MINISTERIO
DE SANIDAD, SERVICIOS SOCIALES
E IGUALDAD

agencia española de
medicamentos y
productos sanitarios

DIRECCIÓN DE LA
AGENCIA ESPAÑOLA
DE MEDICAMENTOS Y
PRODUCTOS
SANITARIOS

COMMENTS OF THE SPANISH AGENCY OF MEDICINES AND MEDICAL DEVICES (AEMPS) TO THE EC PUBLIC CONSULTATION ON THE PAEDIATRIC LEGISLATION.

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?

AEMPS comments

Yes, in our opinion this is the case. However, the results of its implementation may not be appreciated yet if judged in terms of new medicines available for children as a vast majority of the Paediatric Investigation Plans (PIP) include some deferred measures. What we have observed at national level is that certainly the number of initiatives (scientific meetings etc.) intended to raise public and professional awareness of the specificities of the paediatric population has increased since the entry into force of the legislation.

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

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

AEMPS comments

Yes, it is likely that to assess the real impact of the paediatric regulation further time is needed (see also our previous comment).

Regarding off-label use it is really difficult to tackle it as there does not seem to be single databases that permit to obtain an overall overview of this off-label use. In the absence of this, let's say, baseline measure any comparison before and after the legislation may be difficult to perform/interpret. Paediatric Investigation Plans (PIP) represent a prospective approach (rather than a retrospective one as in the case of art. 45/46) and this is seen as a major improvement regarding potential off-label use in the future.

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?

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AEMPS comments

The idea of providing age-appropriate formulations and generating some additional clinical data (if needed) for off-patent medicinal products used off-label in the paediatric population was unimaginable before the paediatric legislation and is seen as a major achievement. However, it is agreed that the operational model to put this into practice, i.e. the PUMA and incentives/rewards foreseen in the paediatric legislation have not adequately worked so far.

It is likely that to improve the outcome in terms of PUMAs national measures dealing with substitution and funding have a major impact. In Spain, for instance, where prescription was done by active substance the PUMA concept has not been attractive.

Since Royal Decree 16/2012 formulations specifically intended for the treatment of the paediatric population are excluded from the system of prices of reference. This may stimulate the engagement of small and medium enterprises in the development of age-appropriate formulations.

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.

AEMPS comments

This seems to be the case, i.e. that the development in adults has not impact on timelines in adult development. Obviously, there are some exceptions, e.g. where PIPs are not agreed after first submission but the system in place ensures appropriate communication between PDCO co-ordinators, PDCO rapporteurs/peer reviewers and Applicants. Furthermore, PDCO members and staff are vey aware of the fact that adult marketing authorisation should not be delayed because of the paediatric development. Deferrals certainly help to smooth the process but for any deferral a measure should be included in the PIP and they mostly obey to scientific reasons and not merely to avoid delays in adult marketing authorisations.

A completely different issue is whether all Competent Authorities are aware of the requirements for a PIP and do not validate marketing authorisation applications in the absence of a PIP/deferral/waiver regardless whether this is needed or not according to the legislation.

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?

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AEMPS comments

The majority of the paediatric developments are preceded by adult development in similar (although not equal) conditions. The paediatric development certainly needs to be closely related to the adult one for the purpose of extrapolation, i.e. for bridging adult data into paediatric development that can be used to streamline the latter. However, if the progress in terms of authorised products for use in children is left to company's product strategy with respect to the adult population then areas of higher medical need such as Oncology and neonates will continue to be orphan. In the case of Oncology because extrapolation from adults may be really difficult due to the different types of tumours that children suffer and in neonates due to the specificity of their diseases that most of the times are not comparable to any adult disease.

THE BURDEN/REWARD RATIO — A BALANCED APPROACH?

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

AEMPS comments

It is agreed that measures have been implemented to streamline the PIP submission and assessment in an attempt to reduce burden for PIP Applicants. Regarding the reward as this is a competence of the patent offices is difficult for us to comment. However, the fact that there are different interpretations in Member Sates regarding whether patent extensions can be granted or not is not reassuring. A more homogenous approach would be essential. Similarly, restrictive interpretations of the timing requirement of Article 36 (see below) should, perhaps, be avoided.

TITLE V
REWARDS AND INCENTIVES
Article 36
1. Where an application under Article 7 or 8 includes the results of all studies conducted in compliance with an agreed paediatric investigation plan, the holder of the patent or supplementary protection certificate shall be entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92.

The first subparagraph shall also apply where completion of the agreed paediatric investigation plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the summary of product characteristics
and, if appropriate, in the package leaflet of the medicinal product concerned.

2. The inclusion in a marketing authorisation of the statement referred to in Article 28(3) shall be used for the purposes of applying paragraph 1 of this Article.

3. Where the procedures laid down in Directive 2001/83/EC have been used, the six-month extension of the period referred to in paragraph 1 shall be granted only if the product is authorised in all Member States.

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4. Paragraphs 1, 2 and 3 shall apply to products that are protected by a supplementary protection certificate under Regulation (EEC) No 1768/92, or under a patent which qualifies for the granting of the supplementary protection certificate. They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC) No 141/2000.

5. In the case of an application under Article 8 which leads to the authorisation of a new paediatric indication, paragraphs 1, 2 and 3 shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies, in accordance with Article 14(11) of Regulation (EC) No 726/2004 or the fourth subparagraph of Article 10(1) of Directive 2001/83/EC.

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?

AEMPS comments

Overall it is agreed that the rationale behind art. 45 and 46, i.e. to update product information of authorised products with information that is relevant for the paediatric population is a very valid one.

However, it can also be argued that in some cases as a consequence of the assessment process restrictions are imposed to the SmPC of medicinal products with indications/posology authorised in children. In these cases it seems essential to address whether for these medicinal products there is a long-standing well-established use. If this were the case the aim should not be to fit these long standing well-established products into new templates tailored for new drugs.

Overall, our opinion is that article 45 in particular has not been successful mainly because the provided information is in many cases of low quality and outdated.

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?

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AEMPS comments

The issue in our opinion that health care professionals, paediatricians in particular, may not be completely aware that they are using some medicinal products off-label. They may be also convinced that the available evidence is sufficient and have the feeling that there are no further needs. In this regard, it would be difficult to engage them precisely in clinical trials investigating off-patent products.

As previously said identifying which medicinal products are being used off-label and for which indications and at which doses it is not easy as there is no single database collecting such data. A first step would be to have a common definition of off-label use and try to identify per paediatric sub-speciality the most frequent off-label use.

The available evidence should be reviewed and updated recommendations, if available, implemented in the SmPC (rather than looking at outdated data). A criticism of art. 45 assessment process is that its outcome is not always implemented in the SmPC, either because the MAH is not willing to do so or due to delays in the regulatory process. However, it is likely that this improve if agencies at national level track this process and implement changes in the SmPC on their own motion.

Several initiatives are taken place outside the regulatory environment to update the information on the use of medicinal products in paediatrics such as the Committee for Medicinal Products of the Spanish Paediatric Association (CMED- AEP), a working group which has as its aim to adjust the use of drugs in children in our country by reviewing and compiling the available evidence.

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?

AEMPS comments

In our opinion the paediatric legislation has fostered a new setting in which the assessment of clinical trials in the paediatric population has considerably improved both at the level of national agencies and Ethics Committees. New concepts such as extrapolation and how to make it operational, measures to reduce pain or stress, blood volumes to be drawn etc. are now systematically taken into consideration.

Therefore, increasing the expertise in the assessment of paediatric data is on its own a great achievement in our opinion.

UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

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

AEMPS comments

No additional comments.

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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?

AEMPS comments

Yes, we agree on that. See also our comment on consultation item No. 9.

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?

AEMPS comments

For us the most disappointing aspect would be that the paediatric development is mainly driven by Companies' strategy regarding adult development instead of being driven by the medical need in the paediatric population.

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