EURORDIS
European Organisation for Rare Diseases

"MEDICINES FOR CHILDREN: BETTER, MORE AND FASTER"

EURORDIS POSITION PAPER ON THE PROPOSAL FOR A REGULATION ON MEDICINAL PRODUCTS FOR PAEDIATRIC USE

EURORDIS - the European Organisation for Rare Diseases - represents 225 rare disease organisations from 23 countries, 15 of which are EU member states, and thereby reflects the voice of 30 million patients affected by rare diseases, both children and adults, in the enlarged Europe.

Eurordis strongly welcomes the Commission's proposal for a regulation on medicinal products for paediatric use, and supports the overall objective of this proposal. Children in general, as they are still developing, respond differently to medicines than adults do. About 50% of all people affected by rare disorders are less than 19 years old, these children are particularly vulnerable to the impact of the lack of knowledge in the absence of paediatric studies.

Doctors are often required to prescribe medicines to newborns, infants, toddlers, children or adolescents based on non-validated (i.e. experimental) medical practices, in an attempt to manage or relieve some of the symptoms associated with their medical conditions. We estimate that two-thirds of these children are being prescribed unlicensed or off-label drugs. The risks of inefficacy and/or immediate or long-term adverse reactions are clear.

These figures do not fully reflect the lack of information regarding the use of new medicines in children, which concerns approximately 60% of medicines approved by the Centralised Procedure and up to 85% approved by Mutual Recognition or Nationally. It is particularly paradoxical to observe that even for designated orphan drugs, of which 66% have an indication exclusively for children or both for children and adults, very few sponsors are submitting data from paediatric studies when requesting marketing authorisation, or raising specific questions on paediatric populations when requesting protocol assistance.

For these reasons, EURORDIS strongly supports the Commission's proposal, which aims to remedy this inequitable situation. We are particularly pleased with the proposed extension to twelve years of the current ten-year orphan market exclusivity, if the requirements for data on use in children of designated orphan medicinal products are fully met (Article 37), and also with Article 22, paragraph 1, which regulates and sets the limits of the deferral.

Nevertheless, we would like to raise some concerns and propose some improvements. In particular, we are concerned that the incentives proposed may not be attractive enough for the sponsors, while the regulatory procedure may be too complex, particularly for small companies. In addition, we fear that the sponsors' obligations may prove too non-committal to guarantee the expected paediatric studies.

Therefore, we put forward the following ten proposals:

1. Renouncement to paediatric development: a clear choice

In order to increase the responsibility of the industry, when a company is developing a new drug it has to make a clear choice: to develop or not develop the paediatric form. When it is not willing to develop the paediatric form, the marketing authorisation holder should be obliged, within a period of six months from the application for marketing authorisation, to officially renounce its interest in developing the paediatric studies. In fact, repetition of deferrals or delays in a Paediatric Investigation Plan, are not acceptable when children are waiting. The official renouncement to paediatric development by the Marketing Authorisation holder will constitute an incentive for other companies to develop the paediatric form.

This system would avoid the abusive utilisation of deferrals as a stalling tactic and accelerate the availability of medicines for children. It should apply at least to areas where there is a recognised unmet medical need and identified children public health priorities.

Due to the lack of competition between adult and paediatric forms, data protection granted for the adult form will not apply to the development of the paediatric form. The list of products affected by such a decision should be published on the European Medicines Agency website.

2. New products and deferral

- We believe that the six-month extension for the Supplementary Protection Certificate is a satisfactory incentive for performing studies in paediatric populations. But we fear that the Paediatric Committee would systematically be asked to grant a deferral in order not to delay the authorisation of medicines for adults. We would like to include a provision, which would oblige the sponsor to submit the Paediatric Investigation Plan at least two years before submitting a marketing authorisation application. This would avoid sponsors rapidly putting a medicine for adults on the market while delaying undertaking the paediatric studies for years – in contradiction with the spirit of the Regulation**.** After a request for deferral, the MA holder of an adult form of a medicine should be asked to take a definite stand, either by submitting a Paediatric Investigation Plan or by officially renouncing to develop a medicine for paediatric use. (cf 6. Renouncement).

- Deferrals should be detailed opinions, stating milestones and deadlines, including different stages for discussion between the Paediatric Committee and the sponsor for "go" – "no go" decisions.

- Article 35, paragraph 3 foresees that «in the case of a deferral, the marketing authorisation holder shall submit an annual report to the Agency providing an update on progress with paediatric studies (…)». We believe that in order for this provision to be effective, the non-respect of the commitments specified in the PIP should be made public**.** In case of repeated non-respect of the commitments, the MA holder should, as for the submission of the PIP, choose between renouncing or developing the medicinal product as agreed. This information should be made available on the European Medicines Agency website.

3. PUMA through Centralised Procedure

The Centralised Procedure should be compulsory to obtain PUMA. This would be more coherent with the other centralised tools such as the Paediatric Investigation Plans and the SAWG as it would help ensure consistency of the decision-making process.

4. Paediatric Committee and its tasks

We would like to ensure the proper coordination of work between the EMEA scientific committees and working parties, such as the COMP, the SAWP for Protocol Assistance, the Paediatric Committee and the CHMP. This coordination would ensure that opinions and advice are consistent and supportive to each other, geared towards helping sponsors to succeed in their drug development.

When implementing the Regulation, the scientific co-ordination could be a critical issue. We propose that "tutors" be assigned for each Paediatric Investigation Plan in order to follow its development as external experts, and to provide scientific advice, protocol assistance and risk/benefit assessment at the time of the marketing authorisation application. These tutors could be either EMEA scientific staff members or assigned national agency rapporteurs.

We believe that the tasks assigned to the Paediatric Committee should go beyond assessing the Paediatric Investigation Plan and include the following responsibilities:

- To publish a list of unmet medical needs in medicines for paediatric use on the basis of the inventory referred to in article 42. We also propose that the inventory be updated "annually" rather than "on a regular basis";
- To publish a children's public health list of priorities based on a set of criteria developed by the Paediatric Committee and made public;
- To publish targeted calls for submission of Paediatric Investigation Plans to address critical unmet medical needs;
- To support and advise the Agency in liaising internationally on matters relating to paediatric medicines and in liaising with patient associations, medical experts, and learned societies.

In order to simplify the procedure and lower the risks of increased bureaucracy, it could have been envisaged to revamp and enlarge the missions of the SAWP to include the missions of the Paediatric Committee.

5. Public awareness, information and training for patient groups, patient access to paediatric clinical trials and drugs, direct reporting of adverse events

Because the general public is unaware of the current practice of non-validated prescriptions for children, it is reluctant to have its own children participate in a clinical trial. As a result of this Regulation, paediatric studies are expected to increase in Europe but a bottleneck might be the lack of willingness of parents to give their consent. We believe that a communication effort towards the public, through patient groups, is a crucial element for the success of the Regulation's implementation. We suggest:

- Including a new article providing the Paediatric Committee with the mandate and appropriate resources to support public awareness efforts, through information and relevant training for patient groups. The trained patient organisation representatives could be potentially used as external experts by the EMEA;
- All ongoing clinical trials for children should be made public, waiving confidentiality on EUDRAC;
- We suggest clarifying in the Regulation who will monitor information on market availability in each Member State and how this will be done. This information should be made public.

We continue to support the provision of a patient-parent system for reporting adverse events. This would give parents the comfort, especially when their child is undergoing a new medical treatment, of reporting their concerns directly to an independent system Provision should be made for this special reporting system to be promoted by the company to all patients e.g. through the patient information leaflet.

6. Paediatric Investigation Plan

- There should be a reference within the Regulation to the specificities of the design and statistical methods for clinical studies on small populations and to the specific need for high ethical standards for studies involving children.

- The opinions adopted by the Paediatric Committee on the Paediatric Investigation Plans should be binding and opposable to the CHMP.

- The Agency shall adopt a decision on the opinions of the Paediatric Committee within 30 days and not "without delay" as currently proposed by the Regulation in article 26, paragraph 4.

- Provision should be made to allow the Paediatric Committee to publish the names of organisations that are least supportive of the development of medicines for children. A table of the most recently approved medicines for children and all deferrals should be published on the European Medicines Agency website.

7. Labelling for all products: paediatric and adult

- For new products, when a Market Authorisation is granted for a paediatric indication, then the "P" should appear on the packaging to distinguish it from adult formulation.

- When paediatric studies have been performed for a medicinal product marketed for the adult population - either new or off-patent through the PUMA - then a "P scratch" or an "A" should appear on the packaging and in the patient leaflet. In this way, cheaper adult formulation cannot be sold for treating a child with the wrong dose, regimen or inadequate pharmacovigilance. This would ensure safety for children but also "commercial loyalty" towards the sponsors having performed the paediatric studies.

8. Waiver

- We believe that waivers should also be granted when satisfactory alternative methods of treatment exist for the same indication in children. It would not be ethical to perform unnecessary clinical trials in paediatric populations when a satisfactory treatment already exists in a given therapeutic class. A list of products reviewed by the Paediatric Committee should be published on the European Medicines Agency website.

- Article 15, paragraph 3, stipulates that «if a waiver (…) is revoked, the requirement set out in Articles 8 and 9 shall not apply for 36 months from the date of its removal from the list of waivers». We do not understand why this period is so lengthy, and consider a one year period of re-launching of the paediatric studies sufficient. If the sponsor, under exceptional circumstances, needs more time, the request for further delay should be presented to the Paediatric Committee with an adequate justification.

9. Pre-existing studies

- All available data should be used. It would be unethical to duplicate studies in children when data are already available, either from studies performed elsewhere in the world or from the use of unlicensed or off-label products. The Paediatric Committee should be authorised to evaluate all existing clinical data and request additional data only when necessary. The Agency will need to have the appropriate resources, either internally or through collective expertise groups, to perform the above-mentioned evaluation tasks.

- When a medicinal product has been studied in the paediatric population and has been reviewed by a EU national regulatory agency or by the FDA (using the EU-FDA confidentiality agreement), then the Paediatric Committee will review these data and avoid any duplication of studies or Paediatric Investigation Plan differing significantly from the EU national or the US Written Request.

10. Medicines Investigation for the Children of Europe (MICE)

We strongly favoured the project of establishing MICE within this regulation. In fact, the absence of adequate financial support in the Regulation seriously undermines the scope of the legislative framework. However, now that the proposed Regulation refers MICE to a future legislative proposal, we urge the Commission to advance rapidly on this issue.

In conclusion

We suggest that the Regulation, in order to reach its goals and objectives in the implementation phase, should ensure the following elements:

- To better balance financial incentives with responsibilities in order to really create an attitude and cultural change of all interested parties: paediatricians, clinical research centres, regulators, major pharmaceutical companies, SMEs specialising in paediatric drugs, parents and the public, and national health authorities.

- To focus on medicines really needed in paediatric use – and only on those – while taking into consideration the specific methodologies and statistical methods of clinical trials in small populations, as well as the highly specific ethical issues related to the inclusion of children.

- To increase the sponsors' responsibility by submitting their Paediatric Investigation Plans in due time, avoiding over-use of deferrals and officially renouncing the paediatric development.

- To simplify the procedures by: strengthening the policy continuity and consistency between the scientific committees of EMEA, making the Paediatric Investigation Plans binding and opposable to the CHMP, promoting pro-active support of the sponsor, and establishing an obligatory centralised procedure for PUMA.

- To guarantee transparent information on real paediatric drug availability in each Member State.