Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report: PRESCRIRE'S RESPONSE (20/02/2017)

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: __PRESCRIRE_____

Transparency Register ID number (for organisations): __ 982539711698-79_____

Country:__FRANCE_____

E-mail address:___rkessler@prescrire.org_____

Received contributions may be published on the Commission's website, with the identity of the contributor. Please state your preference:

- My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication YES
- My contribution may be published but should be kept anonymous; I declare that none of it is subject to copyright restrictions that prevent publication
- I do not agree that my contribution will be published at all

Please indicate whether you are replying as:

- A citizen
- A business
- A non-governmental organisation (NGO) YES
- An industry association
- A patient group
- A healthcare professional organisation

  Academia or a research or educational institute

  A public authority
- Other (please specify)

If you are a business, please indicate the size of your business

- Self-employed
- Micro-enterprise (under 10 employees)
- Small enterprise (under 50 employees)
- Medium-sized enterprise (under 250 employees)
- Large company (250 employees or more)

Please indicate the level at which your organisation is active:

- Local
- National YES
- Across several countries YES
- EU YES
- Global

2. PART II – CONSULTATION ITEMS

(You may choose not to reply to every consultation items)

2.1. More medicines for children

Consultation item No 1: Do you agree that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines?

According to the EMA 10-year Report, the application of the 2006 Paediatric Regulation had a positive impact on the number of paediatric drug developments:

- 1000 paediatric investigation plans (PIPs) agreed
- 99 PIPs completed
- over 230 new medicines authorised for use by children

From the analysis of the international experience (EU, US, Canada, Japan), it appears however that to effectively support the development of paediatric medicines, specific legislation needs to be based not only on incentives but also on obligations.

Notwithstanding an increase in the number of paediatric drug developments due to the provision of considerable financial incentives and rewards, such a rise is not a guarantee for obtaining medicines that truly meet patient needs. The pitfalls of the application of the Paediatric Regulation were outlined in *Prescrire*'s response to the consultation in 2012 (1). The case of *losartan* (Cozaar°), an oral suspension for the treatment of hypertension in children, marketed in an inadequate pharmaceutical form and unsuitably packaged, clearly illustrates the problem of a paediatric medicine that does not fully meet paediatric needs while taking advantage of the rewards provided by the Paediatric Regulation (1). *Atorvastatin* (Tahor°) and *rosuvastatin* (Crestor°), both treatments for hypercholesterolaemia, are examples where limited evaluation was carried out without examining morbidity and mortality in the first case, and without investigating long-term effects in the second case (2,3).
It must also be acknowledged that paediatric-use marketing authorisations (PUMAs) were put in place with the main aim of stimulating research on off-patent products to reduce ongoing off-label use in children. Despite the incentives, after 10 years of experience, only 2 PUMAs have been granted (see also section 2.12).

2.2. Mirroring paediatric needs

Consultation item No 2: Do you have any comments on the above? To what extent and in which therapeutic areas has the Regulation contributed to the availability of important new treatment options?

Public resources are limited and have to be used efficiently to meet the interests of the general public. Incentives and rewards offered to encourage the development of medicines suitable for children should therefore be restricted to R&D that addresses real or unmet paediatric needs.

According to Article 43 of the Paediatric Regulation, the Paediatric Committee must continuously establish the real therapeutic needs of highest priority for children and ensure that drugs with paediatric indications represent a tangible therapeutic advance. This information is published on the EMA website. Unfortunately, the information on paediatric needs for some therapeutic areas (anaesthesiology, immunology, obstructive lung disease, pain, psychiatry) dates from 2005, 2006 and 2007.

It is also crucial to adapt the pharmaceutical form (requiring evaluation of pharmaceutical excipients in children and the ongoing revision of the 2003 European guideline on excipients) and the packaging of paediatric drugs to make them suitable for paediatric use. Particular attention should also be paid to dosing accuracy, adaptation of SmPCs and the package leaflets (for parents and care givers), and the prevention of medication errors and accidental ingestion.

The experience with R&D of new paediatric medicines however raises doubts over whether real therapeutic needs are a fundamental objective for pharmaceutical companies. The problems with *losartan* are already outlined above. In addition, it might be questioned whether there was a real need to develop two other sartans (*valsartan* and *candesartan*) for children once *losartan* had been authorised. Another example of how unmet paediatric needs are not the driving force behind pharmaceutical companies' R&D strategies is that, in France, no ACE inhibitors have been developed in an oral liquid form to treat children. An oral liquid form of the ACE inhibitor *captopril* (Noyada°) has been used for many years through a compassionate use programme to treat the paediatric population.

National health agencies also adopt ambiguous practices: in the case of *tramadol* (analgesic) for use in children below the age of 1 year, the agencies on the one hand refused to allow its use for this new patient group (infants under 1 year) and on the other hand considered that the data provided would be useful to healthcare professionals and as such should be reflected in the SmPC (section 5.2 on pharmacokinetics and section 4.2 on posology). This information might be confusing for healthcare professionals.

2.3. Availability of paediatric medicines in the EU

Consultation item No 3: In your experience, has the number of new paediatric medicines available in Member States substantially increased? Have existing treatments been replaced by new licensed treatments?

2.4. Reasonable costs

Consultation item No 4: Do you have any comments on the costs for pharmaceutical companies to comply with an agreed paediatric investigation plan?

2.5. Functioning reward system

Consultation item No 5: Do you agree that the reward system generally functions well and that early, strategic planning will usually ensure that a company receives a reward?

2.6. The orphan reward

Consultation item No 6: How do you judge the importance of the orphan reward compared to the SPC reward?

The experience with the incentives and rewards provided by the Paediatric Regulation clearly illustrates that the pharmaceutical industry 'plays the system' strategically to obtain the highest possible financial and economic results.

The case of Glivec° (*imatinib*) perfectly illustrates the industry's strategic behaviour to maximise financial returns from intellectual property rights (IPR) protection. Novartis obtained orphan status for Glivec° in 2001. The patent protection period was extended in the Netherlands until June 2016 by a supplementary protection certificate (SPC). In April 2012, Novartis asked the European Commission to remove the orphan designation for all its therapeutic indications. In June 2012, Novartis applied for an extension of the marketing authorisation to include a paediatric indication. On the basis of the completed paediatric investigation plan (PIP), Novartis obtained a 6-month paediatric extension of the SPC providing protection in the Netherlands until December 2016. Novartis brought an infringement procedure against Teva, seeking an injunction to prevent Teva from launching its generic product before the 6-month paediatric extension of the SPC had expired. Based on the key principle of the Paediatric Regulation that paediatric research should be rewarded, the Dutch court confirmed that a former orphan designated medicinal product can enjoy a 6-month paediatric extension of an SPC.

The intention of the legislator when adopting the Paediatric Regulation was probably not to provide a catalogue of incentives to enable companies to choose the most attractive or profitable option. For *Prescrire* this is yet another example of how the pharmaceutical R&D system is overwhelmingly driven by financial interests, supported by an underlying misuse of the international IPR system.

2.7. Improved implementation

Consultation item No 7: Do you agree that the Regulation's implementation has improved over time and that some early problems have been solved?

2.8. Waivers and the 'mechanism of action' principle

Consultation item No 8: Do you have any comments on the above? Can you quantify and qualify missed opportunities in specific therapeutic areas in the last ten years?

2.9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?

2.10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?

2.11. Biosimilars

Consultation item No 11: Do you have any comments on the above?

2.12. PUMA — Paediatric-use marketing authorisation

Consultation item No 12: Do you share the view that the PUMA concept is a disappointment? What is the advantage of maintaining it? Could the development of off-patent medicines for paediatric use be further stimulated?

According to the 10-year Report, the 10-year data protection incentive, intended to stimulate the development of off-patent products for paediatric use, has not been very effective. Their off-label use in children continues to be a reality. Even after 10 years of experience with the application of the Paediatric Regulation, only 2 paediatric-use marketing authorisations (PUMAs) have been granted: for *midazolam* (Buccolam°) as an anticonvulsant and *propranolol* (Hemangiol°) to treat haemangioma (4,5). This clearly indicates the lack of interest and motivation among pharma companies to develop medicines adapted to the paediatric population despite the potential incentives to do so. It therefore appears that incentives alone are not enough to encourage research on medicines suitable for children. In order to work, incentives need to be accompanied by obligations.

Continued off-label use of off-patent products has significant limitations. Off-label use denies patients and health professionals the safeguards offered by marketing authorisation, such as an evaluation framework, approved posologies stated in the SmPC and package leaflet, and packaging suitable for paediatric use. Without these, healthcare professionals must rely on their own experience and what they can find in the scientific literature. This is a risky practice. To overcome this persistent problem, it is essential to provide public research funding for projects to investigate how these products can be used safely and effectively in children. *Prescrire* therefore calls on the EU institutions and Member States to encourage public research aimed at developing off-patent products for paediatric use. Public funding, for example from Horizon 2020, should be dedicated primarily to research initiatives related to clearly identified public health priorities and/or unmet needs, including research on off-patent products for paediatric use.

2.13. Scientifically valid and ethically sound — Clinical trials with children

Consultation item No 13: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above discussion?

2.14. The question of financial sustainability

Consultation item No 14: Do you have any views on the above and the fact that the paediatric investigation plan process is currently exempt from the fee system?

2.15. Positive impact on paediatric research in Europe

Consultation item No 15: How do you judge the effects of the Paediatric Regulation on paediatric research?

2.16. "Mirror, mirror on the wall" - Emerging trends and the future of paediatric medicines

Consultation item No 16: Are there any emerging trends that may have an impact on the development of paediatric medicines and the relevance of the Paediatric Regulation?

2.17. Other issues to be considered

Consultation item No 17: Overall, does the Regulation's implementation reflect your initial understanding/expectations of this piece of legislation? If not, please explain. Are there any other issues to be considered?

In summary, the 10-year experience gained with the Paediatric Regulation has shown the limitations and/or abuses of a reward/incentive system aimed at stimulating private for-profit R&D in areas of major medical need. *Prescrire* invites the European and national public authorities to invest more in independent public or academically-driven clinical research focused on real health needs, including paediatric medicines. Independent, publicly-funded trials aim to guide healthcare professionals in making the best therapeutic choices.
Governments have a duty to allocate public resources efficiently and transparently to serve the public interest and meet their citizens' needs. Therefore, when public money is used to support R&D projects (e.g. Horizon 2020, IMI, etc.), public returns should be demanded, including among others: an obligation to provide information on the actual cost of the drug's development and production; public sharing of the data and results of clinical research; and licensing conditions that ensure affordable access to medicinal products.
In addition, rather than focusing on data protection, it is time to launch large-scale open science initiatives to ensure that research findings and all associated data remain widely available, thus accelerating patient-centred scientific progress.

References:
1- Prescrire "Who benefits from the European Paediatric Regulation?" 28 November 2012: 6 pages.
2- Prescrire Rédaction "*atorvastatine* chez certains enfants" *Rev Prescrire* 2012; **32** (345): 500.
3- Prescrire Rédaction "*rosuvastatine* chez certains enfants" *Rev Prescrire* 2012; **32** (345): 500.
4- Prescrire Rédaction "*midazolam* par voie transmuqueuse buccale" *Rev Prescrire* 2013; **33** (354): 248-249.
5- Prescrire Rédaction "*propranolol* et hémangiomes graves des nourrissons" *Rev Prescrire* 2015; **35** (378): 246-250.