GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION

(ARTICLE 50(2) OF REGULATION (EC) NO 1901/2006)

'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT'

SUBMITTED FOR PUBLIC CONSULTATION

Deadline for Public Consultation: 28 November 2012

Villejuif, November 28th 2012

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ITCC

(the European Consortium for Innovative Therapies for Children with Cancer)
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ITCC is a network of 42 academic institutions in 9 European countries running comprehensive programmes of preclinical and early clinical evaluation of new drugs in children and adolescents with cancer.

ITCC is a not for-profit organisation and a category 1 member of Enpr-EMA.

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Dear General Director of DG Health and Consumers,

We thank the European Commission for providing the 5-year survey of the Paediatric Regulation and for asking comments on key topics identified.

Hereafter, we address, in details, each of the 11 questions raised, and we summarized our position in item 12 with concrete proposals to change the implementation of the regulation in order to better address the needs of children and adolescents with cancer.

ITCC is very much committed and keen to help and contribute in making the Paediatric Regulation a success for children in Europe.

King Regards,

Pr Gilles Vassal, President of ITCC

A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Before the entry into force of the Paediatric Regulation many pharmaceutical companies considered the adult population as their key market. Research into the potential use of a product in the paediatric population was sidelined or not considered at all. With the obligations introduced by the Paediatric Regulation, forcing companies to screen every new (adult) product for its potential paediatric use, the situation has been turned around. Feedback from companies proves that pharmaceutical undertakings now consider paediatric development to be an integral part of the overall development of a product.

The requirement to develop and discuss with the Paediatric Committee of the European Medicines Agency a paediatric investigation plan, which normally should be submitted not later than upon completion of the human pharmaco-kinetic studies in adults, obliges companies to think early on about paediatric use so as to avoid any delays in general product development.

Consultation item No 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

ITCC comments

- The Paediatric Regulation has significantly changed the landscape and all companies developing oncology drugs for adults now consider children with cancer. This is a major positive advancement compared to before the paediatric regulation when companies did not consider the paediatric population with cancer.
- The introduction of novel agents is the only way to increase the number of children being cured of cancer and to improve the quality of that cure. The Paediatric Regulation has a pivotal role to play in this area.
- Due to the Paediatric Regulation very few first in child paediatric oncology studies sponsored by pharmaceutical companies have been performed
- However, most companies still consider the development of a drug for paediatrics only or primarily in order to comply with regulatory obligations. Therefore paediatric drug development is not embedded into the overall development program for new drugs. This is a major concern.
- Consequently, there is often no clear strategy for the development of new anticancer drugs in children and adolescents that addresses the specific scientific and medical needs of this core population and in reality, children are still being denied the opportunity of new drugs.
- Most companies do not comply with the regulation that states: “a paediatric investigation plan should normally be submitted no later than upon the completion of the human pharmacokinetic studies in adults”. The EMA and the PDCO regularly and repeatedly remark that companies are making late PIP submissions, yet there are no penalties for this.
- This clearly illustrates that many companies wait to fulfil their regulatory obligations as long as possible (and beyond) instead of starting discussions with the Paediatric Oncology Groups during the phase I studies in adults. We believe that to anticipate the potential needs of paediatric development for a given oncology drug and to design a paediatric investigation plan (PIP) the optimal time to commence discussions is during the adult Phase I study.

- To the best of our knowledge, only one company has run a paediatric phase I study of an oncology drug early within the drug development program in adults, and even before submitting a PIP. We strongly believe this is a way to consider in order to significantly increase access to new drugs for European children with life-threatening malignancy, providing there is a strong biology and preclinical rationale.

2. HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

One of the explicit goals of the Paediatric Regulation is to reduce the off-label use of medicinal products in the paediatric population and to increase the number of products that have been researched, developed and authorised for use in children.

The main tool provided by the Regulation to achieve this result is to oblige companies to establish a paediatric investigation plan for each newly developed product or for the line extension of an already authorised product that is still under patent protection. The plan is meant to ensure — under the supervision of the Paediatric Committee — that the necessary data is generated to determine the conditions in which a medicinal product may be authorised to treat the paediatric population.

Since 2008 nearly 500 paediatric investigation plans have been approved by the European Medicines Agency. However, only a minority of them has been completed. This is due to the long development cycles of medicinal products, often lasting more than a decade.

While the Paediatric Regulation has led to a certain amount of new authorisations that include paediatric indications, the regulatory instrument is recent and the data does not provide a sufficient basis for a comprehensive review. It will probably take at least a decade before the regulation can be judged in terms of its output. That said, it will always be a challenge to establish appropriate benchmarks for comparing off-label use with and without the Paediatric Regulation.

Consultation item No 2: Do you agree with the above assessment?

ITCC comments

- There is, thus far, no impact of the Paediatric Regulation on the off-label use of anticancer drugs in paediatric oncology.
- More disappointingly, the application of the concept of **class waivers** (a regulatory loophole whereby if a malignancy that exists in adults does not exist in the paediatric population, develop in children) gave a strong negative and counter-productive message to the paediatric oncology community and to the pharmaceutical industry
- **The assessment of the appropriateness of evaluating new drugs in children should be based on the mechanism of drug action and not the adult condition or indication.**
- As an example, sorafenib, a multi-kinase inhibitor, is approved for the treatment of kidney cancer and hepatocellular carcinoma in adults, two diseases that almost never exist in children. Sorafenib received a class waiver and consequently there was no paediatric development by the company and no obligation to fulfil a PIP Sorafenib, which is commercially available in Europe, is prescribed off-label in certain member states for the treatment of paediatric malignancies, such as paediatric liver cancer and acute myeloid leukaemia with FLT3-mutations. This is one of many lost opportunities where valuable information on paediatric safety, pharmacokinetic and prescribing data could have been gained and children could have access to a novel drug in the context of a clinical trial.

- Since **the Paediatric Regulation has failed thus far to significantly increase the number of oncology drugs being evaluated in paediatric phase I and II trials in Europe**, parents who want access to innovative treatments for their child suffering from an incurable progressive malignancy are denied access to sufficient options of clinical research trials with new drugs. Some parents are prepared to make major sacrifices and cross the Atlantic at great expense to participate in clinical trials of innovative therapies in the US. In such circumstances, European paediatric oncologists often consider the off-label prescription of a commercially available adult oncology drug as a relevant and preferable option, in an attempt to spare a family unnecessary trauma and expense.
- Only one PIP thus far has led to the authorisation of an oncology drug in a paediatric indication. This is for the treatment of an extremely rare paediatric malignancy, subependymal giant cell astrocytoma (SEGA) associated with tuberous sclerosis complex.
- **We do not agree** with the Commission's statement that this was expected "***due to the long development cycles of medicinal products, often lasting more than a decade***".
- Whilst it is acknowledged that it will take time for PIPs that were agreed during the first 5 years of the Paediatric Regulation to be fulfilled as studies need to be completed (and in many cases companies have been granted deferrals for either starting or completing paediatric studies) it is very likely that a number of PIPs will never be completed because the design of the early clinical study is unrealistic or patient numbers make it unfeasible, for example an early clinical study in a very rare "adult type" tumour which is seldom seen in children.
- ***O***ncology products currently being developed are extremely different from the cytotoxic chemotherapy products that were authorised by the EMA in the 20th century. Indeed, most of them are targeted against specific molecular alterations occurring in tumours. Providing that such an alteration drives tumour progression, that a drug effectively interacts with this target and a tumour biomarker can identify patients who may benefit, the interval between a Phase I study and marketing authorisation can be less than 10 years. There are clear recent examples in adult oncology such as vemurafenib in BRAF mutated melanoma and vismodegib in basal cell carcinoma.
- Crizotinib is one of the other striking examples of an inappropriately granted class waiver. Only 4 years have elapsed between the first patient treated in the first phase I (2007) and the FDA conditional approval (2011) for the treatment of non-small cell lung cancers (NSCLC) with an EML4-ALK translocation. The drug was authorised for marketing in Europe in October 2012.
- Interestingly **crizotinib is a paradigmatic example of the failure of the regulation in the field of paediatric oncology:**
    - A class waiver was issued in 2010 for crizotinib on the grounds that "NSCLC does not exist in children".
    - However, it was already known at that time that ALK is mutated in hereditary and sporadic neuroblastoma in children and is an oncologic driver in anaplastic large cell lymphoma [Actually, the gene (ALK for anaplastic lymphoma kinase) was named after this rare disease that occurs in children, adolescents and young adults].
    - There was thus a clear and evident need and rationale for an ALK inhibitor in several paediatric malignancies. But the regulation allowed the company exemption from developing a paediatric program, by virtue of the class waiver list.
    - In June 2012, the US Children's Oncology Group (COG) presented the preliminary results of a NCI-funded paediatric phase I study of crizotinib

showing 7 out of 8 complete responses in children with relapsed ALCL and several tumour responses in neuroblastoma patients.

- In conclusion a paediatric phase I of crizotinib should have been started at the time the adult dose-escalation phase I trial was expanded at the recommended dose in NSCLC patients but a waiver was issued to the company.
- Considering the outstanding antitumour activity observed in children with ALCL, crizotinib may have been authorised in relapsed ALCL in a relatively timely fashion, before the end of a decade.

- The crizotinib example also illustrates further the off-label use issue. What is the risk? Crizotinib is likely to be commercially available in Europe for the treatment of NSCLC very soon. Based on the results of the COG phase I, it is likely that crizotinib may be prescribed off-label by paediatric oncologists in ALCL and neuroblastoma in children. Moreover, parents are likely to ask for crizotinib for their child since detailed information is available on the internet. Another valuable opportunity has been lost to gain highly necessary paediatric data
- We therefore consider that it is not too early to make valid judgements and believe that changes need to be implemented as soon as possible in order to ensure that more can be gained out of the Paediatric Regulation for children with cancer before another 5 years pass.
- We propose:
  - Revocation of the class waiver list
  - PIP and waivers should be based on the relevance of the drug mechanism of action for paediatric malignancies and not on the condition or indication for the drug in adults.

3. THE PUMA CONCEPT: A DISAPPOINTMENT

The Paediatric Regulation introduced a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA). As an incentive to carry out research in the potential paediatric use of off-patent medicinal products that have been authorised for adults, this marketing authorisation offers 10 years of data and market exclusivity to any new off-pat product that has been developed exclusively for use in the paediatric population. Thus, the main goal of the PUMA concept is to stimulate research in existing products. This scheme has been supported in the past by EU funding through the EU Framework Programmes for Research and Technological Development.

However, to date only one paediatric-use marketing authorisation has been granted.

Neither industry nor academic networks have responded to this opportunity as widely as the Regulation intended and aimed for. It would seem that the incentive of data and market exclusivity does not work for those products, or at least that the market opportunities in this sector are currently considered insufficient to outweigh the inherent economic risks of pharmaceutical development.

In terms of output, the PUMA concept is a disappointment.

Consultation item No 3: Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

ITCC comments

- The European Paediatric community welcomed the PUMA concept and identified at an early stage (before the Paediatric Regulation was launched) what the needs for off-patent medicines in paediatric oncology are, through a piece of work performed with the EMA Paediatric Expert Group.
- Cytotoxic chemotherapy drugs are used daily in multi-agent chemotherapy protocols established prospectively through clinical trials run by the Paediatric Oncology cooperative groups. These drugs have been responsible for curing up to 80% of children with cancer. However, most of these drugs are off-patent and used as generics.
- The bulk of information relating to off-patent off-label drugs has been generated through such clinical research programmes. Even though information generated in this fashion has not been included in the SmPC of drugs in most instances, this information is being used daily in standard protocols which are delivered to cure children. Thus the need for new information to be gained from prospective clinical trials was rather limited and this may partly account for a lack of enthusiasm in pursuing this option.
- Three real paediatric needs have been identified for off-patent oncology drugs:
    - Increased knowledge on the pharmacology in young children and infants (below the age of 1 year) in order to improve dosing, tolerance and efficacy
    - Age-appropriate formulations of oral off-patent drugs for which only capsules for adults exist
    - Evaluation of long-term sequelae in survivors following use of such drugs
- Few projects have been launched under the FP7 Off-patent medicines call.
- The real challenge in paediatric oncology is access to innovative therapies and most paediatric oncologists working the area of early phase trials choose to focus their efforts in this area which is regarded as more promising.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS

Within the regulatory framework provided by the Paediatric Regulation, the need to comply with a paediatric investigation plan is subject to the commitment that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations. The main instrument in this regard is the possibility to defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan.

Experience has shown that deferral is a widely used instrument and that in general no delay in the processing of 'adult' applications is encountered. Problems may occur, but only in exceptional cases, especially if a company is late in discussing its planned paediatric research programme with the Agency and the Paediatric Committee. This is also one of the main reasons why the Paediatric Regulation requires companies to submit the paediatric investigation plan no later than upon completion of the human pharmaco-kinetic studies in adults.

Consultation item No 4: Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

ITCC comments

- Based on information from our colleagues in adult oncology, we agree that paediatric obligations have not had a negative impact on timelines in adult development.
- However, our major concern is that the class waivers and the deferral process significantly delay access to potentially effective novel drugs for children and adolescents with incurable progressive disease. Indeed, the initiation of more than 70% of oncology PIPs is deferred and we strongly believe that in the majority of cases such delays can not be adequately justified. This issue contributes significantly to the Paediatric Regulation falling short of what it has promised to deliver.

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

The starting point for the majority of paediatric investigation plans is an ongoing research and development programme for a medicinal product for the adult population. An intrinsic consequence of this approach is that the conditions those products primarily target are adult conditions. They are developed in areas where there is a need (or a market) in the adult population. That need in the older population does not necessarily correspond to the paediatric, population's need.

While the Paediatric Regulation ensures that these future products are screened for their potential use in children, its regulatory framework cannot guarantee that products become swiftly available in all paediatric conditions. Rather, progress in terms of authorised products for use in children depends to a considerable extent on a company's product strategy with respect to the adult population.

It might be argued that this is perfectly normal, as medicinal development is company driven.

Moreover, as in the past, companies will continue to develop products specifically for children. The Orphan Regulation also provides incentives for the development of medicines in areas of unmet therapeutic needs.

It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system. It aims to ensure that every innovation and every new product is screened for its potential use in children so that over time there will be a significant increase in the number of products for which specific paediatric data is available.

Consultation item No 5: Do you have any comments on the above?

ITCC Comments

- We fully agree that the development of new drugs is driven by the pharmaceutical industry and that the Paediatric Regulation does not aim to replace an established system of medicinal product development by a new regulatory system.
- We very strongly believe that medicinal development in children should meet the real needs of children. Early collaboration between companies and paediatric cooperative groups is the best way to design and execute a PIP which will benefit children, can be delivered on time, will be feasible and eventually lead to a European regulatory approval.
- The opinion of expert paediatric oncology cooperative groups should be sought more frequently by the regulatory authorities.
- The implementation of the Paediatric Regulation simply ignores the fact that the same drugs are used on a daily basis to treat adult and paediatric cancers, for different

indications, for example, cyclophosphamide and doxorubicin are used for the treatment of breast cancer (which does not exist in children) as well as on the treatment of paediatric malignancies such as neuroblastoma, rhabdomyosarcoma, Ewing and osteosarcoma.

- Driving the PIP process through the adult condition and indication of a drug has had a major negative impact in paediatric oncology and this needs to be rectified urgently
- The current Paediatric Regulation may also act as a potential disincentive for the paediatric development of new drugs in some instances. Pharmaceutical companies are less inclined to support investigator studies, as these may indicate efficacy in children of an agent with an "adult only" indication, thereby requiring a full PIP evaluation.
- One of the major unintended consequences of the need for PIPs is a **delay in companies initiating early phase clinical trials** in the US and in Europe. PIPs require a very detailed and complete development plan, rarely even through to phase 3 trials, to be reviewed and approved before any paediatric clinical data exist. Commitments that extend to such levels before there is any paediatric experience does not meaningfully advance the field, as it is the early phase clinical data that can and should inform on whether a drug should be fully developed, and if so, how. The result is that companies may delay initiating phase 1 plans while developing complex later phase development plans without underpinning such plans with key data.
- Thus, **at this time, the implementation of the Paediatric Regulation has not succeeded in** *"ensuring that every innovation and every new oncology product is screened for its potential use in children so that over time there will be a significant increase in the number of products for which specific paediatric data is available*".

6. THE BURDEN/REWARD RATIO —A BALANCED APPROACH?

There can be no doubt that the Paediatric Regulation places a considerable additional burden in pharmaceutical companies with its obligations regarding research in products for use in children. However, this approach was adopted because market forces alone had proven insufficient to stimulate adequate research.

At the same time the Paediatric Regulation introduced a number of incentives intended to offset the additional burden, at least partially. One of the main incentives is the 6-month extension of the Supplementary Protection Certificate. While it is too early to assess the economic impact of the rewards — a topic which will be covered in a second Commission report due in 2017 (Article 50(3) of the Paediatric Regulation) — the European Medicines agency and its Paediatric Committee have made acknowledged efforts to simplify the, regulatory process wherever possible and within the limits of the regulatory framework. In addition, information is published systematically and Questions and Answers documents are updated for frequently asked questions.

Consultation item No 6: Do you agree with the above?

ITCC comments

- From our understanding, regulatory obligation has been the main driver of the PIP activity while the positive impact of effective rewards cannot be assessed at the moment.
- We acknowledge that information is available about agreed PIPs on the EMA website. However, the information is summarized far too much and more detail should be made public. It is, sometimes, difficult to understand the differences between two PIPs when they address the same disease or involve same type of compound. The entire process would gain in efficiency and transparency if the full content of PIPs were to be made available and not only the title of the studies to be conducted.

- We believe that information about all PIPs that have been submitted should also be published. At this time, companies can and frequently withdraw their PIP application before day 120 of the PIP process if a negative opinion by the PDCO is likely or pending. It would be far more helpful to the paediatric oncology community and to patients if pending negative opinions were also published. This could appropriately encourage companies to put forward better PIPs rather than attempting to get away with the bare minimum needed to fulfill regulatory requirements.
- In addition, we believe that PIPs are much too detailed overall. The process is still too complicated and takes too long. Indeed, the burden of the current process is very high and is paradoxically a disincentive for companies to evaluate drugs in children.
- We recommend a faster simpler process is introduced, so that the burden is less for companies, as well as for the PDCO. We believe this would benefit children with cancer.
- We believe it is time to have a global analysis of the content of oncology PIPs that have been approved thus far in order to make the modifications needed to improve the entire process and better meet the paediatric needs. A meeting with EMA, PDCO, Cooperative Groups and Pharma is worth considering. Such meetings are regularly held by the FDA (Paediatric Oncology Drug Advisory Committee). The aim of such meetings would not be to criticize the work done so far by any stakeholder. Indeed, all stakeholders are on a learning curve, but there is a real opportunity to share and learn from the lessons of the past for the future implementation of the Paediatric Regulation. and for the benefit of children with cancer

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

To provide better information on the use of medicinal products in the paediatric population, Article 45 of the Paediatric Regulation requires companies holding data on the safety or efficacy of authorised products in the paediatric population to submit those studies to the competent authorities. In this way the data can be assessed and, where appropriate, the authorised product information can be amended. Additionally, Article 46 of the Regulation requires companies to submit newly generated paediatric data.

Since 2008 more than 18.000 study reports on roughly 2 200 medicinal products have been submitted to the competent authorities, revealing the large amount of existing paediatric information available at company level.

These study reports have been, and continue to be, assessed by the competent authorities thanks to an impressive work-sharing project. This has led to the publication of assessment reports covering more than 140 active substances and, in a considerable number of cases, to recommendations for changes to the summary of product characteristics of authorised product.

While competent authorities are empowered to vary marketing authorisations as a result of the assessment, marketing authorisation holders have shown little interest in updating the summary of product characteristics and product information on a voluntary basis5.

Nevertheless, the requirements of Articles 45 and 46 have provided an efficient and appropriate instrument for collecting existing paediatric studies and reaping the benefits.

Consultation item No 7: Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?

ITCC comments

- The purpose and principles of Article 45/46 of the Paediatric Regulation are understood and largely supported by the paediatric oncology community, and it is recognised that a vast amount of work has been done on the parts of pharmaceutical companies and by regulatory authorities in attempting to collate and publish information on previous paediatric studies and medicine usage. However, this is extremely time-consuming and labour-intensive, and there is clearly an enormous backlog of information yet to be published, so it may not yet have reached the stage of being considered 'efficient and successful'. It is key that even negative results and information are published.
- We have little visibility thus far of the concrete output from the huge activity that has been performed both by EMA and pharmaceutical companies to comply with articles 45/46
- Additionally, oncology products are authorised centrally and so the paediatric oncology community may have expected to have access to more paediatric information about cancer drugs than is currently available in the public domain. It is critical that this information is made public as soon as possible, in order to avoid duplication and unnecessary trials in children, one of the key aims of the Paediatric Regulation.
- As a community we are extremely keen to prioritise early access to novel drugs for paediatric cancer patients, but are, in parallel very concerned about having adequate mechanisms in place for the accurate collection of long term outcomes and safety data, since as more children are cured and become long term survivors, the quality of this survivorship becomes more critical.
- Drug companies generally face difficulties in collecting long-term data as necessary, and mandated in PIP the long-term measures. This is partly due to the added expense and practicalities of collecting such data, and partly because they can claim rewards earlier for completion of PIPs without such long-term measures. The community would like to see robust regulatory mechanisms in place to facilitate collection of such important long-term safety and outcome data, as well as clear obligations for new and emerging information to be included in product information (Summary of Product Characteristics).
- To this extent, The Europe Paediatric Oncology has a long track record, skills and expertise in the field of follow up of patients being cured in order to explore the long-term effects of therapies. We believe that three is a need for a academic platform to set up prospective follow up of children exposed to new drugs. Such a platform, in partnership with Pharmaceutical companies, will be able to generate data according to the long term measures that are included in most oncology PIPs.
- The key challenge in pediatric oncology is to adequately address information on all new compounds and to set up a strategy that will increase the activity in the early phase for patients with life-threatening relapsed or refractory malignancy. We would caution against spending too much time and effort collating information on old cytotoxic agents, which the pediatric oncology community has vast experience in using safely, at the expense of focusing on new agents.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Some studies published in the medical literature suggest a lack of recognition by general practitioners of the actual amount of off-label prescribing to children6. It is argued that paediatricians are not always aware of the off-label status of the products they prescribe or that they do not consider that some of the frequently used medicines for children are in fact not authorised for use in this age group.

Moreover, it is claimed that the prescribing habits of practitioners are often strongly, influenced by personal experience rather than by evidence-based information.

Such observations may point to a significant hurdle to achieving the goal of the Paediatric Regulation, that is to reduce the amount of off-label prescribing. If the instrument is to be a success, it is necessary not only that the data on the use of a specific product in the paediatric population is assembled, but that this data is then also appropriately communicated to, and used by, paediatricians in their day-to-day practice for the benefit of their patients.

National competent authorities as well as healthcare professional organisations would seem to be specifically qualified to consider appropriate ways of ensuring an adequate flow of information. On their own, the regulatory instruments provided by the Paediatric Regulation seem to be reaching their limits here.

Consultation item No 8: Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

ITCC comments

- In paediatric oncology, healthcare professionals are receptive to new scientific information and eager to propose safe and effective innovative treatments to children who still die of cancer.
- Whilst it may be true that some health professionals and even paediatricians in certain specialty areas lack awareness with regard to the extent of off-label prescribing, such statements generally do not reflect the experience of the paediatric oncology community internationally, who are usually all too aware that they are prescribing off-label due to a shortage of necessary and available information and of products authorised for paediatric use; yet are faced with paediatric cancer patients who need to be treated. Such prescribing is usually carried out on the basis of best available evidence, be that extrapolation from adult data or by compilation of available evidence from (often limited) paediatric data available.
- By virtue of the rare population of children we treat, the paediatric oncology community has a long and successful history of conducting collaborative clinical research at both national and international levels and are extremely interested and engaged in such research.
- It is critical that pharmaceutical companies are encouraged/obliged to engage with such networks of experts at an early stage in a drug's development processes to ensure that appropriate trials and compounds are prioritised based on unmet paediatric needs; healthcare professionals are far more likely to be engaged in research which they believe is relevant, necessary and likely to answer priority questions and lead to meaningful results. Engagement with network experts by regulatory authorities at early stages, such as via existing initiatives (such as the Paediatric Task Force at the EMA) is welcomed and should be further built upon.
- Such highly organised European international networks (e.g. ITCC, tumour specific groups such as the International Society Paediatric Oncology European Neuroblastoma Group (SIOPEN), European Paediatric Soft Tissue Sarcoma Study Group (EpSSG), the IBFM group in leukaemias and the overarching European Network for Cancer Research in Children and Adolescents (ENCCA) contribute actively to and are very receptive to receiving new scientific information and can also act as essential channels for

dissemination of such new information; thus dissemination of information can be successfully achieved via both national and international routes.

- Paediatric oncologists are still in a situation of prescribing off-label new drugs (which are commercially available) to children with life threatening diseases and no curative therapeutic options because those drugs are not available in early clinical trials.
- The Paediatric Regulation was expected to significantly increase the number of new drugs in early clinical trials and to provide access to innovation for patients in a safe and controlled way.
- The Regulation appears to have failed in this area since there is no significant increase in early clinical trials, yet.
- Thus the off-label used is still important and the introduction of effective targeted agents on the market is likely to continue to increase off-label use of promising drugs (with information available on the internet for the parents) in paediatric malignancies.
- Thus, the European paediatric oncology network is well organized and can deliver within scientifically relevant PIPs that are designed to adequately meet paediatric needs. We believe and have demonstrated that new drug development and clinical research on therapeutic strategies in paediatric oncology must be developed at the European level, and in some cases (e.g. for very rare tumours), at the international level.
- **Healthcare professionals in paediatric oncology are very much interested and engaged in clinical research.**

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

In order to compile additional data on the use of products in children, medicinal products need to be tested more frequently in the paediatric population. It is therefore quite likely that the Paediatric Regulation will lead to more clinical trials in that population.

The figures in the EudraCT database7 do not yet show an increase in paediatric trials. The number of paediatric trials remained stable between 2006 and 2011, hovering, with some ups and downs, around an average of 350 trials per year. It should be pointed out, however, that EudraCT is limited to clinical trials that commence in the European Union and that while the number of paediatric trials remained stable, the number of clinical trials in all populations decreased between 2007 and 2011.

It is also generally accepted that the aims of the Regulation should be achieved without subjecting the paediatric population to unnecessary clinical trials. There is therefore a continuous effort to explore alternative means, e.g. the use of extrapolation of efficacy8.

Especially sensitive are the youngest paediatric age subsets, including neonates. It will be a continuous challenge to balance the therapeutic needs of those age groups against their specific vulnerability when reflecting and deciding on the appropriateness of specific clinical trials or about the specific settings of any study in that population (subsets).

Another challenge is how to avoid duplicating trials for different paediatric investigation plans from different applicants. Companies embarking on product development in similar areas may be required by an agreed paediatric investigation plan to conduct studies within similar settings. While this seems to be a way of avoiding discriminatory treatment between different companies, it may potentially lead to a duplication of trials which from a scientific point of view would be unnecessary.

Here, the key to avoiding such unnecessary trials is transparency with regard to ongoing and completed trials.

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

ITCC comments

- After 5 years of implementation of the Regulation, there is no significant increase in the number of paediatric phase I and II trials of oncology drugs. This is a major concern. Most European children with life-threatening malignancies are still denied access to innovative therapies within clinical trials.
- Under the EU clinical trial directive, the obstacles for initiating clinical studies in children are very important and formidable. The development of clinical trials is much too slow and the requirements mean that early clinical trials are not easily achievable at least in the academic setting. This impacts immensely on investigator-driven clinical trials. Thus there is a major need for a Clinical Trials Regulation that facilitates academic trials.
- The number of paediatric trials is not the best measure of success of the Paediatric Regulation. Better ultimate metrics are the number of:
    - Drugs that have reached phase III trials;
    - Drugs that have reached clinical use;
    - First-in-child studies that have been conducted in Europe;
    - Academic early clinical trials;
    - Companies that have provided cancer drugs for academic early clinical trials (and also for academic preclinical studies);
- Trials in extremely rare paediatric diseases, such as gastrointestinal stromal tumour (GIST), melanoma or chronic myeloid leukaemia (CML), have been (perhaps unintentionally, but still inevitably) promoted by the Paediatric Regulation.
- The Paediatric Regulation has not facilitated the access to new medicines for children with cancer within the context of clinical trials. There remains a significant inequity in access to clinical trials across the 27 EU member states.
- For paediatric oncology, the Paediatric Regulation has not made a significant contribution in increasing knowledge about the pharmacokinetics of anti-cancer drugs in infants and neonates, a clear need.
- Extrapolation has only been used for infrequent paediatric conditions such as melanoma, but it has not benefited the far larger population of children with more common childhood cancers (for example neuroblastoma and sarcomas).
- Overall, the regulatory burden has made the development of new drugs within academic settings impossible. Using the same regulation and criteria for a first-in-child trial as for a trial with a new schedule of cyclophosphamide or a dose reduction of a schedule used for 30 years does not seem appropriate.
- The issue of pharma competing with drugs against the same targets is important in Paediatric Oncology, especially when several companies are developing those targeted drugs in an adult condition in a competitive setting and they are expected to run a PIP for each of these drugs in these diseases occurring extremely rarely in children. The best example is CML in children, with at least five different PIPs already approved because CML in adults has been a field of intensive drug development since the imatinib proof of concept.
- There is thus **the key question of prioritization** in an area where patients are rare and there is no need to develop “me too” drugs.

- This question of prioritization is difficult to answer in the current context of implementation of the Regulation.
- We believe that this could be best addressed by taking into account that developing new drugs for children with cancer is a non-competitive or pre-competitive approach rather than a competitive approach.
- We should aim to avoid a situation where pharmaceutical companies would compete to have access to rare or very rare patients in order to comply with PIPs for similar drugs against the same target.
- This could be addressed in multi-arm, multi-pharma trials.
- We believe that the opinion and advice of expert EU cooperative groups should be taken into account at an early stage in the prioritization process.

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

The Paediatric Regulation requires companies to submit paediatric investigation plans at an early stage of product development (end of 'phase I'). However, research in some active substances which have completed phase I may be discontinued at later stages, if further studies fail to show potential with respect to the safety and efficacy of the product. For every, successful authorised medicinal product there are many that fail to make the finishing line.

Hence, not all approved paediatric investigation plans will be completed, as companies may decide to stop the corresponding adult development. It is too early for reliable statistics showing the ratio between completed and non-completed paediatric investigation plans, but in the current context it is an unavoidable fact that not all approved plans will eventually result in an approved medicine with a paediatric indication.

In terms of output, this leads to some unnecessary efforts involving the compilation and screening of paediatric investigation plans. On the other hand, early submission of and agreement to the paediatric investigation programme is necessary for the paediatric development to fit smoothly into the overall product development.

Consultation item No 10: Do you have any comments on this point?

ITCC comments

- We acknowledge that some oncology PIPs will not be completed because the drug will fail in adults and development will be stopped by the pharmaceutical company.
- This is again a concern if a strong rationale (based on tumour biology) to further develop in a paediatric malignancy exists.
- Considering paediatric development at the end of phase I in adults is still regarded as very early Considering paediatric development at the majority of pharmaceutical companies given that a large proportion of drugs will not be developed further (80 to 95% of drugs in phase I trials will not reach a Marketing Authorisation). Companies are only starting PIPs when proof-of-concept studies have been completed and the decision to start phase III in adults is taken, or even when the phase III trials are ongoing and filing is planned. This situation needs to be improved.
- Clearly providing early access to drugs for childhood cancers has the risk of attrition. The parents and academic community are aware of this risk, but it is still preferable to explore new drugs earlier rather than waiting five years until Marketing Authorisation is reached while children continue to die.

- IGF-1R inhibitors are an example: they have shown efficacy in Ewings sarcoma, one of the commonest childhood and adolescent sarcomas and have provided significant benefit to a small proportion of patients (approximately 10%). The development of most IGF-1R inhibitors has been discontinued because of failure in randomised phase III trials in lung cancer. No PIPs have been delivered in this area. Although there are no agents currently authorised, many patients have benefited from those still clinical trials and successful IGF-1R inhibitors will be further explored in this setting.
- There should be incentives for repositioning such drugs within the paediatric oncology setting, where they could fulfil unmet paediatric needs.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

The Paediatric Regulation has led to the establishment of a comprehensive network of expertise within the European Union in paediatric matters, with the Paediatric Committee at the forefront bringing together a high level of expertise and competence in the development and assessment of all aspects of medicinal products to treat the paediatric population.

Additionally, the European Network for Paediatric Research at the EMA (Enpr-EMA) was established in 2009. This is a unique European network of national and European networks, investigators and centres with specific expertise in the design and conduct of studies in the paediatric population.

The adoption of the Paediatric Regulation has acted as a form of catalyst, gearing up and coordinating expertise and bringing the topic of medicines for children to the fore.

Consultation item No 11: Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise n the European Union?

ITCC comments

- ITCC was created in March 2003 to anticipate the EU Paediatric Regulation. Indeed, the goal was to build a network of expert centres in Europe able:
    - to run a biological and pre-clinical program in order to prioritize drugs for paediatric development;
    - to run early phase trials (Phase I and II) of innovative medicines
    - to take into account the unique dimension of evaluation of new treatments in children with life-threatening malignant diseases
- We anticipated that, under the Regulation, Pharma would need access to expertise, patients and qualified centres to efficiently run their early trials according to GCP, in Europe. We anticipated there would be a significant increase in early trials in Europe due to the Paediatric Regulation.
- The ITCC is now an appropriate source of contacts, expertise and capacity to run early trials which are included within in PIPs as well as capacity to innovate in design and methodology and to run search and validation programs of biological targets.
- The ITCC has developed joint collaborations with the European Tumour Groups (running late phase II and phase III trials). Indeed, there are also a number of other very well established networks of expertise (tumour specific groups e.g. International Society Paediatric Oncology European Neuroblastoma Group (SIOPEN), European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) and the overarching European Network for Cancer Research in Children and Adolescents (ENCCA).

- Thus, full development of a PIP is feasible within Europe through a network of qualified centres with experts who have been accustomed to running clinical trials for the last 40 years and who are eager to propose new drugs and trials to their patients.
- Thus **the Paediatric Regulation contributed to the establishment of the ITCC network BEFORE it was launched, since the** Paediatric Oncology community was expecting the Regulation whilst the project was being developed by the European Commission.
- The Paediatric Regulation has not contributed to the establishing of a framework of expertise for paediatric oncology.
- This is the reason that our concern that the Regulation has not adequately delivered in the field of paediatric oncology (for the reasons described above) is so deep.

12. ANY OTHER ISSUE?

Consultation item No 12: Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?

ITCC comments

- We acknowledge that the Paediatric Regulation has significantly changed the field of paediatric development of new oncology drugs with, on one hand, more interactions between cooperative groups and pharma, and on the other hand, an enormous amount of activity under the auspices of the EMA and the Paediatric Committee. This is illustrated by the more than 45 PIPs for 43 oncology drugs approved thus far.
- However, the implementation of the Regulation does not reflect our initial understanding and our expectations. The major issues are:
    - there has not been better access to new drugs for children with cancer;
    - there has been no significant increase in the number of drugs in early trials and hence;
    - a number of important drugs have not been studied in children because of waivers granted based on their “adult” conditions and indications;
    - there has been no impact on the off-label use of commercially available from drugs in children with non curable life-threatening malignancies;
    - the agreement of barely feasible or unfeasible PIPs in some extremely rare diseases whilst paediatric malignancies with major needs are not a being addressed at all;
    - in deciding and agreeing the content of PIPs, the ongoing and planned therapeutic strategies developed by cooperative groups are not adequately taken into account, especially when phase III trials in newly diagnosed patients or patients at first relapse are concerned;
    - the Paediatric Regulation has not resulted in major improvements in gaining paediatric information and knowledge of drugs with existing Marketing Authorisation;
    - early clinical trials in paediatric oncology run by “academic“ sponsors now face significant logistical and operational difficulties and it has become very difficult to have early access to new drugs for academic phase I studies. This is due to the fear that these studies will increase the risks for the PIPs, which in turn will

affect the whole development of the agent if academic studies are not adequately delivered or demonstrate unexpected efficacy.

A significant change in the implementation of the Regulation is needed.

We propose:

- Revocation of the class waiver list
- PIPs should be based on the relevance of the drug mechanism of action according to paediatric tumour biology and not on adult condition/indication.
- The content of a PIP should better take into account the therapeutic strategy run in each disease by the cooperative groups. They should not mandatorily include the phase III development in newly diagnosed high-risk patients or in first relapse.
- The use of innovative methodology and designs to speed up development should be improved, and better use should be made of extrapolation from adults to children, when relevant.
- Consider multi-drug studies (from several PIPs) within the same trials and multi-company trials in a pre-competitive and non-competitive approach.
- Simplify and shorten the PIP evaluation process and approve less detailed PIPs that include the necessary flexibility for an efficient drug development process.
- Make public the full content of PIPs
- Set up a prioritization process that will include input from the pediatric oncology cooperative groups at an early stage.
- Set up workshops with all stakeholders simultaneously to look anonymously through the oncology PIP strategy run by EMA and PDCO during the last 5 years in order to draw lessons and improve the process, altogether.
- The Clinical trial Regulation under discussion at the EU parliament must facilitate the implementation of investigator-driven clinical trials.

Major gaps to be filled:

- Europe should consider paediatric oncology as an unsolved public health issue and invest in clinical research and cooperative networks because the Paediatric Regulation can and will, for sure, contribute to increase cure rates and quality of cure but will not be at all sufficient to achieve these aims without such investment.
- There is no incentive for the development of drugs targeting specific paediatric targets that do not occur in adults.
- There is no incentive for repositioning a drug that fails in adults for development in paediatric malignancies.
- The involvement of cooperative groups should be significantly increased in the process and should be at a far earlier stage
- Patients and Parents associations should be partners in research.

ITCC is not asking for a cancellation of the Regulation, which is regarded as an ambitious and inspirational piece of legislation, but strongly believes that changes in its implementation are urgently needed and feasible in order to ensure that the Regulation can adequately help meet the needs of children and adolescents with cancer.