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

Comments from:

Name of organisation or individual
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When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

Consultation item n° 1: A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

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?

Comment

I fully agree with such a general statement and I greatly appreciate the adoption of the Paediatric Regulation as well as most of the provisions laid down in this legal text

However a more balanced point of view should be introduced as far as some specific medicinal products are concerned
Medicines such as vaccines have been and are still developed in many instances for Paediatric use (even, for many of these, exclusively). As they are preventative medicines , the pharmacological effect being achieved through solicitation of the immune system, any developments of a paediatric vaccine shall be (and has always been) developed in the paediatric population that is intended to be given the products
In addition, pharmacokinetic studies are not applicable to those medicines and the Paediatric Investigation Plan has to be submitted as soon as a "proof of concept" is made available, i.e. at a time setting up the terms of a realistic development plan is not feasible.
Some special provisions would be needed for this type of medicinal products

Consultation item n°2: HAS THE REGULATION DELIVERED IN TERMS OF OUTPUTS? TOO EARLY TO JUDGE
Do you agree with the above assessment?

Comments

I indeed agree. However, again, the strategy of the companies is often modified more than once during the development of medicinal products as this strategy is established in function of the successive clinical observations and events occurring along the successive clinical trials
Therefore, this would justify not to submit a Paediatric Investigation Plan before the end of phase II, at a time the company sufficiently knows its medicinal product's characteristics.
Such a measure would prevent heavy administrative burden and delays due to successive amendments and modifications to the Paediatric Investigation Plans

Consultation item n°3: The PUMA CONCEPT. A DISAPPOINTMENT
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?

Comments

No. PUMA is an excellent rule
However, the condition of success would imply from the EMA scientific experts and regulators an approach differing from the one so far applied.
In fact, we are dealing here with a medicinal product that is on the market and well known, with a positive risk/benefit ratio.(at least in some categories of the population)
Clearly, the paediatric use requires a cautious scientific assessment.
But the (limited) experience has shown that the paediatric use product is considered as a brand new entity.
The regulators are not taking into account the existence and performance of the authorized product, used since several years in other populations. This is hard to accept.

It is my understanding that, reviewing a PUMA as a fully new medicinal product
Does not comply with the spirit of the law
Here is the disappointment and the reason for some failures!
Companies have realized this fact and this might explain their reluctance in submitting PUMAs

Consultation item n°4: WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS
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.

Comments

This statement is verified in some instances
In other instances, delays have been experienced –even in MAA of medicinal products intended for adult populations
This results from difficulties due to bureaucratic approaches in the implementation of the Paediatric Regulation by EMA, in particular at the level of compliance checking.
The Regulation itself is not responsible for these delays, that are due to extremely detailed and complex requirements in interpretation of the PIP system itself and in particular of the (often interim) compliance checking system
("interim compliance", i.e. for medicinal products with deferrals does not appear to have been foreseen by the law!)

Consultation item n°5: MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

Do you have any comments on the above?

Comments
No personal comment

Consultation item n°6: THE BURDEN/REWARD RATIO – A BALANCED APPROACH?

Do you agree with the above?

Comments
It is a fact that this does not apply to all medicinal products , for example vaccines, that are anyway developed in almost all cases for the paediatric population **In addition, such medicinal products DO NOT BENEFIT FROM ANY REWARD/INCENTIVES: they are biologicals. Generic medicines are not feasible and , in addition , biosimilar medicinal products rules are not applicable to vaccines. Each vaccine is a new product.** **Therefore, data protection is of extremely limited use.** **Few vaccines are patent protected (there are exceptions) and the extent in SPC of low interest** **For these reasons, it should be reasonable to reduce the burden of the Paediatric Investigation Plan that as implemented today by EMA, and that is particularly requiring for vaccines**

Consultation item n°7: ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

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?

Comments
In theory, I agree with this statement However, Art 46 sometimes leads to additinal discussions and new requirements at CHMP level In addition, -in the case of vaccines again- the completion of the Final study Report within 6 months is often very unlikely to be feasible

Consultation item n°8: LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

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?

Comments
No specific comments: yes, additional information is needed Will this modify the behaviour of practitioners? They in general are not strongly influenced by national authorities actions

Consultation item n°9 : CLINICAL TRIALS WITH CHILDREN : NO SPECIFIC PROBLEMS DETECTED – Do you have any comments on the developments in clinical trials with children following the adoption of the Regulation and in view of this description

Comments

1. First comment: duplication between studies with similar medicines are unavoidable; No company would agree to share results of pre-authorisation clinical trials with competitors for evident reasons

2 Second remark: Many studies are today carried out outside EU as the Clinical Trials Directive (fortunately to be replaced by a Regulation,) creates unbelievable burden and alterations to the clinical protocols due to divergent reactions from individual MSs and also from Ethics Committees

3 Third remark: At least in some therapeutic areas (such as vaccines), the Ethics Committees are regularly reluctant to accept studies recommended by the Paediatric Committee: as an example, vaccination with vaccines against viruses that do not circulate (yet) in the EU are hardly accepted in children . This is the case of vaccines involving viruses with a potential Influenza Pandemic.

Consultation item n°10: UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

Do you have any comments on this point?

Comments
Not all "medicinal products" starting clinical trials phase I will lead to the development of actual medicinal products. **Many of these will be abandoned during the clinical development for reasons related to safety or efficacy results** **Thus requiring a Paediatric Investigation Plan so early in the development inevitably creates burden, workload and expenses in many instances useless.** **At least mid of phase II results in adults should be reached before a company might expect to be sure that it will be able to achieve the development of a new medicine**

Consultation item n°11: SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union

Comments
Agree

Consultation item n° 12: ANY OTHER ISSUE?
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?

Comments

As a conclusion, it is my opinion that the Paediatric Regulation is an excellent initiative and the provisions laid down in this law are in general excellent: tools well defined, reasonable requirements…
In this sense, it meets the expectation and I really appreciate the adoption of this legal document

<u>However they are two major issues responsible for high burden , additional workload and delays:</u>

1 <u>The Paediatric Investigation Plan is required too early</u> in the development of a medicinal product. Today, it shall be submitted at a moment where the company does not have sufficient information on its adult future product (dosage? Schedules? Safety? Specific presentation for children? Efficacy?...and timelines.) and does not have any information on its paediatric use

2 As a consequence,--- and in addition, due to the huge level of specific information required by PDCO, such as exact number of subjects, precise timelines that shall be strictly met-- various major <u>amendments to the Paediatric Investigation Plan</u> have to be submitted all along the development.
In case of failure of the development, burden and workload are shown useless.

3. <u>Despite the fact that this is not the objective of the current consultation, it must be stressed that the over bureaucratic rules set up by EMA staff</u> –and in some instances questionable interpretation of the law- are leading to significant workload that is of no added value and represents a risk of delay in the Marketing Authorisation Applications of the paediatric medicinal products (sometimes significant delay) and this has been true as well for some adult indications.
This is due to amendments required for extremely minor reasons followed by a complex interim Compliance Checking system

4. Also, <u>divergences</u> occasionally occur between the PDCO requirements and the CHMP views. Coordination between the committees would be highly helpful

5. Finally no rewards/incentives are available for some categories of products for which the Committees are particularly requiring (such as vaccines)