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

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

'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT' SUBMITTED FOR PUBLIC CONSULTATION

Deadline for Public Consultation: 28 November 2012

This document does not represent an official position of the European Commission. It is a tool for exploring the views of interested parties. The statements and conclusions contained in this document do not prejudge the content of the future report by the European Commission.

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I. ABOUT THE CONSULTATION

A. INTRODUCTION

The Paediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use[1]) was adopted on 12 December 2006 and entered into force on 26 January 2007. Its main provisions started to apply from July 2008 (Article 7) and January 2009 (Article 8), respectively.

The Regulation was seen by the legislator as a response to the absence of sufficient numbers of suitable, authorised medicinal products to treat conditions in children in the European Union. Studies had shown that at that time over 50% of the medicines used for children might not have been tested for use in this specific age group. The lack of suitable, authorised medicinal products to treat conditions in children can be explained by the fact that pharmaceutical companies frequently did not carry out the necessary research and development to adapt medicinal products to the needs of the paediatric population. This left healthcare professionals with no alternative but to use off-label products and unauthorised products with the associated risks of inefficacy or adverse reactions.

To address this problem the Regulation establishes a system of requirements, rewards and incentives together with horizontal measures to ensure that medicines are researched, developed and authorised to meet the therapeutic needs of children.

The key objectives of the Regulation are:

- to ensure high-quality research into the development of medicines for children;
- to ensure, over time, that the majority of medicines used by children are specifically authorised for such use;
- to ensure the availability of high-quality information about medicines used by children.

The key measures included in the Regulation are:

- the establishment of an expert paediatric committee within the European Medicines Agency (EMA);
- the requirement, when applying for marketing authorisation for medicines and line-extensions for existing patent-protected medicines, to submit data on the use of the medicine in children in accordance with an agreed paediatric investigation plan;
- a system of waivers from the requirement for medicines unlikely to benefit children and a system of deferrals of the timing of the requirement to ensure that medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;

[1] http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1901:20070126:EN:PDF.

- a reward for compliance with the requirement in the form of a six-month extension to the supplementary protection certificate;

- for orphan medicines, a reward for compliance with the requirement in the form of an additional two years of market exclusivity added to the existing ten years awarded under the EU's Orphan Regulation;

- a new type of marketing authorisation, the PUMA, which allows ten years of data protection for innovation (new studies) on off-patent products;

- measures to strengthen pharmacovigilance and maximise the impact of existing studies on medicines for children;

- an EU inventory of the therapeutic needs of children to focus the research, development and authorisation of medicines;

- an EU network of investigators and trial centres to carry out the required research and development;

- a system of free scientific advice for the industry, provided by the EMA;

- a public database of paediatric studies;

- a provision on EU funding for research leading to the development and authorisation of off-patent medicines for children.

In accordance with Article 50(2) of the Regulation, in 2013 the Commission will present to the European Parliament and the Council a general report on experience acquired as a result of the application of the Regulation. This report will include a detailed inventory of all medicinal products authorised for paediatric use since its entry into force.

This '5-year report' should be distinguished from a second more comprehensive report due in 2017, which will include an analysis of the economic impact of the rewards and incentives, together with an analysis of the Regulation's estimated consequences for public health, with a view to proposing any necessary amendments. Quite wisely, the legislator has considered that in view of the development cycles of medicinal products, it will take at least 10 years of application to reach a comprehensive understanding of the impact of the legislation.

Consequently, the 2013 report is to be seen as an interim report which presents a first glimpse of the experience gained.

The purpose of this consultation paper is to support the Commission in drafting this report and to seek views and feedback from stakeholders on the first five years of application.

This 'lessons learnt' paper is now being put out for public consultation. Replies or comments should be submitted by 28 November 2012 at the latest.

B. CONSULTATION TOPICS

1. SPECIFIC CONSULTATION ITEMS

The consultation text consists of eleven statements reflecting on possible lessons learnt from the first years of application of the Paediatric Regulation. They build on the 'Five-year Report to the European Commission' drafted by the European Medicines Agency with its Paediatric Committee, the experience of the Commission departments and reflections on the Paediatric Regulation published in the literature and discussed at stakeholder conferences. The statements do not necessarily represent the Commission's position. Rather, they are a means of exploring further the views of interested parties. Each statement is followed by specific consultation items in boxed text raising questions on which the Commission seeks the input of interested parties.

Respondents are invited to address those points specifically.

2. FURTHER BACKGROUND READING

- The Paediatric Regulation (EC) No 1901/2006.
- Five-year report to the European Commission — General report on the experience acquired as a result of the application of the Paediatric Regulation as prepared by the European Medicines Agency with its Paediatric Committee (hereinafter referred to as 'EMA-PDCO report');
- Judgment of the General Court of the European Union in case T-52/09 of 14 December 2011.

C. HOW CAN I CONTRIBUTE?

Stakeholders are invited to comment on this consultation paper, and on the boxed text in particular, by 28 November 2012 at the latest. Responses should be sent (preferably by e-mail) to sanco-pharmaceuticals-D5@ec.europa.eu, or by post to Directorate-General for Health and Consumers, Unit SANCO/D/5, BE-1049 Brussels. The subject line of the letter or e-mail should refer to 'PCPD/12/01 — Public Consultation on Paediatric Report'.

When you send your comments and responses, you should state whether you are a stakeholder association or a private individual. If you represent an association, please indicate clearly what type of association it is (patients, health professionals, manufacturers, marketing authorisation holders, etc.). If you represent a company, please state whether it falls within the EU definition of a small and medium-sized enterprise (i.e. less than €50 million annual turnover and fewer than 250 employees).

An acknowledgement of receipt will be issued for each contribution received.

The contributions received and the identity of the contributors will be made publicly available on the 'public health' website[2], unless the contributor objects to the publication of his or her

[2] http://ec.europa.eu/health/human-use/index_en.htm.

personal data on the grounds that it would harm his or her legitimate interests. In this case the contribution may be published in anonymous form. Otherwise the contribution will not be published nor will, in principle, its content be taken into account. For more information on the processing of your personal data in the context of this consultation, you should read the specific Privacy Statement available on the dedicated consultation page on the public health website.

Professional organisations are invited to register in the Union's Register of Interest Representatives (http://ec.europa.eu/transparency/regrin/) set up as part of the European Transparency Initiative to provide the Commission and the public at large with information about the objectives, funding and structures of interest representatives.

D. WHAT WILL HAPPEN NEXT?

All contributions will be carefully analysed. The final paediatric report will build on the consultation.

II. EXPERIENCE ACQUIRED / LESSONS LEARNT

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?

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

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

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?

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?

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.

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?

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?

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[4].

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[5].

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?

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[6]. 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

4 EMA-PDCO report, p. 31.
5 EMA-PDCO report, p. 34.
6 EMA-PDCO report, p. 41.

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?

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[7] 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[8].

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.

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

8 EMA-PDCO report, p. 17.

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?

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?

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?

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?

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