and a business strategy that can go forward to the Matrix trial. Genentech Roche would like to share those tools with any other companies that wish to come to the table, to share data in an open platform.

**Project 2:** To develop a **common clinical trial platform** to match patients to the most promising therapy. And to enrich the label through subsequent Investigator Sponsored Trials (IST) once the main industry-sponsored trial is completed. Industry would supply the baseline data that would enable academia to move forward with trials. Europe probably needs a mechanism such as the NCI in the US that can sponsor multi-company trials, such as a common sponsoring platform led by academia, with sufficient funds to run trials. Legal issues would need to be discussed. Raphael Rousseau stated that in his view discussions with the regulatory authorities are positive and this would fit with the purpose of the European Paediatric Regulation.

Next steps for the Matrix Trial:

- The Matrix Trial concept could be submitted for Joint Qualification Procedure to EMA/FDA;
- Development of a Matrix Trial protocol and Master IND/Master WR;

- Joint meetings with PDCO/FDA on harmonisation of trial design across US/EU

**Project 3:** To set up a long-term follow-up (LTFU) initiative of 20 years for all children who are given oncological drugs. It is a logistical challenge, a long-term commitment that needs ongoing discussion and will require a concerted effort of all parties.

***The Innovative Medicines Initiative (IMI)*** (presented by Nathalie Seigneuret)

Although the IMI does not have direct application to paediatric oncology, it provides a number of examples of new ways of working, some within the paediatric field, which could have utility in paediatric oncology. IMI, a collaboration between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA) (2008-2024), is the result of science-driven changes in drug development away from the old compound-focussed 9-13-year development model to a more patient-focussed, 2-5-year model. It focuses on patient and societal needs, integrates healthcare solutions, supports competition in the European biopharmaceutical industry, and progresses regulation. Its key concepts are to focus on unmet needs, non-competitive collaborative research, public-private consortia for open collaboration, data sharing, and industry contribution in kind. IMI aims for flexible intellectual property that will be enabling for all concerned.

From 2008-2014 IMI1's international cross-sector community comprised 7,000 researchers and 59 public-private consortia, including 764 academic teams, 17 regulators, 25 patient organisations, 433 EFPIA teams and 146 small and medium enterprises (SME). These continue in IMI2 from 2014-2024 with goals to increase success rates of clinical trials for new medicines and vaccines, to speed up early stages of drug development, to develop new treatments for unmet needs and new prognostic and predictive BMs, and to improve drug development processes. Its scientific focus will be patient and societal needs, alignment with World Health Organisation (WHO) priorities, improved access to innovative and personalised medicines, and broader, simpler rules and procedures, to include greater eligibility for funding.

Although there are no projects looking directly at paediatric oncology, projects in paediatrics looking at systems biology and development of biomarkers, projects where consortia are discussing treatment guidelines with regulators, and new approaches to clinical trials through clinical networks of excellence are all examples that could have utility in paediatric oncology.

**Discussion:** Q = question; A = answer; C = comment

**C:** LTFU has been a project since 2011 with little progress; it could be academia led supported by industry at all levels as a joint effort and needs to become an active project this year.

**C:** There is an ENCA survivorship passport, and maybe this can be linked into a CDDF WG Platform for LTFU and ultimately become part of a European cancer plan.

**C:** PanCare, the pan European group, has a well-developed network and links with the International Guideline Harmonization Group for Late Effects of Childhood Cancer.

**C:** Is there anything to stop groups taking drugs 'off the shelf' and using them in their own trials?

**A:** The problem with off-label use is that data is not accrued.

**A:** By the time a drug gets near to MA, we should know whether it is off use for childhood cancer without having to carry out myriad new trials. So this goes back to the point of starting earlier. We are starting too late. Paediatric data need to be accrued; we are not doing the appropriate studies to provide the right data.

#### **Session 4: Innovative European regulatory initiatives**

##### ***The Creating Hope Act – a successful initiative*** (presented by Katie Miller)

Types of incentive for paediatric oncology drug development were described: push occurring pre-MA and pull awarded post-MA. Examples of patient-led initiatives including legislative ones were outlined, such as the Creating Hope Act (see [www.kidsvcancer.org](http://www.kidsvcancer.org)) and the US Orphan Drug legislation, as well as non-profit/for-profit partnerships, for example, the Cystic Fibrosis Foundation.

An overview of the Creating Hope Act and Priority Review Vouchers was given, plus the successes and limitations of the Act and whether it could translate to the EU given the different legal frameworks of the EMA and the FDA. The US Orphan Drug Act (1983), with both its pre- and post-market mechanisms was outlined, as well as its limitations and successes. Limitations see drugs developed that may not be the most needed or important, but conversely hundreds of drugs have been approved. Similar legislation was passed in the EU in 2000. The potential, limitations and successes of patient-led partnerships and collaborations were described, with the Cystic Fibrosis Foundation given as an example.

A brief outline of the lead up to the Creating Hope Act was given. The Act is now being defended against government pressure to extend it to other diseases and requires industry support to remain as it is. Although the Act could not in itself be extended to the EU, its principles could and it therefore remains an example of what is possible.

##### ***Industry viewpoint of incentives and development costs*** (presented by Christina Bucci-Rechtweg)

The framework for all 4 major stakeholders was outlined: i) for patients and families this included the fact that 40% of childhood cancers are not adequately diagnosed and treated; ii) for industry



research & development and commercial drivers, and for academia the barriers and challenges of studying new agents in paediatric oncology; iii) a global regulatory framework which has legislation for paediatric drug development only in the EU and US, while voluntary paediatric data submission with and without incentives is present in some countries, but the majority have no established paediatric policy at all.

The obligations and rewards of the European Paediatric Regulation show the complexities of PIPs, as well as the non-orphan and orphan medicinal product reward system, which should result in a 6-month extension of the supplementary protection certificate (SPC). The SPC provides legal protection for innovators of products in the form of patent rights, patent protection extension, and IP protection.

As of January 31st 2015, there have been 74 agreed paediatric oncology PIPs, 38 full waivers, 10 exclusively paediatric PIPs, and an average 2 trials per oncology PIP. Despite attempts to innovate, completion of PIPs is too lengthy. Conversely, non-orphan rewards granted for developed drugs since the European Paediatric Regulation number 21.

In the US, paediatric exclusivity rewards increased between 2000 and 2009, but since then there has been a decline. Possible reasons for this include fewer WR and more mandated studies because of the Pediatric Research Equity Act, 2003 (amended 2007), an increase in academic studies, loss of the 'blockbuster model' of development, and transition to targeted, cell and gene therapies over the past decade. With an average of 9 years from MA of an adult drug to updates that include paediatric data in any one given drug, off-label use has grown.

The current framework is not working, and incentives that offer value to the developer and drive development are needed. In other areas incentives have been shown to work through expedited review times, better access to advice, tax credits and vouchers, and orphan drug exclusivity, and could be applied to paediatric development. De-risking is needed in early development. However, such changes will only work if necessary procedural changes are made to the European Paediatric Regulation, and EU and US laws are aligned, if international cooperation grows to facilitate feasible studies producing robust data, and streamlining and harmonisation of regulation takes place.

#### ***Proposals from WG4: New incentives to further incentivise paediatric drug development***

WG4 led by Patricia Blanc is composed of 14 people from the 4 stakeholder groups (one PDCO observer). During the last 12 months, they met regularly via telephone conferences. An industry survey was conducted.

The group presented their strategy towards achieving their goal to further incentivise paediatric drug development. This involved liaising with industry via a questionnaire to gauge the actual situation and identify potential incentives; analysing the US Creating Hope Act; proposing new incentives; discussing their feasibility with EFPIA and the EMA.

### Obstacles to further incentivising paediatric drug development and potential solutions

|             | Obstacle   | Possible solution  |
|-------------|--|--|
| Industry    | Financial: investments and return  | Government funding; easier access to other funding                                 |
| Regulatory  | Limiting of creativity; regulation as a burden vs opportunity; lack of incentives                | Flexibility, exclusivity and timing  |
| Clinical    | Lack of awareness and expertise  | Cooperation between industry, academia and regulators; increasing public awareness |
| Feasibility | Difficulty in recruiting patients; in patent extension; in conducting trials and in their timing | Increasing efficiency, cooperation, and better patient recruitment                 |

A SWOT (Strengths, Weaknesses, Opportunities and Threats) analysis of industry's support for a new European incentive such as the Creating Hope Act in the US was relatively even, but with greater potential problems anticipated for smaller companies. Incentives that might attract industry to develop paediatric oncology drugs included: a variety of incentivising vouchers; changes within regulation to IP, patents, negotiation on price, and decoupling of adult/paediatric development; and community led cooperation through consortia in collaboration with academia.

Incentives, were suggested by the group. Patient-led incentives were also discussed, including a legislative package and the setting up of a drug development foundation. Their work will continue on the feasibility of proposals. The patient organisations are also aware of the need to prepare for changes to the European Paediatric Regulation in 2017.

**Discussion:** Q = question; A = answer; C = comment

**C&Q:** *[from academia] It is too complicated. The barriers for industry are too high. There can be incentives, but the pull needs to be more straightforward. Also, the differential between the US and the EU is too great. Paediatric drug development needs to be attractive and easy for industry to do. What would industry like and how can we work with the regulatory sector to sort this out? The FDA has made changes that are making a difference to paediatric oncology in the US but the burden is still too great in Europe. What needs to be done to change that?*

**Q:** *Does 'one nation' in the US versus 27 countries in the EU make a difference to logistics?*

**A:** It makes it more complicated, but not insurmountable in Europe. The problem is getting trials started.

**C:** *We don't know which is the most useful incentive. But with the expertise here from paediatric oncology, there is a huge opportunity. Put in place push and pull mechanisms, increase communication between the drug developers and the EMA; put as many pieces as politically possible into one legislative package.*

**C:** *The burden of a full PIP to conduct Phase I, II, and III trials is a big problem, so the possibility that there may be greater flexibility is very encouraging and will make a big difference to industry.*

**C:** *The regulatory function is there to help applicants, but we need to put in place mechanisms that support development and also to give rewards commensurate to effort.*

**C:** *Why has the orphan drug regulation been so successful, and why hasn't it made an impact on paediatric drug development? There has been high political commitment at an EU Commission level to invest in rare diseases and the same is needed in paediatric oncology. Can we learn anything from the orphan drug example? We need to put paediatric oncology high on the political agenda; parents need to demand action on a European Childhood Cancer Plan.*

**C:** *The Cystic Fibrosis Foundation is a good example of action being taken by parents and producing results.*

**C:** *The Cystic Fibrosis Foundation it is not necessarily the right model for paediatric oncology drug development; it involves enormous amounts of money and it is not without its problems.*

**C:** *There are many groups around Europe, raising large and small sums of money, but they don't always have an agenda or focus. With both of those they could do much more.*

**C:** *It is not the responsibility of such groups and with public money to develop paediatric oncology drugs, it is the responsibility of industry because once drugs are licensed, the money goes back to pharm. If timelines are shorter, drugs can be licensed sooner, more money is made more quickly; modifications to the European Paediatric Regulation could help with this. Make the hurdles less complicated and lower.*

**Q:** *On the question of uncoupling adult and paediatric drug development, how often has that actually been an issue? That children have responded in a bizarre way?*

**A:** *It is not an issue.*

**C:** *There are things that can be done now to make changes through implementation of the European Paediatric Regulation, but we need also to start thinking **now** what changes we would like to see in the Regulation; we need to identify a forum or an extension of WG4 or 5 to work on that.*

**A:** *It will be up to the Regulator whether changes are made in 2017 based on available information. Potential change should be thought of in a structured way. There are four possible ways:*

- 1. Address problems and find ways to make changes within the current implementation of the European Paediatric Regulation;*
- 2. Propose changes to the Commission guideline that manages implementation of the Regulation;*
- 3. Changes to the Regulation itself may be necessary to provide solutions to some of the problems;*
- 4. Additional legislation may be necessary.*

**C:** *In the next 10 years we should see incentivisation for the development of specific paediatric drugs by small biotech companies. At the moment there are no incentives for small companies to develop drugs for a specific paediatric target and there needs to be this provision in the European Paediatric Regulation.*

*C: There have been some useful and good suggestions for progress, but there is still misunderstanding, even though this is the 3rd meeting, of the cost of drug development. Industry does make money from incentives, but it needs 32 drugs in the pipeline for 1 to reach the market; 10 years to get a drug and at least US\$1 billion spent. We work with CDDF not because we have to but because we want to. We need to reinstate a climate of trust. Many of those here working in industry were previously working in paediatric oncology and they are advocates within industry for paediatric oncology drug development. We just need to find a few more advocates to involve in this deliberation. We need parents affected by paediatric cancer who are lawyers, active in the EU Commission, lobbyists, political leaders. These people will be critical to the next steps.*

*C: We need to use the European Paediatric Regulation to reach out to people. We need a media strategy to raise awareness and bring people into this group who can really make a difference in this arena.*

*C: We also need to be mindful of getting new agents into upfront treatment; to getting novel agents to front-line strategies. This is a challenge to the academic community.*

### **Further development of the multi-stakeholder paediatric oncology drug development forum**

There is direction for the WGs in the next year and beyond with defined goals to be taken to the Platform Steering Committee for implementation. The overwhelming message is the need to speed up. Some very relevant quotes from the meeting:

“Waiting is not an option”

“Plan early and execute promptly”

“At the moment it’s far too complicated”

AND

“With the right regulation you can have a whole range of products available to you at your convenience”

The following changes in the working groups have been discussed and proposed. They will be ratified by the Executive Committee when defining the work and goals of the platform for 2015.

**WG1:** Is ready to implement plans: creation of an aggregated database and facilitation of access to paediatric models; publication of an MoA based strategy and a development review summary with recommendations; review development in certain compound classes; plus a potential meeting to explore multi-company cooperation, sharing of data and how to move forward.

**WG2:** Next steps include: **Project 1:** company surveys to find out what they would be willing to share; a definition of variables to share; to build an aggregated portfolio of companies and set up a legally-based framework for collaboration; from academia a list of what it is useful to know; suggestions on making this a living document, thinking on logistics and structures. Then to identify

an aggregated list of drugs; organise a core committee of regulators possibly, and members of SIOPE to oversee the collaboration. With this we can compare needs with what's in the pipeline to look at ongoing trials and available patients (2015). **Project 2:** it is proposed to extend the Matrix pilot project to other companies (2016). **Project 3:** establishing a WG to implement long-term measures with long-term follow-up of patients.

A proposal to merge WG1 and WG2 is supported.

**WG3:** [Work did not start] Remit: Innovative design and methodology for drug development to include better extrapolation from adult data. This will be included in the objectives of the new WG1.

**WG4:** To put together a group to work on specific proposals/solutions to come from the last year's work on incentives; to discuss the Regulation and quick wins for quick effect; discussion with the EU Commission, politicians, EMA; create awareness. This WG will take on the examination of other ways of working within the Regulation or the potential changes that need to be made to the Regulation to put forward for its reassessment in 2017.

There was a proposal to create a dedicated multi-stakeholder Working Group to examine implementation of LTFU measures.

### Overall suggestions

- Have a multi-company meeting later in the year hosted by PDCO/EMA
- Look at a lifecycle mode of action outside of the PIP
- Evaluate the content of a PIP and its minimum scope
- Make practical suggestions on how to improve current implementation of the Regulation, but without adding layers of complexity to an already complex process
- And for the future, look at time-points, validation, registration package, practical parameters
- Avoid one size fits all; instead provide tools to be used in different circumstances
- Have ongoing dialogue that enables flexibility
- Prioritisation process needs to be discussed
- Examine the Regulation, check its intent, check if it is ok, but only the implementation that is not; try to make any change as simple and therefore as quick as possible.
- Have joint efforts internationally to be more efficient through greater harmonisation
- Help parent stakeholders to engage with the processes, meetings etc
- Create a decision making process to enable FDA/EMA to coordinate regulatory decisions and avoid duplication

- Formalise the progress made so far.

### **Communication strategy**

- Send out clear messages of what the group is trying to do
- High level narrative about what the problem is, what we're doing about it, where we're going
- Take the messages to others that count but are not yet involved in the field
- Start a movement, start a campaign, use social media to work for us
- Celebrate successes, get stories out
- Identify the risks and how to mitigate them
- Join forces as a voice for children
- Have a public face for the group.

### **Strengthening the Platform**

- Frame some terms of reference for stakeholders
- Should we enlarge the stakeholder group to include NICE and such groups?
- How to foster awareness of paediatric oncology drug development in individual companies?
- At ASCO, or similar meetings, gather companies for one hour and raise awareness
- CDDF could provide connection between pharma companies.

### **Conclusions**

Very significant progress was made over the last year and during the meeting; there was tangible momentum and a very strong sense of collaboration between all stakeholders. The meeting ended with 2014-2015 progress logged and plans for work to be done and goals to be achieved identified for each Working Group and new ones through 2015–2016.

Apart from the individual WG's plans for the year there are more general ideas to improve and promote the Platform's visibility vis-à-vis the general public and at international oncology meetings, as well as a communication strategy to strengthen the Platform's overall position, potentially in relation to other new stakeholders, but certainly with a larger number of pharmaceutical companies. The involvement of all stakeholders as equal partners is pivotal to the success of this initiative to bring new drugs more rapidly to the clinic for children with cancer.