Consultation in relation to the Paediatric Report

Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

Your name or name of the organisation/company: European Society for Child and Adolescent Psychiatry (ESCAP)

Transparency Register ID number (for organisations): _____

Country:___Belgium_____

E-mail address:_stephan.eliez@etat.ge.ch; info@escap.eu _____

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

- X My contribution may be published under the name indicated; I declare that none of it is subject to copyright restrictions that prevent publication
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Please indicate whether you are replying as:

- o A citizen
- o A business
- X A non-governmental organisation (NGO)
- o An industry association
- o A patient group
- o A healthcare professional organisation
- o Academia or a research or educational institute
- o A public authority
- o Other (please specify)

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

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

Please indicate the level at which your organisation is active:

- o Local
- o National
- o Across several countries
- X EU
- X 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?
Yes

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?
We do agree that the reliance on adult needs/developments is not sufficient to cover all paediatric needs. Especially in the area of mental and behavioural disorders aspects of developmental biology are crucial since brain maturation extends throughout adolescence well into early adulthood. Safety and efficacy cannot be extrapolated from adults. Further, disorders with an early onset may not be sufficiently covered by clinical research in within the focus as compared to disorders with an adult onset. Thus, paediatric mental and behavioural disorders with dire needs for effective drugs are e.g. autism spectrum disorders, feeding and eating disorders, and early onset mood disorders. However, overall there is a lack of thoroughly investigated drugs for many child psychiatric disorders. Off-label prescription continues to be frequent despite insufficient data partly on short-term and, particularly, on long-term efficacy and safety. Since the paediatric regulation came into force, only two new medicines received authorisation and paediatric investigation plans (PIPs) concerning psychopharmacological drugs comprise but about 2% of all agreed PIPs. The 10-year Report of the European Commission cites WHO data that the disease burden based on DALYs in the EU is highest for mental and behavioural disorders (20% total DALYs). However, the Report states that "the need for medicines is not that high in this area" due to non-pharmacological treatment options. We strongly disagree with this statement. On the contrary, there is an urgent need for better medicines in the area of paediatric mental and behavioural disorders. 50% of all serious, chronic adult psychiatric illnesses start before the age of 14 (and 70% before 23). We are talking about often lifelong psychiatric disease starting in youth, which through early diagnosis and treatment could prevent decades of suffering in adult life. Of course well trialled medication is an essential part of a bio-psycho-social treatment approach. The number of psychopharmacologically treated children and adolescents as well as the duration of exposure increased substantially in the past decades. Due to the complexity and duration/chronicity of most psychiatric disorders drugs are often needed in combination with non-pharmacological treatment options as reflected in many practice guidelines. Further, for the most part, comorbidity in child and adolescent psychiatry is the rule, not the exception. It has contributed not only to the combination of non-pharmacological with pharmacological treatments but also to an increase in the concomitant medication with two or more psychotropic drugs over the past decades. It is worrisome that millions of children and adolescents in the EU are treated annually with psychopharmacological drugs. Drug use is increasing further. Negation of this reality will entail increased risks for the thus exposed children. We need a concerted effort 1) further the development of novel drugs for child and adolescent disorders and 2) to boost research into both efficacy and side effects of psychopharmacological drugs. We cannot accept that the youngest segment of the population is exposed to potentially inefficacious and potentially long-term harmful side effects.

Efforts to delineate both efficacious and safe paediatric medications should be a major focus of regulatory agencies; the societal implications of mental disorders are too grave to duck away.

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?
With only two new authorisations, in the area of mental and behavioral disorders the number of available licensed paediatric medicines has not substantially increased. Moreover, with some variation across countries, new treatment habits are but slowly integrated in the daily clinical work. E.g. fluoxetine has been approved for the treatment of paediatric depression for about ten years. However, although gradually decreasing, tricyclic antidepressants with proven inefficacy and critical side-effects, still display notable proportions of antidepressant prescriptions in Germany and the UK.

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?
no comment

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?
Yes

2.6. The orphan reward

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

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?
Yes

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?
no comment

2.9. Deferrals

Consultation item No 9: Do you agree with the above assessment of deferrals?
We agree, that the initiation of a paediatric trial should be in balance between collecting further information from adult trials concerning safety issues on one hand, and the delayed availability to treat paediatric diseases on the other hand. However, with about 12% completed PIPs of all agreed PIPs, the extension of deferrals seems a bit frustrating.

2.10. Voluntary paediatric investigation plans

Consultation item No 10: Do you have any comments on the above?
The majority of medicines for which a therapeutic need has been identified is off-patent, whereas most PIPs refer to new active substances. Thus, the investigation of off-patent substances is of much less interest for the pharmaceutical industry. The incentives seem not to be sufficient to compensate for the efforts (cf comment on item No 12).

2.11. Biosimilars

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

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?
We agree that the PUMA concept has been disappointing. In child and adolescent psychiatry most medications are off-patent as well as off-label, thus, there is an urgent need for more data on efficacy and safety (cf. comment to item No 2). Continued funding from public sources is crucial to achieve that goal. Funding of projects should not only aim at facilitating clinical trials but also at systematically compiling data already available to build registries / formularies for off-patent medicines as well as the use of statistical methods to assess the evidence.

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?

We agree that paediatric trials pose particular challenges. Especially in the area of mental and behavioural disorders, recruiting is difficult since many parents have reservations about a psychopharmacological treatment of their children. Multi-centre trials with few patients per site create not only operational challenges but may decrease experimental sensitivity due to larger placebo responses. Further, the heterogeneity and frequent comorbidity of psychiatric disorders limit the generalizability of clinical trials with highly selected populations e.g. by exclusion of comorbid disorders or concomitant psychotropic medication (cf. comment on item No 2).
Consequently, a widespread public education on the need for paediatric trials is needed. Clinical trials should be granted enough time to compensate for recruitment difficulties and high drop-out rates and the study population should aim to represent the clinical target population.

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?

no comment

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?

We agree. The Paediatric Regulation had a positive effect on paediatric research e.g. by establishing the Enpr-EMA. However, further development of research infrastructure is needed. Also, the necessary basic research on the diseases e.g. the genetic and neurobiological underpinnings requires funding from public sources.

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?

RCTs represent still the gold standard for the evaluation of efficacy and safety of a substance under investigation. However, limited generalizabilty due to pathogenetical heterogeneity and small sample sizes needs to be adaequately adressed. Potential ways could include e.g. stratification of the sample due to relevant biomarkers, add-on studies, or adaptive clinical trial design.

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?
no comment

References

Bachmann et al. (2016) Eur Neuropsychopharmacol 26, 411-419
Persico et al. (2015) Eur Neuropsychopharmacol 25, 1513–1531
Stoyanova-Beninska et al. (2011) Eur Neuropsychopharmacol 21, 565–570
Wimmer et al. (2014) Pediatr Drugs 16, 397–406