**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**

## ANSWER FROM PARENTS ORGANIZATIONS

**This is a collective answer to the Public Consultation co-signed by :**


- Patricia Blanc, President IMAGINE FOR MARGO – Children without cancer, France
- Marianne Naafs-Wilstra, President ICCCPO International Confederation of Childhood Cancer Parent Organizations, Netherlands
- Nancy Goodman, President Kids v Cancer, USA
- Denis Strangman, Chair, IBTA International Brain Tumor Alliance, England and Wales
- Simon Davies, Chair, CANCER 52, UK
- Serge Grilhault des Fontaines, President Fédération ENFANTS et SANTÉ, France,
- Servanne Jourdy, President l'Etoile de Martin, France,
- Lucie Fagedet, President Tous avec Clément , France

PARENTS ORGANIZATIONS PRESENTATION

**IMAGINE FOR MARGO – Children without cancer**

is actively acting to develop new drugs in Europe for kids and adolescents with cancer, in partnership with ITCC ( Innovative Therapies for children with Cancer) which is an European network of researchers in 42 centers of 7 European countries.

P Blanc attended the December 2011 BDA 1st paediatric oncology workshop on New oncology Drug development in children and adolescent in Europe and was invited at the European Parliament on February 15, 2012 to advocate on the Pediatric Regulation.
*See www.imagineformargo.org*

**International Confederation of Childhood Cancer Parent Organizations**

represents 158 parents associations in 86 countries worldwide- of which 30 countries in Europe and 20 countries of those belonging to the European Union.

ICCCPO is working closely together with physicians and scientists in paediatric oncology in order to improve the situation for children with cancer in Europe as well as world-wide.
See *www. icccpo.org*

**Kids v Cancer**

is an American organization focused on changing the landscape of paediatric cancer research.

Nancy Goodman authored and championed the Creating Hope Act, signed into law on July 9, 2012 (as section 908 of the FDA Safety and Innovation Act of 2012).
She is also very active in promoting US and EC Regulatory compatibility in drug development . *See www.kidsvcancer.org*

**The International Brain Tumor Alliance**

is a not-for-profit organisation registered in England and Wales. The IBTA is an alliance of support, advocacy and information groups for brain tumour patients and carers around the world and also includes researchers, scientists, clinicians and allied healthcare professionals who work in the field of brain tumours. See www.theibta.org

**CANCER52 (C52)**

Cancer52 represents 61 members (as of last quarter 2012) united in improving the future for everyone affected by rare and less common cancers, which account for more than half of all cancer deaths in the UK. C52's overarching vision is that it becomes the 'go to' organization of choice for rare and less common cancers for all stakeholders. *See www.cancer52.org.uk*

**Fédération ENFANTS et SANTÉ**

is a national organization gathering 13 regional associations in France.

The federation is funding 1 million euros per year for the development of clinical and biological research for 30 paediatric oncology centers in France.
See www.enfants-sante.asso.fr

**Etoile de Martin**

Is a major contributor to paediatric oncology research mainly at the Institute Gustave Roussy, (Villejuif, France) and is acting for the well-being of hospitalized children.
*See www.letoiledemartin.org*

**Tous avec Clément**

is acting actively to raise awareness on kids cancer and is doing actions to benefit the Institute Gustave Roussy research center (Villejuif, France) for children and adolescents with cancer. See www.tousavecclement.jimdo.com

**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?**

We do agree that the Paediatric regulation has paved the way for paediatric development, thus, forcing pharmaceutical companies to indicate any potential paediatric use.
But it has not made paediatric development an integral part of the overall product development in the European Union.

To date, parents who want their children to have access to innovative treatment fail to have a chance.

**Paediatric regulation seems to be only a regulation to which companies are obliged to answer rather than a programme developed on the basis of a scientific evidence.**

There is no strategy to address the drug development life cycle as for the adults: the lack of any paediatric investigation plan (PIP) witnesses this.

Nearly no pharmaceutical companies have any specific budget for paediatric oncology development.
In order to reduce costs, **Pharmaceutical companies are willing to present Paediatric Investigation Plan as late as possible in the drug development process**; this is creating delay for product development and this is some potential paediatric use not analysed as the later you make the study, the less potential paediatric active substance you have left.

What we propose:

-Create financial sanctions for a PIP not submitted on time or a more significant incentive for early start
-Develop a new drug development strategy to address specific scientific and medical needs; Healthcare professionals and pharmaceutical industries to get together and discuss the priority and possible paediatric use of active substance in the pipeline or rejected after phase 1 process.
-Lighten up the PIP process and review PIP model

## 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?**

**We do not think it is too early to judge**.

The Paediatric Regulation does not give the expected benefits in paediatric oncology and **majors improvements need to be done**.

- Statistics already show that there are less PIP than before and most of them are not completed (only 11 approved PIP in paediatric oncology since 2007).
- Anticancer drugs are still mainly off label drugs
- **The class waiver concept is unacceptable** since it "adopts a list of conditions that occur only in adult populations". This definition shows the intrinsic limits of the class waiver since these conditions do not forcibly occur in pediatric cancers

  This is clearly and completely contradictory to the idea of developing innovative therapies in pediatric oncology
- The delay in accessing to innovative therapies forces parents to turn elsewhere by making the so called western hope rush in order to find new opportunities for their children.

What we propose:

**-Time is a major concern**: We have tragic figures on paediatric cancer and kids are dying each day.

Remember the figures for children and adolescents with cancer:

-Cancer is the leading cause of death from disease in children
-15 000 kids are diagnosed each year in Europe
-25% will die within 5 years of diagnosis

-Many may relapse after 5 years and most will be left heavily handicapped due to treatment toxicity
-Decrease in cancer mortality remained stable for the last 10 years
-Kids cancer increases by 1% per year, and by 1.5 % per year for adolescents.
-23% of survivors will require lifelong treatment

Most survivors will be more or less handicapped adults to integrate into our society (for example 1 adult out of 1500 is a survivor of a brain tumour) and the death of a child has a devastating effect on families and the people around them.

**We can not just wait for another 5 years to change the law and make any improvement in the drug development process.**
**This is a global Public Responsibility and a Public Health issue**

**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?**

We know and we experienced that many drugs are off-patent and used as generics

We do not know if the PUMA concept can provide a solution since it does not solve the possibility to access to innovative therapies.

## 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.**

We believe that paediatric obligations did not have impact on timelines in adult development.

But **the class waiver concept is strongly disappointing** since **it significantly delays the access of children affected with incurable progressive disease to innovative therapies**

## 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?**

- We fully agree that It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system.
- As of today, paediatric product development is dependent on adult development and the **Paediatric Regulation is not an incitation nor an obligation to develop paediatric product based on Paediatric needs**.
- If the Paediatric Regulation is an incitation to develop new paediatric product, it is an absolute fact that **it is leaving aside numerous children with cancer**.
- We believe that **the approach adopted for adults should not guide the process in paediatric oncology. This is a major mistake**.
- The PIP should be designed by taking into account the scientific rationale that lies on the advances in the discovery of the inner mechanisms of paediatric cancers
- Also, in order to be timely approved and completed, **PIP should be designed in an early cooperation between companies and healthcare professionals**

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

There can be no doubt that the Paediatric Regulation places a considerable additional burden on 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?**

**The administrative burden created by the regulation is a key issue that could be improved starting now.**

- Statistics show that PIP preparation has lead to more administrative tasks and increase of staff.
- EMA and its Paediatric Committee have already started to simplify the PIP process, this is good and this should continue as much as possible.

- EMA announced in September 2012 the revocation of the class waiver list that was negatively impacting the development of new oncology drugs for children; this is a good decision

What we propose:

-Simplify the PIP process: standardize PIP model, electronic format in an electronic database easy to share between member states.
-Only ask for agreement from member states in which the Clinical Trial will be done and not from all member states

## 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?**

No specific comment

## 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?**

- If healthcare professionals are not aware that most of the drugs they prescribe are not authorised for use in this age group, it is then even more important and a key public health responsibility to encourage and oblige paediatric drug development in a safe and measurable environment which is not the case today.

- As parents and parents' representatives, even if we trust our doctors, it is unacceptable to learn that most oncology drugs are « off label », meaning not formally authorised for children as they have not been tested in a secure and measurable clinical trial.
  They are then given by reliance on personal experience and not by using evidence-based information.

## 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?**

- We do not accept the comment that there are no specific problems detected for clinical trials with children;

- The number of clinical trials has decreased since the new regulation.
- This means that there are less innovative and specific drugs for children with cancer.
  -We still have children given old chemotherapy, mostly given to adults
  -We have new standard protocols approved by the FDA in the US, but not authorized on a timely basis in Europe
  -We still have many more paediatric clinical trials in the US than in Europe
  -We still have to look for innovative treatment in the US even though we have some of the best research centres and researchers in Europe.
  -We still have duplication of clinical trials

What we propose :

-a global updated registry for on-going clinical trials
-a better cooperation between EU EMA and the FDA in order to speed up the authorisation process for new approved drugs /protocol and to harmonize regulation
-Proceed with clinical trials on an European scale
-Create a European foundation for clinical trials funded by the European Union

## 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?**

If a PIP is approved but the active substance is discontinued, it is a major concern to find a way to avoid unnecessary effort

What we propose:

-Pharmaceutical industries and healthcare professionals to collaborate from the beginning (pipeline) on the active substances strategy to have successful PIP
- Free access to drugs for investigators: pharmaceutical companies to give the discontinued substance to healthcare professionals for further analysis with pre-approval to market the product in case paediatric potential is confirmed

## 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?**

No specific comments

**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?**

The Paediatric Regulation is a good improvement and has positive effects, but **there is a need for significant improvement that should not wait the 2017 review**.

Our concern, as parents' representatives, is that **progress is very slow** and that, with the difficult economic situation, pharmaceutical companies are going to disregard even more paediatric product development.

In this context, the Paediatric Regulation is a determinant factor to improve the situation

In international oncology congress and workshops with academia, pharmaceutical industries, and regulators, we can clearly see that progress has been made, in term of awareness and willingness to make progress, but there is still a long way to go in terms of:

-Increasing early access to drug development
-Better prioritizing drug development
-Improving cooperation between regulators, pharmaceutical industries and healthcare professionals to clinical development.

**We need you to create and adapt a legal framework that will lead to an efficient European cooperation that not only will speed up the process, but will also lead to the development of more specific and innovative drugs for our kids.**

**As parents' representatives, we urge you to make it happen.**