

COMMENTS FROM THE SPANISH SOCIETY OF CLINICAL PHARMACOLOGY (WORKING PARTY GROUP OF PEDIATRICS CLINICAL PHARMACOLOGY) ON THE EXPERIENCED ACQUIRED AND LESSONS LEARNT AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION

1. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Consultation item no. 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

The entry in force of Paediatric Regulation has been an important contributor for development of specific medicines for children considering that this development is an obligation for companies. We must not lose sight of the fact that the needs of the children do not always coincide with those of adults and the latter are the ones that mark the development of medicines. Therefore, although in the future it is expected that many medicines that will be used in children have been investigated in them, but only those that are going to be used in adults.

2. HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

Consultation item No 2: Do you agree with the above assessment?

Certainly, it would be necessary more time to assess the impact of Paediatric Regulation in terms of output. In any case, only comparing off-label use with and without the regulation doesn't seem an indicator adequate on results of the implementation. We must not lose sight of the fact, that the most of the "off-label use of medicinal products" are old medicines widely used and endorsed by recommendations and guides; some of them have been investigated in small academic non-profit trials and other are used based in experience. Therefore, it is likely that many clinicians will continue to use these old medicines instead innovative that will have an authorised indication.

3. THE PUMA CONCEPT: 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?

Probably the reasons for the disappointing uptake of the PUMA are the ignorance for this opportunity, the lack of economic resources by non-commercial researchers and small companies and the ignorance of the administrative procedures in the patents application. If the opportunity is disclosed and provides administrative support for patent applications, it is likely that PUMA will become more attractive.

The off-patents drugs are often very old. Therefore the economic interest of the companies could be low even with the offer of 10 years exclusivity. Moreover, the results of the clinical trials with this kind of medicines would be negative and the industry may not be eager to take the risk of lack of efficacy. PUMA may be more attractive in the coming years when there are more modern and with higher economic value off-patent drugs.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS

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.

No comment

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

Consultation item No 5: Do you have any comments on the above?

We agree with the drugs are developed in areas where there is a market in the adult population. Hence, the paediatric investigation plan should evaluate the innovative medicines already investigated in adults, because these pathologies are orphan when it happens in children.

Obviously, since a Healthcare Professional (HCP) point of view the real issue is due to drugs are developed attending to expectations of the market, but not to the public health needs. In recent years, we have known about the decrease in research of prevalent pathologies, due to difficulties or failures in the developed of new drugs, with a parallel decrease on the development on paediatric medication; for example: obesity, antibiotics. In this sense, it should be stimulated the research in areas of low economic interest or unattractive commercially.

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

Consultation item No 6: Do you agree with the above?

Yes, the Paediatric regulation may be an additional burden for pharmaceutical companies, but is a necessary regulation. We have considerer the rewards and that EMA and Paediatric Committee has tried to reduce this burden as much as possible.

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

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?

We are agreed that articles 45/46 have been a successful tool for obtaining new paediatric data. Contrary to the assumption that very few paediatric data had ever been collected, since the implementation of this tool it has been obtained results from more than 18.000 completed paediatric studies.

But we are disagree with the point that it have been an efficient tool taking into account that since 2008, study reports of approximately 2200 medicinal products were submitted to the competent authorities and up to date (5 years after), only it has been published assessment reports of 140 of them. Many of these reports included recommendations for updating the Summary of Product Characteristics (SmPC) for paediatric information but not all of these updates have been done.

We understand that the assessment of all paediatric data submitted to the competent authorities represent a large workload since resources are limited but it is necessary to be quicker in the assessment in order to improve efficiency. Other alternatives should be studied.

It is certain that Marketing Authorization Holders (MAH) have shown little interest in updating SmPC and Package Leaflets (PL) on a voluntary basis and even after the recommendations included in the assessment reports. But it is important to highlight that even when recommendations are not yet implemented in the SmPCs the outcome of the work-sharing

procedure is useful to health care professionals because they are made public systematically. Perhaps, in order to ensure that this information reaches all health professionals, the usefulness of the published assessment reports should be directed to them by national communications.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

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?

Against the following statement "*Healthcare professionals not as receptive as expected*", we consider that professional in direct contact with paediatrics' health are very sensitive to deepen the knowledge about the better use of medicines in children; therefore any new scientific information would be welcome. Obviously, the improvement of children's access to necessary medicines as well as improved legal and scientific conditions for the adequate use of medicines in paediatrics constitutes an important objective among HCP. The fact that in practice numerous medicines used in children have never been studied in this population and they are prescribed as off-label must not be in itself a problem. So, numerous and widely accepted therapeutic recommendations or practice guidelines in children regarding medicines, are not in accordance with the formally approved conditions of use in the summary product characteristics, even in cases where good supporting scientific evidence is available.

In any case, an adequate flow of information about to the actual use of drugs in clinical practice should be established between professionals and National Competent Authorities (NCA). We agree that it is at national level where it is necessary to work in order to explore new ways of collaboration between authorities and healthcare professional.

Regarding clinical research, it is necessary to arrange of resources and support's structures at different level (NCA, hospital, universities, scientific societies...) to facilitate the paediatric clinical research. Besides on, it is very important to promote the formation in certain related areas such us methodological, regulatory...We consider that HCP are interesting in having the best tools in the health care for the children and they are willing to actively participate in many activities, including research, are directed to obtain that goal.

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

We agree that it is necessary to investigate and evaluate medicines in children to get the data to optimize the potential benefits and minimize risks related to drugs in this population. The scientific community recognizes that clinical trial is the best tool to evaluate the efficacy and safety of medicines, while conducting clinical trials in this population presents certain "special" considerations on ethical, methodological and practical to be taken into account. We would like to do a reflection about ethical and methodological aspects, taking into account its importance in this vulnerable population.

Regarding ethics, the conduct of any study in children should be carefully balanced with the need to protect you from the potential risks and inconvenience for participation. When assessing the acceptability from the ethical point of view, a study in children is of special relevance to establish the level of risk of interventions that will be performed. The European Commission guidance on ethical consideration in conducting trials in children, published in 2008, set out three level of risk. However, there is no agreement on the definition of what constitutes "minimal risk" and "minor increment over minimal risk" nor on how these definitions apply to different study populations (e.g. sick children enrolled on therapeutic trials versus healthy volunteer children, different age groups). It is presumable a heterogeneous categorization of risk, it is subject to subjective considerations by both researchers and members of the REC who bear the assessment and approval of these studies. In a survey performed in our country among investigators and Research Ethical Committee (REC) members, a significant variability of the categorization of risk by paediatric researches and REC members and confirm the findings of similar published study (performed in USA)**. For example, 54% of participants considered arterial puncture in healthy 12-year old as minor increase over minimal risk (level 2), whereas 28% classified it as more than a minor increase over minimal risk (level 3) and 18% as minimal risk (level 1); this is variability was also detected in the newborn (49% level 2, 39% level 3 and 12% level 1).

In our view, this variability in assessment of risk suggests that these judgments are based on subjective criteria and personal experience. A European consensus on recommended criteria would be necessary to facilitate and standardize the work of RECs and researchers. There is a need for specific training of both on the risks children face in daily life and during routine physical or psychological tests.

Since a methodological point of view, several factors have been pointed out such as: pharmacokinetic variability, available efficacy end-points, validate scales, adequate exploration test and invasive procedure, follow-up periods..... In addition to these, it is worth mentioning the choice of comparator in non-inferiority clinical trials. We reinforce and support the use of "off-label medicines" (usually the gold standard treatment) as comparator in non-inferiority trials; the data from these studies would contribute to take clinical decisions regarding to choose of a medicinal product considering its comparative safety and efficacy.

**MINIMAL RISK FOR PEDIATRIC RESEARCH. SPANISH CONSIDERATIONS. Cabrera García L., Salcedo de Diego I., Sancho López A., Ruiz Antorán B. Clinical Pharmacology Department. University Hospital Puerta de Hierro Majadahonda, Madrid. XXII Congress of Spanish Society of Clinical Pharmacology*

**Seema Shah, Amy Whittle, Benjamin Wilfond, Gary Gensler, David Wendler. How Do Institutional Review Boards Apply the Federal Risk and Benefit Standards for Pediatric Research? JAMA. 2004;291:476-482*

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

Consultation item No 10: Do you have any comments on this point?

A way to avoid unnecessary efforts may be that a form with a preliminary description and the commitment to submit a complete plan would be presented at the end of phase I; the complete research plan (PIP) would be submitted after complete phase II only if it has been successful and the development plan is going to continue.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

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?

No comment

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?

In general, we think that the implementation of this regulation has had a positive impact in the development to medicines for children. Nevertheless, at present the real impact in the clinical practice have not been relevant. One area with less progress is the off-patent medicinal products that are still widely used in the paediatric population. In many cases, there are sufficient data in the published literature and the use of numerous off-label products have been endorsed by accepted clinical guidelines, however this knowledge have not been suitably

transferred to healthcare professionals. In our view, any alternative to the classical way to incorporate new relevant data in the Summary Product Characteristics (SPC) should be explored, in order to be able to include efficacy and safety data from independent clinical studies in children in different sections of SPC (e.g.: 4.2, 4.4, 4.8, and 5.1).