



**EUROPEAN COMMISSION**  
HEALTH AND CONSUMERS DIRECTORATE-GENERAL

Health systems and products  
**Medicinal products — authorisations, EMA**

Brussels,  
SANCO/D5/FS/ci D(2013) 27105

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

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

**SUMMARY OF THE REPLIES**  
**TO THE PUBLIC CONSULTATION**

# I. ABOUT THE CONSULTATION

## A. INTRODUCTION

1. On 19 September 2012 the Commission launched a public consultation on the experience acquired as a result of the application of the Paediatric Regulation (Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use).<sup>1</sup>

This consultation relates to the obligation of the Commission to present in 2013 a general report on experience acquired as a result of the application of the Regulation (Article 50(2) of the Regulation). This report will include a detailed inventory of all medicinal products authorised for paediatric use since its entry into force.

2. 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. The legislator has considered that in view of the development cycles of medicinal products, it will take at least 10 years to gain a comprehensive understanding of the impact of the legislation.

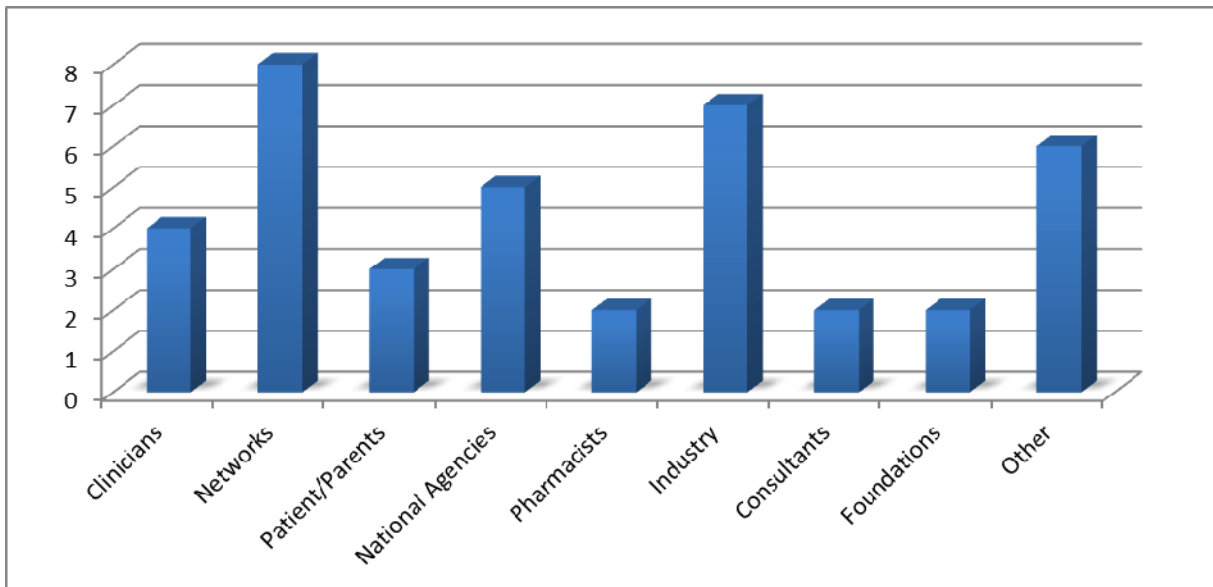
Consequently, the 2013 report is to be seen as an interim report that presents a first impression of the experience gained.

3. The purpose of the public consultation was to support the Commission in drafting the report and to seek views and feedback from stakeholders on the first five years of application. To this end, the Commission published eleven statements reflecting on possible lessons learnt from the first years of the Paediatric Regulation. They built on the ‘Five-year Report to the European Commission’ drafted by the European Medicines Agency together with its Paediatric Committee,<sup>2</sup> the experience of the Commission departments, and reflections on the Paediatric Regulation published in the literature and discussed at stakeholder conferences. The statements did not necessarily represent the Commission’s position. Rather, they were a means of exploring further the views of interested parties.
4. At the end of the consultation period on 28 November 2012, the Commission had received 43 responses from a variety of stakeholders, the majority of which came from either pharmaceutical companies or paediatric networks. Additionally, replies were received from national competent authorities, ministries and agencies, including the European Medicines Agency and the coordination group (CMDh), clinicians, patient and parent organisations, pharmacists, consultants, foundations, and other entities, including individuals.

---

<sup>1</sup> [http://ec.europa.eu/health/files/paediatrics/2012-09\\_publicconsultation\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2012-09_publicconsultation_en.pdf).

<sup>2</sup> [http://ec.europa.eu/health/files/paediatrics/2012-09\\_pediatic\\_report-annex1-2\\_en.pdf](http://ec.europa.eu/health/files/paediatrics/2012-09_pediatic_report-annex1-2_en.pdf).



5. In accordance with the applicable guidelines, the responses have been published by the Commission.
6. This paper briefly summarises the responses to the public consultation document. In doing so, it not only reflects the majority views, but also tries to present a 'snapshot' of the range of responses.
7. This paper is in no way to be understood as an endorsement of any comments.
8. For the sake of brevity, the paper reproduces neither the consultation items nor the detailed replies. Therefore, this summary should be read in conjunction with the consultation items set out in the concept paper as well as the published responses.
9. The public consultation is part of the ongoing preparation of the Commission report. The information and views gathered in this public consultation will be taken into consideration in the further drafting process.

## **B. GENERAL REMARKS**

10. The public consultation was generally appreciated by stakeholders. It was noted that the consultation items and the specific statements helped to provide targeted feedback.
11. Some respondents criticised the Commission's intention not to consider any amendments of the Paediatric Regulation at this point in time. Moreover, some had the impression that companies were portrayed in the consultation paper in an inappropriate and negative way. It was argued that the hesitance of companies to test their products in children reflected a general societal paradigm that children should be protected from clinical research. This has shifted in recent years to the concept of protecting children through clinical research.

### **C. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT**

12. A large majority of respondents agreed that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of overall product development. Nowadays, paediatric development strategy is frequently discussed simultaneously with adult planning and many companies include a systematic evaluation of each new compound for potential value for children within their research and development (R&D) process. What is more, several companies have established dedicated internal and/or external advisory teams that are consulted during the development process. In this context, it was argued that the Regulation provided leverage for industry to engage and join with investigators in meeting a legal obligation.
13. However, some respondents criticised that this achievement came at the price of significant administrative burden and added to the many competing regulatory activities to be managed during the pre-authorisation phase. Some respondents also claimed that, in terms of strategy, many companies still see compliance with a paediatric investigation plan more as the fulfilment of regulatory obligations than the establishment of a full and independent R&D programme.
14. It was also claimed that some small companies, especially those established outside the EU, are not yet fully aware of the paediatric requirements in the European Union, which may then lead to complications if they try to enter the European market with their products.
15. A few respondents also highlighted that the majority of studies are deferred, sometimes for too long, meaning that there is little evidence that companies are performing clinical trials. Instead, many studies are at present just a commitment, which has yet to pass the reality check. Finally, some respondents noted that R&D activities are not evenly spread between different paediatric conditions. For example, paediatric investigation plans rarely cover the area of paediatric oncology. Moreover, companies' paediatric R&D budgets are claimed to be now primarily focusing on research required in order to meet obligations under the Paediatric Regulation, thereby affecting the available funds for other areas.

### **D. HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.**

16. Respondents in principle agree that it is too early to judge. Some note encouraging signs, indicating that the Regulation is starting to deliver, primarily for those diseases that affect adults and children similarly. It is argued that the Regulation has put a framework and structure in place, which is a major step forward in terms of public health protection for the paediatric population. It has also increased cross-national collaboration to facilitate clinical research.
17. Others, however, observe that off-label use is still prevalent across the EU. While the contribution of the Regulation to new products and new compounds is recognised, the off-label use of 'well-established' products may remain an issue. Moreover, the impact of the Regulation on rare diseases or diseases that occur only in children is doubted. In this context, reference is often made to paediatric oncology, where it is claimed that encouraging signs of preliminary achievements are lacking.

18. Some respondents argue that while it may not be possible to judge the full impact of the Regulation, there should be sufficient information to identify already now areas for improvement and to take action on those.
19. As far as benchmarks to measure the success of the Regulation are concerned, it is suggested not only to focus on off-label use, but also to take account of other criteria, such as paediatric studies funded by industry, the number of children included in clinical trials, and improvement of the information available on the use of products in children.

#### **E. THE PUMA CONCEPT: A DISAPPOINTMENT**

20. Respondents generally agree that the fact that only one paediatric use marketing authorisation (PUMA) has been granted to date is a clear disappointment. However, views differed as to whether the PUMA concept would be more widely used in future.
21. Several respondents doubt that a PUMA will be more attractive. It is pointed out that the incentive of 10 years of data and market exclusivity does not work in practice. Many companies fear that market exclusivity will not prevent physicians from continuing to use products with the same active ingredient off-label, at lower costs. Hence, the expectation that off-label use will be redundant when a PUMA is granted is questioned. It is suggested that national authorities should pro-actively intervene to prevent off-label use once a PUMA has been granted. On the other hand, national reimbursement rules in Member States often do not allow for the additional research done to obtain the PUMA to be rewarded in price negotiations.
22. Other respondents point out that the target population for a PUMA is too small to make up for the costs. It was also questioned whether generic companies that hold authorisations for off-patent products have the necessary resources to invest in additional research. Academic networks that could step in would be put off by the obligations linked to the authorisation process and post-authorisation requirements. In addition, the commitment for those networks in terms of compliance with paediatric investigation plans is considered to be very high. One respondent also doubts that academic networks would be willing to invest as they might be convinced that most current off-label use already relies on sufficient data. Hence, such research would not meet unmet paediatric needs.

#### **F. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS**

23. The majority of non-industry responders either felt unable to respond to this statement or agreed that there is no evidence for delays. Reference was made to the massive use of deferrals. Some regulators pointed to initial misunderstandings by applicants of their obligations when the Paediatric Regulation was first introduced. In such cases, cooperation between the competent authorities, EMA and the applicant has helped to resolve situations as rapidly as possible. Likewise, the operation of the deferral system and the ability to modify a paediatric investigation plan (PIP) to ensure compliance with key binding measures are claimed to only have become fully understood more recently with the benefit of experience.

24. As far as industry respondents are concerned, the picture is more negative. It is claimed that there is some evidence of an impact on adult development. Some argue that ‘bureaucratic approaches’, in particular to the compliance check, could lead to delays. The change management process following a negative compliance check is considered to be very resource-intensive. One respondent also argued that longer development cycles compared to the situation prior to the Paediatric Regulation have been observed in products that primarily target children. Additionally, some transitional problems have been noted where the adult programme had already been established before the Regulation entered into force.
25. Several respondents raised the issue of early submission versus late submission. While the Paediatric Regulation requires companies to submit the paediatric investigation plan at the latest upon completion of human pharmaco-kinetic studies in adults, many companies prefer late submission as they consider that the research results are not yet sound enough to predict whether the adult development will succeed. They are therefore hesitant to extend the investment to paediatric research. However, any late submission of a paediatric investigation plan bears the risk of compromising initial timelines for the adult marketing authorisation, given that all paediatric points have to be clarified and agreed prior to validation of the marketing authorisation application.

#### **G. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS**

26. Respondents recognise that the Paediatric Regulation was not designed to solve all problems. Some criticise that the Regulation focuses too much on the marketing authorisation aspects. Its system for establishing the paediatric investigation plan is mainly disease-driven and not driven by the mode of action of the compound. However, even if there may have been some missed chances, some argue that the Regulation has made it possible for the Paediatric Committee to encourage companies in directions where there are specific unmet paediatric needs.
27. Several respondents claim that the dependency on adult developments leads to insufficient results in diseases that occur frequently or exclusively in children. Those paediatric-specific diseases are underrepresented and poorly addressed in the agreed paediatric investigation plans.
28. Industry respondents welcomed the recognition that ‘medicinal development is company-driven’ and that ‘it is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system’. Some argue though that the “paediatric need” element might be over-emphasised, ignoring other important factors like practical feasibility and economic impact. Other respondents voiced concerns that companies will be forced to develop medicines in therapeutic areas where they have no expertise or experience and with limited opportunity to pursue a viable business.

#### **H. THE BURDEN/REWARD RATIO — A BALANCED APPROACH**

29. Not all respondents commented on this point. To the extent replies were received, a broad range of opinions were expressed.

30. As far as incentives are concerned, it was argued that the value of the 6-month extension of the Supplementary Protection Certificate varies widely. It can be economically significant in the case of blockbusters. Some respondents called it even excessive, leading to unnecessary additional costs for payers. Here, the introduction of a cap system for 'super profits' was suggested.
31. Other respondents mentioned that the orphan reward has not yet been obtained and that vaccines often do not benefit from the reward on account of their specific life-cycle. Moreover, it was claimed that incentives are inadequate for unmet needs and not encouraging enough for the development of complex, innovative medicines, such as biotechnology medicines.
32. Concerning burden, some respondents called for a faster, simpler process, including modifications of approved paediatric investigation plans.

#### **I. ARTICLE 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION**

33. The view that Article 45/46 should be considered the hidden gem of the Paediatric Regulation was not shared by all respondents. Several weaknesses were pointed out. For instance, the work-sharing evaluation process is rather long and time-consuming and the final assessment reports are claimed not to be widely known among healthcare professionals and other stakeholders and consequently should be better communicated. Others pointed out that the hard work is partly wasted unless ways are found to include important information in the labelling and/or the summary of product characteristics. In particular, the lack of interest among marketing authorisation holders in updating the summary of product characteristics on a voluntary basis was mentioned as a concern.
34. Further problems relate to the fact that some of the old studies submitted do not meet modern requirements for scientific data. Moreover, competent authorities would usually limit their assessment to the submitted data and refrain from taking into account other available data or well-established medicinal uses. According to some respondents only a holistic assessment will deliver real progress.
35. It was also suggested to better prioritise the assessment (which is something the national competent authorities are currently looking into) or to use means such as a European paediatric formulary to disseminate knowledge derived from an Article 45/46 assessment, when there is not enough evidence for a paediatric marketing authorisation.
36. In turn, several respondents agreed that Article 45/46 proved in principle to be an efficient mechanism for updating product information, and pointed to the number of new paediatric indications and safety information. While the process might be considered slow, such reviews are the best way of getting additional paediatric indications or dosage recommendations for off-patented products included in product information.

## **J. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED**

37. Different views were expressed on this point. While the majority of respondents shared the view that paediatricians could be more interested in paediatric research, there was no general agreement on why this would be the case and how to best improve the situation. Moreover, several respondents argued that healthcare professionals are quite a heterogeneous group, so their receptiveness may differ significantly depending on their work settings and their specific areas of specialisation. It was for example pointed out that professionals who work in areas where suitable products are scarce closely follow new, emerging information.
38. Especially for general paediatricians not linked to major academic centres or clinics, the easy accessibility and presentation of information is key to improving knowledge transfer. In this context, reference was made to a certain ‘off-label culture’ starting at medical school. Additional information may not easily alter well-established habits and practices. It is therefore important to target education by reviewing the study curricula of future paediatricians.
39. Respondents generally agreed that solutions must be found at national level, and referred to existing projects and best practices in Member States (including e.g. national formularies). Reference was also made to policies in third countries such as the United States. However, some respondents argued that action could also be taken at EU level by ensuring better coordination and making full use of networks of paediatricians and researchers. Some felt that further collaboration between senior healthcare professionals across Member States might be helpful in order to share and direct funding to the most appropriate areas and to stimulate (clinical) research.

## **K. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED**

40. As regards clinical trials with children, a number of points were raised. Respondents often agreed that no major problems have so far been detected; but referred to several challenges that still are awaiting a satisfactory response or have to be monitored closely.
41. Concerning the number of paediatric trials, some respondents pointed out that they have seen in e.g. the UK a massive increase in the number of industry studies conducted in the past four years. 90% of those studies seem to be related to a paediatric investigation plan (PIP). Similarly, a considerable increase has been observed in France.
42. However, some paediatric networks were disappointed by the bad planning of some trials, and in some therapeutic areas — vaccines were mentioned as one example — national ethics committees seem to be reluctant to accept studies recommended by the Paediatric Committee.
43. Moreover, for certain diseases the number of children is very limited. If several products, including me-too products, are in simultaneous development for such areas, companies are competing to find investigators and to recruit and enrol study participants. It was even claimed that in specific indications experience suggests that patient groups are smaller than the number of patients required to do all studies. To



avoid any unnecessary and unethical duplication of studies, consideration should be given to collaboration between regulators, researchers and sponsors.

44. Besides transparency, calls were made for smarter study design, truly international collaboration between the EU and the US and regular use of extrapolation, modelling and simulation techniques to decrease the number of study subjects as far as possible.
45. Finally, it was argued that an increase in the number of paediatric trials should not be seen as the most important measure of success: the quality of the trials and the availability of products and information for paediatric use are as important, if not more so.

#### **L. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS**

46. Some respondents claimed that the issue of ‘unnecessary efforts’ is more a theoretical than a practical problem as many companies already delay the submission of the paediatric investigation plan and spend resources only at a later stage when the most likely candidates/compounds are known. Others called for a two-step approach: first a preliminary programme with high-level elements, then a full review later. This would also ensure better alignment with the approach followed by the FDA in the United States.
47. Some stressed that earlier identification of efficacy and safety issues and appropriate timing of paediatric studies using the deferral system should minimise the holding of unnecessary trials where the adult development eventually has to be abandoned.
48. Other respondents mentioned that the information collected, even if the programme is discontinued, could still be of value for other similar development programmes. Moreover, consideration should be given to obliging pharmaceutical companies to give the discontinued compound to healthcare professionals or research networks for further analysis if the initial studies confirmed a sound paediatric potential. Similarly, incentives may be provided to allow repositioning of the compound, especially within the paediatric oncology setting, where it could fulfil unmet paediatric needs.
49. Several respondents also called for a comprehensive evaluation of the efficiency of the paediatric investigation plan process. The resources mobilised should be compared to the number of on-going and completed plans. It was suggested to lower the administrative burden in the early phases, given that the combination of early and very detailed submission would make the current system more burdensome than necessary.
50. Finally, some respondents asked for a system to ‘de-activate’ paediatric investigation plans in order to be able to easily identify discontinued research programmes.

#### **M. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED**

51. The contribution of the Paediatric Regulation to the network of expertise within the European Union is generally recognised by respondents. However, some respondents argue that Europe is still far away from a comprehensive framework of expertise when it comes to the development and scientific study of paediatric medicines. Many

experts will only have a short and limited experience in this field. Additionally, some respondents point out that in certain disease areas, such as paediatric oncology, a close-knit network of experts already existed prior to the Regulation. In view of the limited number of paediatric investigation plans covering paediatric oncology, the Regulation has not really contributed to further improvement of those existing networks.

52. It was noted that the majority of networks rely on the enthusiasm of a small number of individuals with little or no infrastructure support. Some Member States have shown how support can make a difference and increase participation in trials, contribute to the education of healthcare professionals and increase the pool of expert advisors for the regulatory process. In this context, reference was made to the need for financing (national) infrastructure for establishing a comprehensive framework of paediatric expertise in building capacity and conducting trials in specialised investigation settings.

## **N. OTHER POINTS**

53. Other points raised in the public consultation related to occasional divergences between the opinion of the Paediatric Committee and the Committee for Human Medicinal Products, as they intervene at different stages in the process. Efforts should be made to avoid such divergences. Similarly, national competent authorities or national ethics committees may question certain studies that are part of a paediatric investigation plan, resulting in lengthy discussions and sometimes negative opinions on trials and medicine-related research in children. The situation may be further complicated by varying ethical opinions among different Member States. Those comments were often combined with a call to change and/or simplify the ‘bureaucracy’ around clinical trials.
54. Several industry respondents argue that they encounter difficulties due to the administrative burden caused by some procedures for the practical implementation of the Regulation. It is believed that this has led to sub-optimal use of resources both for companies and authorities.
55. It was also claimed that education in paediatric clinical pharmacology is scarce in the European Union, making it difficult for healthcare professionals to enlarge their knowledge.
56. Patient and parent organisations among the respondents highlighted the role those organisations could play in the dissemination of information.
57. According to some respondents, an area for further improvement is the need for suitable dosage forms for the different subsets of the paediatric population (age-appropriate formulations), as well as the issue of suitability of certain excipients.
58. Finally, it was pointed out, and deplored, that neither homeopathic medicinal products nor traditional herbal medicinal products are recognised by the Regulation as contributing to the health of children.

\* \* \*