Document code

Public Consultation on Paediatric Report: the joint GRIP response

GRIP

Global Research in Paediatrics

Network of Excellence

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1. GRIP – Global Research in Paediatrics

The "Global Research in Paediatrics – Network of Excellence (GRiP)" (www.grip-network.org) is an EU-funded project [Seventh Framework Programme: FP7/2007-2013, Grant Agreement n° 261060], started on 1 January 2011 and expected to last until 31 December 2015.

GRIP is aimed at implementing an infrastructure matrix to stimulate and facilitate the development and safe use of medicine in children. This implementation entails the development of a comprehensive training programme and integrated use of existing research capacity, whilst reducing the fragmentation and duplication of activities.

Implementation of paediatric studies requires well trained researchers, investigators and other experts in number and capacity that currently do not exist. GRIP intends to address this problem by developing, as its main objective, a joint paediatric clinical pharmacology training program in collaboration with International stakeholders.

In addition, GRIP promotes sharing of best practices in research, including methodologies and research tools that can be used not just across the Atlantic, but globally. Central to these efforts are activities that evaluate methodologies and research tools that are implemented following GRIP recommendations in a manner that reflects the needs of researchers (including industry) and patients. That is, GRIP will pay close attention to knowledge translation, exploitation and mobilization.

Reaching these objectives requires close collaboration between paediatric health professionals, academics and representatives of the pharmaceutical industries, ethics bodies and regulatory authorities. That is why GRIP is built upon existing European and US excellence and includes partners with direct and strong links in training and with other paediatric research networks. Overall GRIP mobilizes 21 partners from Europe, the NICHD-NIH representing a network of US institutions and the FDA, the NCCHD in Japan, the Hospital for Sick Children in Toronto, Canada, and the WHO. This will allow the mobilization of a total of more than 1000 Institutions worldwide who are linked to the partners affiliated networks or initiatives.

2. AIM OF THE DOCUMENT

To provide comments and suggestions on the consultation paper 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' (SANCO/D5/FS/(2012)1251190), released by the European Commission.
This document is prepared in order to respond to the twelve statements on possible lessons learnt from the first years of application of the Paediatric Regulation.

3. EXPERIENCE ACQUIRED/LESSONS LEARNT

The joint GRIP input is reported for each of the statements included in the consultation paper.

3.1. 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?

The GRIP network agrees that the Paediatric Regulation has **paved the way for paediatric development**:

1. **paediatric development** represents now **a key element** during the development for new "unauthorised" medicinal products and for any requests of new indication, new route of administration or new pharmaceutical form for in patent authorised medicines.

2. The **topic** has been **increasingly discussed** during scientific meetings, professional courses, and is became also a popular topic in the general and specialized press. The knowledge on paediatric trials and the related regulatory aspects is profoundly changing and there is a better understanding of the difference between a well conducted scientific research and research resulting in a new paediatric medicine approval.

However, even if Pharmaceutical Companies are now fully aware that paediatric development must be always considered and included in the R & D process, there is currently **little evidence that Companies are actually performing clinical trials** (e.g. no correlation between the number of clinical trials agreed in PIP and the number of clinical trials included in EUDRACT database).

3.2. 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[1]. 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?

The objectives of the Paediatric Regulation are to stimulate research and to generate data that will enhance the information that will become available and will be incorporated in the patient leaflets for medicines used in the paediatric population. Overall, the Paediatric Regulation outputs to be delivered are several.

Clearly **we agree** that it is **too early to predict** how many agreed PIPs will be completed and there is still limited evidence on increased numbers of new paediatric medicines, new paediatric indications and age-appropriate new pharmaceutical forms.

But on the other hand, we should **acknowledge** that **some outputs** guaranteeing information, transparency and stimulation of research **have been successfully** delivered:

- the procedure to evaluate the PIP was implemented in short time at the EMA;
- a huge amount of paediatric data submitted in accordance with art. 45/46 was collected and made public, even if not yet all evaluated;
- the first European network of national and European networks was set up (EnPREMA)
- public information on paediatric clinical trials are available in the EUDRACT database.

[1] EMA-PDCO report, p.9.

3.3. 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-patent 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?

The GRIP network agrees that the **PUMA incentive has been unsuccessful**: only one product has been granted a PUMA in 5 years!

From the **Pharmaceutical Companies perspective** it seems that the PUMA benefit of **10 years of market protection** as a reward for the development in children is **an unattractive incentive**. The main reason for this failure is that such incentive does not protect pharmaceutical formulations and forms and **will not prevent healthcare professionals** to prescribe other products containing the same off-patent active substance in an **off label** manner, unless it is developed in an *ad hoc* age appropriate formulation that did not exist before (unlikely condition). Also budget constraints forces the hospital and health authorities to purchase drug at the lowest price and this make the return of the investment for a PUMA very unattractive. Reimbursement of paediatric specific pharmaceutical forms is insufficient (most often considered as not adding therapeutic value)

Is it **unlikely** that PUMA will become **more attractive in the coming years,** unless more valuable benefits are provided.

Granting **added protection** specifically **covering the new age appropriate** dosage form/formulation or offering additional incentives to their development, would be a significant incentive to Pharmaceutical Companies. In fact it might make the formulation financially attractive by preventing the Member States for a determined period to use off label generics.

Also the setting up of a **simplified procedure** to file for a PUMA might increase the interest of Pharmaceutical Companies: e.g. to limit the studies required in a PIP to a particular age subset, without necessarily covering all the paediatric ages (particularly for neonates).

Notably, GRIP network underlines that **academic networks** are **more interested** than Pharmaceutical Companies in developing old/off-patent products: 15 projects have been funded within the EU Framework program for developing a total of **20 off-patent medicines** for paediatric use. For 7 projects, a PIP has been agreed with a view to file PUMA. A relatively good positive result! However Pharmaceutical Companies do not show anymore interest in being involved in such projects, again reflecting the currently low return of investment.

3.4. 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.

The GRIP network agrees that no delays were reported in the authorization of medicines intended for adults. This is reflected by the massive use of deferrals (63% of new medicines intended for both adults and children) and the number of full waivers granted (30% EMA Decisions). On the other hand it is not guaranteed that all planned Clinical Trials will be completed before the end of adult patent !

3.5. 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?

The GRIP network **agrees** that paediatric development is currently dependent on adult development, not paediatric needs: *"conditions covered by PIPs do not fully match the known but evolving unmet paediatric needs. Diseases that occur frequently or exclusively in children are both underrepresented and poorly addressed"* (EMA-PDCO report, p. 9). Many paediatric needs are still unmet and some paediatric age categories are more disadvantaged than others. **Neonates are still therapeutic orphans** because:

- neonates studies will be performed late and therefore the medicines may well be off patent at that time, making studies not mandatory anymore:
- relatively few PIPs were submitted exclusively for the therapeutic area of neonatology;
- development and evaluation of adapted formulations are very difficult in this age group.

Efforts should be made **to support Pharmaceutical Companies** in identifying appropriate studies design and innovative methodologies to reduce the burden of research in this vulnerable population. In this sense we **acknowledge** the huge efforts made by the PDCO in introducing innovative elements such as extrapolation, modelling, simulation, etc. Smaller and vey focused studies should be requested for population and diseases where the number of patients is limited.

3.6. 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 GRIP network **agrees** that the burden/reward ratio established by the Paediatric Regulation has led to significant innovation. **Pharmaceutical Companies are forced to think** of the paediatric development as an integral part of the whole drug development. The introduction of obligations has shown that unfortunately, one does not get anything without coercion. Incentives alone are not sufficient.

Nevertheless the burden/reward ratio is **not a balanced approach** if applied to:

- **Off-patent products**: 1 PUMA granted although clinical studies according to agreed PIPs are ongoing (see comments on statement 3.3).
- **Orphan drugs**: for whom the opportunity to access the reward of 2 additional years of market exclusivity (art 37) is not always available. So far *no orphan-designated medicine has yet obtained this orphan incentive but no PIP has been completed in compliance with an agreed PIP* (EMA-PDCO report, p. 20)[2]. Development of medicines for rare diseases is even more difficult and costly than for non-orphan medicines. Access to either reward (the most beneficial) should be left to the choice of the company, without requiring losing the orphan status.
- **For patented products**: the 6-month SPC extension is not always sufficient to cover the cost of the paediatric development (mainly formulation and paediatric clinical trials). This incentive is economically significant in case of blockbuster products, for whom the MAH will be able to recover the investment, but not if one considers products with a small market. In addition, the need to have an supplementary protection certificate (SPC) in order to benefit from the reward is too limitative. Having to request the extension 2 years at least before the expiry of the SPC is another requirement that blocks access to the reward when it is deserved. Having to submit to each Member State patent office is cumbersome and resource intensive. We suggest **to make access to the reward much easier** in order to make it more efficient (in terms also of administrative procedure) **and to modulate the reward on the type of expected market** to avoid excess profit, whilst incentivising research where the paediatric market is small. Thus **better access to the reward is necessary** to allow easier and faster access to incentives in all cases where there has been a completed paediatric investigation plan.

[2] For orphan designated off patent products not falling under art 7 and art 8, the compliance with a voluntary PIP does not entitle to obtain the reward foreseen in art 37. In other words, for applicants already holding a marketing authorisation for an off patent substance that is orphan designated (in the context of the GMA concept) willing to develop a paediatric indication, no incentives/rewards and no obligations to develop the product for paediatrics are available.

3.7. 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 products[3].

While competent authorities are empowered to vary marketing authorisations as a result of theassessment, marketing authorisation holders have shown little interest in updating the summary of product characteristics and product information on a voluntary basis[4].

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?

The GRIP network **agrees** that there is no doubt that **Articles 45/46** were proved to be a **valid tool** for gathering huge amount of (unknown) existing fragmented paediatric data and making it available to the competent authorities and organisations making systematic reviews.

According to the EMA-PDCO report paediatric data on more than *2000 active substances have been submitted, including those published in the literature*. Without this obligation, Pharmaceutical Companies would not have voluntarily submitted all data. The final aim is to increase the information on drugs used in children and consequently to increase the proper use of drugs by updating the SmPCs.

However even if **data were very good** and if a huge amount of data is now available, **the work-sharing process of evaluation of these data is long and time consuming** (it will take years), and so far a small number of Assessment Reports have been released. These Assessment

[3] EMA-PDCO report, p. 31.

[4] EMA-PDCO report, p. 34.

Reports are not widely known among all stakeholders (healthcare professionals and paediatricians).

No resources to evaluate valuable/potentially valuable products are available at national level and *MAHs have shown little interest in updating SmPCs and PLs following the work-sharing procedures for article 45 or 46*.

Such tool still appears to be the hidden gem of the Paediatric Regulation.

Data, which are important, should be in labelling and SmPC. Those are the only places where such data is easily and effectively available for the prescriber. The hard work of the regulatory assessments is largely wasted, unless means are found to include important information in labelling/SmPCs. Means should be found to do that.

3.8. 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 children[5]. 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?

The GRIP network **agrees 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.

[5] EMA-PDCO report, p. 41.

Many healthcare professionals do not yet recognize the need for evidence-based paediatric prescribing, achieved through the conduct of paediatric clinical trials. On the other hand, in some cases, **clinical evidence** derived from literature is available to support scientifically the current off-label use, but this evidence **is not available easily** to healthcare professionals. In this case a better and appropriate knowledge transfer is necessary.

The **first 5 years of Paediatric Regulation are certainly not sufficient to change** 30 and more years of **medical practice**. Change of practice is not achieved by provision of information; **appropriate measures** (educational interventions that have been shown to be effective) have to **be instituted before change of practice can be expected**. Besides no measures to inform and encourage healthcare professionals and families to participate in paediatric clinical trials have been undertaken.

Anyway, **the system is changing**, and healthcare professionals have started to be more collaborative. But the change is not expected to happen in the short term, because the prescribing pediatricians' world may not be fully receptive to new scientific information. A study conducted by RAND Corporation showed very clearly why this process will be very slow: Pharmaceutical Companies nor health professionals in EU are discouraged for pursuing off-label use.

3.9. 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 database[6] do not yet show an increase in paediatric trials. The number of paediatric trials remained stable between 2006 and 2011, hovering, with some upsand 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 efficacy[7].

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 clinicaltrials 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

[6] Database of clinical trials in the EU, established by Directive 2001/20/EC, https://eudract.ema.europa.eu/index.html.

[7] EMA-PDCO report, p. 17.

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?

As reported in the EMA-PDCO report, the number of children involved in clinical trials is increasing (especially neonates who were never studied, and this is good evidence of an impact) however currently there is **no correlation between the number of clinical trials** required by PDCO and **agreed in the PIPs,** and the **number of clinical trials** included in the **EudraCT** database.

As experienced by some paediatric networks who are asked to participate in clinical trials, there are still **too many clinical trial protocols that are wrongly designed and/or conducted** resulting in unfeasible investigations.

For certain diseases (e.g. hepatitis C) the number of children is very limited and there are **several products in simultaneous development, therefore competing for recruitment and enrollment of study participants**. In this case we emphasize the need of EMA to work with Pharmaceutical Companies and independent CT networks on the feasibility to **perform trials involving multiple investigational compounds**.

Another issue that should be **strengthened and further encouraged** is to reduce the number of unnecessary clinical trials by **using innovative tools** for better study design and methodologies (e.g. extrapolation, modelling, simulation, etc.).

Efforts should be directed to the exploitation of results derived by **paediatric investigator driven clinical trials** not falling under article 46. For such studies there is currently no obligation to submit data to the competent authority, as it happens for MAH sponsored trials and in this case significant information may be missed by regulators.

3.10. 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?

Paediatric Investigation Plans that are not completed show that Pharmaceutical Companies **comply with the obligations** to agree a PIP to go through a regulatory submission **but are not willing** to engage into necessary research because the reward is either not accessible or not sufficient to compensate the costs of developments. Paediatric drug development is complex and expensive and **the reward should be commensurate** to the expenses.

3.11. 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 developmentand 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 thepaediatric population.

The adoption of the Paediatric Regulation has acted as a form of catalyst, gearing up andcoordinating 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 in the European Union?

Paediatric expertise networking is developing. Surely, the **PDCO is at the forefront** of the network and bringing together a high level of expertise and competence in development and assessment of paediatric medicinal products. **Enpr-EMA is also expected** to facilitate capacity building and bringing together national and European networks, investigators and centres with specific expertise in design and conduct of paediatric studies. **GRIP network aims at training in paediatric pharmacology investigators and other participants in paediatric clinical research**, and contributing to the infrastructure matrix to stimulate and facilitate the development and safe use of medicine in children.

Notwithstanding we should underline that so far **less attention is given to setting up an EU infrastructure with national components. There is a great need for financing this infrastructure,** for establishing the comprehensive framework of paediatric expertise in building and conducting trials in specialized investigation settings. Everything is depending on the Member States decisions to invest or not in this area, and they have generally proven unwilling to do so.

3.12. 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?

GRIP network will establish the main framework of training and competences for paediatric clinical research on medicines, based on paediatric pharmacology knowledge. However, there is a **crucial issue of sustainability including funding for this activity**. Until such time as the network is attracting enough paediatric clinical trials so as to make it self-sufficient, there is **a need for contribution from the EU**.

It is becoming quite apparent, that if the PIPs with deferrals in some years really lead to the clinical trials that have been planned, as is to be hoped, the **available infrastructure** of networks and centres that are able to perform high quality studies **within the EU is insufficient**. The infrastructure aspect of building research capacity was discussed during the development of the Paediatric Regulation, but no solution whatsoever was proposed (EnprEMA is not infrastructure). Building of European research infrastructure for paediatric clinical trials was left completely to the discretion of the Members State, with the result that it has, with the significant exception of the UK, been largely ignored. The experience from EnprEMA has shown, that such infrastructure cannot be built to sufficient levels to meet future needs on the basis of revenue from industry sponsored trials, simply because such income will only become available when studies are performed. Part of the success of the US paediatric legislation can be assigned to the early creation of an infrastructure in the form of Pediatric Pharmacology Research Units (PPRUs). The success of the UK MCRN also documents the value of developing a good infrastructure in time (Modi N, Clark H, Wolfe I, Costello A, Budge H. A healthy nation: strengthening child health research in the UK. www.thelancet.com Published online November 20, 2012). Leaving one critical component of the EU level paediatric regulation, **building capacity to perform the necessary clinical trials, at the discretion of the Members States may prove detrimental to the success of the Paediatric Regulation.**

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