ViroPharma SPRL

Response to the European Commission Public Consultation:

SANCO/D5/FS/(2012)1251190 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

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Introduction

ViroPharma is an international biopharmaceutical company committed to developing and commercialising innovative medicines that address unmet medical needs in both adults and children. ViroPharma has developed, obtained regulatory approvals, and commercialised three such medicines in Europe:

- Cinryze (C1 inhibitor, human) for the treatment and prevention of hereditary angioedema,
- Buccolam (oromucosal midazolam) for the treatment of prolonged acute convulsive seizures in children and adolescents; and
- Plenadren (modified release hydrocortisone) for the treatment of adrenal insufficiency in adults.

ViroPharma is developing the following products:

- Maribavir (maribavir) for the treatment of cytomegalovirus infection; and
- VP20621 (a non-toxigenic strain of C. difficile) for the prevention of the recurrence of C. difficile infection.

In 2011, ViroPharma was successful in gaining the first Paediatric Use Marketing Authorisation (PUMA) for Buccolam, and to date no further medicine has been granted a PUMA.

Accordingly, ViroPharma has relevant and valuable experience in the Paediatric Regulation and contributes the following views and feedback to the public consultation.

1. A Change of Culture

Commission position

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?

ViroPharma's Response

ViroPharma acknowledges that the Paediatric Regulation has facilitated the development of some paediatric medicines and is now an integral part of the overall development of a product. The development of medicines for children was and remains complex, and the recruitment of children into clinical studies was and remains a considerable challenge. The Paediatric Regulation provided leverage for the industry to engage and unite with investigators and regulators to fulfil a legal obligation. The obligations set out by the Paediatric Regulation encourage physicians to work more closely with industry to conduct appropriate clinical studies with high regulatory standards and parents to consider entering their children into clinical trials. Nonetheless, the Paediatric Regulation does not make the conduct of paediatric studies easier for the industry, in particular small and medium companies (SMEs). Setting out a stringent obligation is far from sufficient for ensuring the effective development of paediatric medicines if it is not accompanied by a flexible application of that obligation, the 'tools' which are necessary for such development (such as an active paediatric network), and a legal environment which effectively protects approved paediatric medicines.

The Commission's statement in the preamble to the question - "forcing companies" to develop paediatric medicines - portrays an inappropriate and negative view of the pharmaceutical industry and the dedicated and caring people who work within it. The employees in the pharmaceutical industry are motivated to help society by advancing medical research, discovering, developing and making medicines but in financially viable companies – because unviable pharmaceutical companies fail to develop medicines. The pharmaceutical industry and its employees need not to be forced to develop paediatric medicines unless they are asked to do so under conditions which are detrimental to the patients or the continuity of their businesses.

2. Output

Commission position

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[3]. 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?

ViroPharma's Response

An explicit goal of the Paediatric Regulation is to reduce off label use of medicines in children. This objective is being undermined by the national regulators, support of unlicensed and off-label use of medicines.

The Paediatric Regulation should not apply in isolation but be part of a system which generally supports the development and marketing of paediatric medicines, both at the European and the national level. So, the failure of national agencies to prohibit the use of unapproved medicines when a tested and approved alternative becomes available neither encourages companies to invest in paediatric development, nor discourages off- label use in children. Our company is experiencing this situation with Buccolam in the U.K.

Buccolam (oromucosal midazolam) is the first PUMA to be approved. ViroPharma invested in research to develop a new dose, route of administration and presentation that would ease and make safer the administration of midazolam to children with epilepsy. Buccolam was granted a PUMA, but this does not effectively protect ViroPharma' s investment. In the UK, the use of an unapproved, and so untested, competitor products continues to be permitted by the national authorities. In the UK, competitor products have been supplied and reimbursed as 'specials' for many years. This situation continues despite a) the approval of Buccolam, b) the competitor products not having been tested in children, and c) two reports in the UK press of safety issues caused by unlicensed medicines:

- The first case caused harm to a child - a 20 times overdose in a 3 year old child due to mislabelling.[1]

- In the second case, an unclear medicine label could have resulted in administration of five times the regular dose of midazolam that 'could have proved fatal' to a 16 year old child.[2]

A similar example exists in the Netherlands. Eurocept developed Medikinet, a medicinal product for slow release of methylphenidate for Attention-Deficit/Hyperactivity Disorder (ADHD) in children. A Dutch pharmacy is manufacturing large quantities of a similar but unlicensed product and promoting it to physicians. Eurocept has sued the Dutch National Health Authority in court for failure to enforce national law.

[1] http://www.gazettelive.co.uk/news/teesside-news/2012/01/11/tot-was-given-20-times-too-high-medicine-dose-says-marske-mum-84229-30100797/

[2] http://www.portsmouth.co.uk/news/health/local-health/unclear-medicine-label-could-have-proved-fatal-1-4398030

As part of the paediatric effort, all national authorities should be asked to support tested and approved paediatric medicines and cease supporting, in any way, untested and unapproved paediatric medicines. Furthermore, "specials" licenses and reimbursement should automatically cease where an approved therapeutic alternative becomes available. Why otherwise would any pharmaceutical company want to invest in paediatric development? Off label uses and governmental support of off label uses are acceptable for therapeutic reasons, but not where approved medicines exist.

The extensive efforts of the Commission, the EMA, national regulatory agencies, HTAs and industry to create this much needed Regulation and to develop paediatric medicines, have been undermined by other national agencies' and organisations' too permissive approach to off label use. The EMA and the Commission must take a proactive role to prevent children from being harmed despite the efforts of pharmaceutical companies to foster safe and effective medicines for children.

3. PUMAs

Commission position

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?

ViroPharma's Response

ViroPharma agrees that it is disappointing that only one PUMA has been approved in five years. The PUMA has not been used by industry because that incentive is insufficient. There is a clear contrast between the success of Orphan Regulation with a significant incentive (10 years market exclusivity)

and the failure of the PUMA with a poor incentive (10 years data exclusivity/marketing protection on paediatric data). Market exclusivity gives industry a real opportunity for a company to recoup its investment. The PUMA exclusivity does not prevent a second applicant from following the road map laid out in the innovator's PIP and EPAR and bringing a copy product to market before the innovator's investment is recouped. Therefore, the industry has avoided taking such risks with its limited development budgets.

The Commission must create a viable incentive for supporting development of paediatric presentations of off-patent medicines currently used in adults . Several options are available. For example, the Commission could give an additional period of data exclusivity for the original medicinal product in cases the medicinal product is still protected by data exclusivity when the PUMA is granted. It could also allow the two-year market exclusivity extension for an orphan medicine that is granted a PUMA. Alternatively, the Orphan Regulation could be amended so that medicinal products to which a PUMA is granted constitute a special category of product that benefit from 10 years market exclusivity. This would incentivise the industry to rapidly fill the paediatric gaps.

The Commission may be concerned that orphan medicines attract very high prices for a period of 10 years. It is, however, better to have these medicines developed, even at high prices to help innovative companies recoup development costs, than to have so few PUMAs. Every child (usually at orphan drug qualifying prevalence) needing these medications should have the opportunity to receive them.

4. Waiting queues

Commission position

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.

ViroPharma's Response

ViroPharma experienced a delay in the validation of a marketing authorisation application for an orphan medicine for both adults and children, due to a too strict interpretation of the rules, in particular Article 46 of the Paediatric Regulation, by the EMA.

ViroPharma had submitted a PIP proposal for Cinryze. The EMA decision on the PIP agreed to a deferral for several studies. ViroPharma filed a marketing authorisation application; of course, the dossier did not include the results of the deferred studies. Those studies however had already been conducted (and the CSRs were being written) so that, pursuant to Article 46, the EMA asked ViroPharma to file the study results for those deferred studies. Article 46 simply requires to submit the results of paediatric studies "covered by a marketing authorisation" to the EMA within six months of completion of the study; it does not derogate from the provisions on deferrals nor to products where there is no existing marketing authorisation. It took a further seven months for ViroPharma to obtain the PIP compliance report and so to complete the validation process of its marketing authorisation application. ViroPharma considered that the EMA over-interpreted the Paediatric Regulation and was intransigent in its application to the detriment of adult and paediatric patients suffering from a rare disease. Moreover, that interpretation could not be challenged meaningfully. The Commission failed to intervene, and a court action was considered to be too expensive and too time consuming to be of any value to ViroPharma.

This is a concrete example of a significant delay in the approval of an important life-saving orphan medicine for adults and children caused by the EMA's inappropriate interpretation of the Paediatric Regulation and inflexibility. This example also illustrates the lack of swift mechanism to arbitrate and resolve disputes with the EMA about its interpretation of the Paediatric Regulation.

With regard to the requirement to submit a PIP proposal at the end of human PK studies in adults and to then modify the PIP as development progresses, the industry in unison seems to have determined not to spend its limited financial and human resources on such activities until later in the development process and the likelihood of the molecule's progression has increased. It is logical to progress several products simultaneously and only spend resources on a PIP at a later stage, when the most likely candidates to be progressed are known. Otherwise, the resources for developing a PIP and having it approved are wasted, and if those resources are spent on the paediatric development of one product, they cannot be spent on the development of another product. The EMA's approach to development resources on paediatric issues at such an early stage limits the number, or slows down, the development of other candidate molecules.

We stress the EMA's lack of understanding of the practical operation and commercial concerns of pharmaceutical companies. Companies' research budgets are not unlimited, and their development strategies must be commercially driven for the companies to remain financially viable. The EMA seems decided to ignore this aspect of the industry and the implications for public health.

5. Paediatric need

Commission position

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?

ViroPharma's Response

ViroPharma appreciates that the Paediatric Regulation is designed to develop paediatric medicines that are needed rather than paediatric versions of medicines developed for adults. We recognise that there are significant formulation and clinical challenges in the development of paediatric medicines, that the markets are often relatively small, and that the opportunity to make a financially viable business is limited. ViroPharma, however, is concerned that companies are forced to develop medicines in therapeutic areas where they have no expertise or experience and with limited opportunity to make or maintain a viable business.

If the Commission were to amend the Orphan Regulation and expand its scope to medicinal products which are granted a PUMA, companies would be able to recoup their investment and so would effectively be incentivised to rapidly fill the paediatric gaps. If the paediatric rewards were attractive in order to make a viable business, companies would not need to be 'forced' to develop paediatric medicines in therapeutic areas they are not interested or experienced in.

6. Burden/Reward Ratio

Commission position

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?

ViroPharma's Response

We are unaware of any simplification of the regulatory process by the EMA or the Commission, be it the paediatric procedure or the marketing authorisation procedure. To the contrary, the EMA recently published a policy document on PIP decisions that drastically increases (yet again) the administrative burdens and thereby delays approvals and wastes companies' resources. The EMA does regularly issue guidelines and Q&As, but those are only rarely to the benefit of companies.

ViroPharma itself has no experience with regard to paediatric rewards except for the grant of a PUMA. Other companies however reported that such rewards are very difficult to obtain and that this could change if the EMA were to be more flexible in its application and interpretation of the paediatric rules.

7. Article 45/46

Commission position

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.

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 basis.

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?

ViroPharma's Response

The proposed purposes of Articles 45 and 46 are appropriate, but as regards ViroPharma in particular, in 2010, the over-interpretation of Article 46 by the EMA caused a seven months delay in the validation of an orphan medicinal product for adults and children. (see above, item 4). This undermined the EMA's commitment to develop medicines for children. The Paediatric Regulation was not intended to cause such delay.

8. Lost information

Commission position

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?

ViroPharma's Response

ViroPharma agrees that healthcare professionals are not being made aware of the development of new paediatric medicines. This is part of a larger issue, i.e., a lack of support for new paediatric medicines or information at the national level. This issue covers several aspects.

One important aspect is the failure of national agencies to prohibit the use of unapproved medicines when a tested and approved medicine becomes available. This discourages companies to invest in paediatric development or encourages off- label use in children. Our company is experiencing this situation with Buccolam in the U.K.

Buccolam (oromucosal midazolam) is the first PUMA to be approved. ViroPharma invested in research to develop a new dose, route of administration and presentation that would ease and make safer the administration of midazolam to children with epilepsy. Buccolam was granted a PUMA, but this does not effectively protect ViroPharma' s investment. In the UK, the use of an unapproved, and so untested, competitor products continues to be permitted by the national authorities. In the UK, competitor products have been supplied and reimbursed as 'specials' for many years. This situation continues despite a) the approval of Buccolam, b) the competitor products not having been tested in children, and c) two reports in the UK press of safety issues caused by unlicensed medicines:

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A similar example exists in the Netherlands. Eurocept developed Medikinet, a medicinal product for slow release of methylphenidate for Attention-Deficit/Hyperactivity Disorder (ADHD) in children. A Dutch pharmacy is manufacturing large quantities of a similar but unlicensed product and promoting it to physicians. Eurocept has sued the Dutch National Health Authority in court for failure to enforce national law.

As part of the paediatric effort, all national authorities should be asked to support tested and approved paediatric medicines and cease supporting, in any way, untested and unapproved paediatric medicines. Furthermore, "specials" licenses and reimbursement should automatically cease where an approved therapeutic alternative becomes available. Why otherwise would any pharmaceutical company want to invest in paediatric development? Off label uses and governmental support of off label uses are acceptable for therapeutic reasons, but not where approved medicines exist.

The extensive efforts of the Commission, the EMA, national regulatory agencies, HTAs and industry to create this much needed Regulation and to develop paediatric medicines, have been undermined by other national agencies' and organisations' too permissive approach to off label use. The EMA and the Commission must take a proactive role to prevent children from being harmed despite the efforts of pharmaceutical companies to foster safe and effective medicines for children.

9. Clinical trials with children

Commission position

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 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 efficacy.

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?

ViroPharma's Response

No comment.

10. Unnecessary efforts

Commission position

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?

ViroPharma's Response

The industry in unison seems to have determined not to spend its limited financial and human resources on such activities until later in the development process and the likelihood of the molecule's progression has increased. It is logical to progress several products simultaneously and only spend resources on a PIP at a later stage, when the most likely candidates to be progressed are

known. Otherwise, the resources for developing a PIP and having it approved are wasted, and if those resources are spent on the paediatric development of one product, they cannot be spent on the development of another product. The EMA's approach to development resources on paediatric issues at such an early stage limits the number, or slows down, the development of other candidate molecules.

The Paediatric Regulation requires an early filing of a PIP proposal but it does not require the PIP proposal to be as detailed as asked by the Commission and the EMA. An early filing would not be such a burden if the PIP proposal did not have to be so detailed. This is the combination of 'early' and 'very detailed' that makes it impossible and resource- wasting for companies.

ViroPharma full agrees that early and detailed PIP proposals lead to unnecessary efforts (for industry and the regulators). On the contrary, it fully disagrees that early submission of and agreement to the PIP is necessary for the paediatric development to fit smoothly into the overall product development. Companies can design paediatric development programs without the PDCO/EMA; paediatric medicinal products have been approved before the adoption of the Paediatric Regulation. PIPs help companies generate the appropriate data, but such assistance was already provided through scientific advice. In reality, the early submission of a PIP proposal only benefits the EMA. Then, the EMA can impose on the company the entire or almost entire paediatric development it wishes and the company has in essence no choice other than to agree and pay. Such situation obviously is unacceptable unless the paediatric studies requested by the EMA were to be reasonable and the EMA were to be flexible as regards to modifications.

11. Sophisticated Framework of experts

Commission position

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 in the European Union?

ViroPharma's Response

We agree that a network of paediatric experts now exists, but it seems to have failed to become a true part of the system. Is it involved in the preparation of the list of paediatric needs ? How does it assist companies in meeting the paediatric challenges?

12. Any other issues

Commission position

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?

ViroPharma's Response

Based on ViroPharma's experience, the main issues with the Paediatric Regulation have been highlighted above, in particular the lack of effective incentive for already approved medicinal products which are not or no longer patent protected and the EMA's too demanding approach as regards to PIPs or compliance checks.

The Paediatric Regulation was welcomed by industry, but the failure to provide an orphan-like incentives for PUMAs has, as predicted, undermined that part of the legislation. Furthermore, even if a PUMA is approved, further support is needed from all stakeholders, in particular the national authorities and ethics boards, to 'promote' new paediatric medicinal products , reduce the use of unlicensed products when licensed products are available and disseminate new paediatric information. A lot still has to be done for approved products which are out of patent protection, starting by finding the appropriate incentive, i.e., an incentive that would really allow companies to recoup their investment and create and maintain viable businesses. We believe that a system which is more like the orphan system would be suited. (see above, item 3).

Children are not small adults, but they do have to be treated as individuals with the best possible care from their healthcare professionals. The fundamental right of children to be prescribed adequately tested and approved medicines is the goal of the Paediatric Regulation. This goal has not been achieved yet and significant changes are required to enhance the future care and lives of children in Europe.