EUROPEAN GENERIC MEDICINES ASSOCIATION

Making Medicines Affordable

# POSITION PAPER

## EGA CONTRIBUTION TO EC PUBLIC CONSULTATION ON "GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION"

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**Further information | Isabel Klinnert**

**EGA - EUROPEAN GENERIC MEDICINES ASSOCIATION**
Rue d'Arlon 50 B-1000 Brussels Belgium
Tel: +32 (0) 2 736 84 11 ~ Fax: +32 (0) 2 736 74 38
E: info@egagenerics.com | www.egagenerics.com

The EGA is the official representative body of the European generic and biosimilar pharmaceutical industry, which is at the forefront of providing high-quality affordable medicines to millions of Europeans and stimulating competitiveness and innovation in the pharmaceutical sector.

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## 1. EXECUTIVE SUMMARY

The EGA fully supports the intention of the Paediatric Regulation to improve the health of children in the EU by increasing the development of paediatric medicines, ensuring that medicines used to treat children are subject to high quality research and are appropriately authorised for use in children. To achieve these objectives the use of off-patent medicines for the paediatric population have to be further supported and strengthened, not only by the PUMA, but also by therapeutic guidelines and adaptation of reimbursement rules at national level. The impact of the 6 month SPC extension for on-patent medicines should also be reassessed. Specifically, the EGA would like to raise its concern on the 6 months paediatric extension for originator products amounting to an approximate € 2, 3 billion loss of savings for the EU healthcare systems. The disproportionate returns for originator companies need to be rewarded by more proportional measures to ensure a sustainable healthcare environment. The EGA would like to propose a cap system for "super" profits of blockbusters, due to a 6 month paediatric extension, by reducing the extension proportionally to the profits. In addition, to aim for a fairer legal process, the EGA would like to ensure that one SPC of 6 months extension is only awarded once for one SPC, the possibility of negative term SPC extension is removed and a more transparent system with a database on PIPs, indicating whether successful or not, is made publicly available.

## 2. 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?*

**EGA comments**:
While the Paediatric Regulation contains many helpful provisions to meet the objective of increased paediatric medication, the proposal does not reflect the fact that the off-patent sector has been identified as most in need of support for new investigations for children.[1] The measures and incentives proposed for Paediatric-Use Marketing Authorisation (PUMA) are inappropriate and do not really stimulate the research on existing medicines for paediatric use, contrarily to the medicines being still on patent. Moreover, the 6 months Supplementary Protection Certificate (SPC) extension of blockbuster products give disproportionate compensation to originator companies amounting up to 600 million € turnover, as it is the case of Lipitor.[2] These products do not cover primarily unmet paediatric needs and delay market entry of generic medicines, which would contribute to savings in healthcare budgets.

## 3. Has the Regulation delivered in terms of output? Too early to judge

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

EGA has no comments.

## 4. The PUMA concept: a disappointment

*Consultation item No 3: In terms of output, the PUMA concept is 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?*

**EGA comments**:
The fact that PUMA has been granted only once to Buccolam (midazolam, oromucosal use) on 5 September 2011 shows that, despite expectations, the PUMA concept is not sufficient as expected to promote off patent paediatric indications. The data exclusivity proposed as an incentive (although the longest in the world) is clearly not an appropriate tool for investment in older and off patent medicines. Low price and low profit margins, limit likely returns of generic medicines. Considering the pressure of prices that the generic

[1] "A Federal Drug Administration survey found that 6 of the 10 products used most frequently off label or on an unlicensed basis in the US were off-patent". Commission consultation on a draft proposal for a European Parliament and Council Regulation on medicinal products for paediatric use (March 2004, p.5)

[2] The 6 month SPC extension of Lipitor is worth 770 million Dollars, "Pfizer gets$800m boost for Lipitor" Financial Times, July 2011, http://www.ft.com/intl/cms/s/0/6892b926-aae3-11e0-b4d8-00144feabdc0.html#axzz2B5LiaEC1

medicines industry has to undergo, the investment in clinical trials for paediatric use is practically impossible in view of high costs of studies and potential return on investments for new paediatric indications.

Reimbursement rules may not evaluate PUMA in a satisfactory manner and may attach little value to old medicines giving them a low reimbursement price or no reimbursement, even if they include a new age-appropriate formulation. National authorities could consider encouraging the development and use of new paediatric medicines in the off patent sector through therapeutic guidelines and adaptation of reimbursement rules.

To date, 15 projects on at least 20 off-patent medicines (active substances) have received EU funding as part of the area HEALTH-(2007-2011)-4.2-1, and 2 investigator-driven clinical trials for off-patent medicines are funded as part of another area, HEALTH.2011.2.3.1-1. The funding amounts to a total of at least € 75 million.[3] The EGA recognises the great value of the Seventh Framework Programme for Research and Innovation (FP7) funding and supports the continuation of the financial aid for off- patent medicines. However, this is only one of the solutions and the results will be proving the effectiveness in the near future. Moreover, as of today 26 applications for Paediatric Investigation Plans (PIPs) for PUMAs have been received by the European Medicines Agency (EMA) and 7 opinions have been given by the Paediatric Committee (PDCO). Nevertheless, it is too early to assess whether the applications for PUMAs have been successful or not.

The fundamental difference between performing peadiatric studies for off-patent and on-patent medicines is related to the decision making process. To get the EU financial support for paediatric clinical trials on off-patent medicine, the company shall respond to the real unmet paediatric needs as published by the EMA in its priority list.[4] In case of products being still under patent, the choice of molecule for eventual paediatric studies, rewarded afterwards by 6 months SPC extension, is driven by the commercial decision of the company. The already given example of Lipitor shows that although paediatric studies were performed for a very rare paediatric indication, it became a very profitable tool for adult formulation due to 6 months SPC extension.

The off-patent medicines for the paediatric population have to be further supported and strengthened not only by the PUMA but also by therapeutic guidelines and adaptation of reimbursement rules at national level.

[3] EMA, 5 year Report to the European Commission, General report on the experience acquired as a result of the application of the Paediatric Regulation, July 2012, http://ec.europa.eu/health/files/paediatrics/2012-09_pediatric_report-annex1-2_en.pdf

[4] EMA, Revised priority list for studies into off-patent paediatric medicinal products, 12 January 2012http://www.emea.europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf

### 5. 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.*

**EGA comments**:
According to the originator industry, out of 159 Marketing Authorisation Applications (MAAs) or variations for a new adult indication, 139 were not postponed due to the requirements of the paediatric regulation. However, 19 MAAs or variations were postponed. Amongst others, reasons for delays were due to the intrinsic length of the PIP/waiver procedure or due to too late submissions of PIP/waiver applications by applicants.[5] According to the EMA, in 2011, more than half of the PIP applications were submitted late. From 44 PIPs submitted late (more than 6 months), 4 included a valid justification (9% PIPs), 28 included a justification that was not considered acceptable (64%), and 12 did not have any justification (27%).[6] The benefits of early dialogue include a better integration of paediatric needs already in adult development for formulations and pharmaceutical forms, toxicology etc. This also avoids delays at the time of submission of the application for adults, if the PIP or waiver has not been agreed on time. Delays on adult development have to be avoided as these affect the generic medicines industry by delaying entry on the market, implying substantial costs for Member States and their healthcare budgets, as they cannot profit from cost-savings and a competitive market.

### 6. 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?*

EGA has no comments.

[5] EFPIA survey on impact of the paediatric regulation on marketing authorization holders (Jan 2007-Jun 2010) http://www.ema.Europa.eu/docs/en_GB/document_library/Presentation/2011/05/WC500106718.pdf
[6] EMA Report to the European Commission, on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligation in this Regulation, covering the year 2011, 12 September 2012, http://ec.europa.eu/health/files/paediatrics/2012-07_paediatric_regulations.pdf

## 7. The burden/reward ratio – A balanced approach?

*Consultation item No. 6: The Paediatric Regulation introduced a number of incentives intended to offset the additional burden, at least partially. One of the main incentives is the 6-month extension of the Supplementary Protection Certificate. While it is too early to assess the economic impact of the rewards, the EMA and its Paediatric Committee have made acknowledged efforts to simplify the regulatory process wherever possible and within the limits of the regulatory framework. Do you agree with the above?*

**EGA comments:**
Even if the European Commission outlines in the consultation document that it will assess the economic impact of the Paediatric Regulation in 2017, Article 50.4 of the Regulation states that "Provided that there are sufficient data available to allow robust analyses to be made, the provisions of paragraph 3 [the economic impact] shall be fulfilled at the same time as the provisions of paragraph 2 [the current general report]." The information outlined below shows that sufficient data are available to examine the economic impact of the Paediatric Regulation.

Economic aspects
The extension of SPC originator products amounts to millions of euros in annual sales for "mid –range" products and even more hundreds of millions of euros for "blockbusters", as is the case for Lipitor[7]. Such a potential windfall seems disproportionate for what is essentially compliance with new mandatory paediatric rules.

The main concern for the EGA is that the SPC extension results in an increase of paediatric research in areas that are mostly economically interesting for originator companies, adding to medicines developed for adults in existing lower priority areas, but not focusing on areas of highest unmet medical need for children.

The SPC paediatric extension is not granted according to a priority list of highest paediatric medical need as is the case for PUMA, which depends on the EMA's priority list, supporting studies into off-patent paediatric medicinal products. [8]

One example is Pfizer's chewable, grape flavored form of Lipitor which was granted a 6 month SPC extension, although there was no significant change in the recommended use of the medicine, which was already authorised for those aged 10 years old or over. Lipitor is prescribed to adults with high cholesterol but given to children with an inherited condition called familial hypercholesterolemia. This suggests a potential pool of some 10.000 of European children of which a very small number have been identified. Data from the IMS suggests roughly 20.000 children are prescribed Lipitor in the EU's largest market.[9]

[7] "Pfizer gets$800m boost for Lipitor" Financial Times, July 2011, http://www.ft.com/intl/cms/s/0/6892b926-aae3-11e0-b4d8-00144feabdc0.html#axzz2B5LiaEC1
[8] EMA, Revised priority list for studies into off-patent paediatric medicinal products, 13 January 2012, http://www.ema.Europa.eu/docs/en_GB/document_library/Other/2009/10/WC500004017.pdf
[9] "Pfizer gets$800m boost for Lipitor" Financial Times, July 2011, http://www.ft.com/intl/cms/s/0/6892b926-aae3-11e0-b4d8-00144feabdc0.html#axzz2B5LiaEC1

The table below shows the loss of savings for some healthcare systems calculated by the UK, Belgian, Italian and Dutch Generic Medicines Associations.

| INN (international non-proprietary name) | Loss of savings for healthcare systems |
|---|---|
| Astorvastatin | UK: £ 161 million<br>BE: € 24 million[10]<br>IT: € 900.000<br>NL: € 130,4 million |
| Anastrozole | UK: £ 25 million (with no usage under the age of 40 years)<br>IT[11]: € 500.000<br>NL: € 18,3 million |
| Caspofungin | NL: € 6,1 million |
| Clopidogrel | IT: € 150.000<br>NL: € 41,9 million |
| Latanoprost | UK: £ 20 million<br>IT: € 40.000<br>NL: € 14,3 million |
| Losartan | UK: £ 32 million (paediatric use of 0.28 %)<br>IT: € 230.000<br>NL: € 47,6 million |
| Montelukast | UK: £ 26 million<br>NL: € 15,3 million |
| Nevirapine | NL: € 11,2 million |
| Rizatriptan | NL: € 11,0 million |
| Valsartan | UK: £ 18 million<br>IT: € 400.000<br>NL: € 32,0 million |
| Zoledronic | NL: € 6,6 million |

More precisely the costs could be calculated **on a European scale** for most blockbuster products[12] listed with a SPC paediatric extension in 2012. By identifying the annual brand sales of each product before the SPC extension and multiplying it by 0.75 (average of 25% price fall as loss of exclusivity) and multiplying it again by 0.5 (6 months paediatric extension, half a year) the costs of most of the blockbusters combined amount to approximate over **€ 2, 3 billion loss of savings for European healthcare systems**.

[10] "L'utilisation un peu facile de la législation pédiatrique européenne pour un médicament anti-cholestérol coûte à l'INAMI pas moins de 24 millions €", Belgian association for generic and biosimilar medicines, http://www.febelgen.be/enews/enews3_fr.html

[11] The cost data reflects only partially the loss of savings for the Italian market as only one company in Italy provided their data on the products with 6 month SPC extension

[12] IMS calculation on annual brand sales on a European scale include Atorvastatin, Anastrazole, Clopidogrel, Latanoprost, Losartan, Montelukast, Nevirapine, Rizatriptan, Valsartan and Zoledronic Acid

In the cases of disproportionate returns, where the clinical trial costs are very low compared to the revenues generated, more proportional measures should be introduced to ensure a sustainable healthcare environment. This could be facilitated by originator companies submitting data on the costs of their clinical trials and achieved revenues. A precedent for this approach exists in the Orphan Medicinal Products Regulation.

The EGA would like to propose a cap system for "super" profits of blockbusters, due to a 6 month SPC extension, by reducing the extension proportionally to the profits (i.e. instead of 6 months, 3 months).

Legal aspects

To ensure a fairer legal process in Europe, the EGA would like to propose the following:

1) One SPC 6 months extension to be only awarded once for one SPC

It should be ensured that the incentive provided by the **six months extension of the certificate should be awarded only to the market authorization holder and only once for one SPC**. It has to be strictly excluded that certificates which are granted to third parties will receive the extensions too. Reference by third parties to already performed studies should not be allowed. Making this incentive exclusive to the company who sponsors the pediatric studies and is responsible for the compliance with the PIP is in full accordance with the compensation concept of the pediatric regulation provision.

2) Impede negative term SPC extensions

It would be convenient to amend Regulation 1901/2006 on medicinal products for pediatric use to remove the possibility of "negative term SPCs". The SPC regulation should govern whether or not an applicant is able to obtain SPC protection. This was set five years from the date of filing the patent application. By permitting the granting of negative term SPCs, the Court of Justice of the EU has now reduced this time frame to four years and 6 months from the filing of a patent before SPC protection becomes a possibility. If this is to be enabled, one can present a forceful argument that this should be possible only through amendment of the SPC regulation (e.g. by amending Article 13, Regulation 469/2009) and not by the provision of an additional incentive in a different legislative regime.

Therefore we suggest the following amendment to the original provision in Regulation 1901/2006: "Article 36.*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."*

The new proposal for the provision is the following: *"Article 36.4. 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 with a positive term. They shall not apply to medicinal products designated as orphan medicinal products pursuant to Regulation (EC)*

*No 141/2000* ***or under a patent which qualifies for the granting of the supplementary protection certificate with a negative term."***

3) A more transparent system

The application for an extension of the duration of a SPC already granted shall be lodged not later than two years before the expiry of the certificate (since January 26, 2012), which improves the planning of a product launch. To aim for a more transparent system, a database with statistics on PIPs, indicating whether they were successful or not, should be made publicly available. Incomplete documents or missing data of PIP applications should not be tolerated. One example of incomplete documents for an authorised paediatric extension is the case of Du Pont. The company was granted a paediatric extension for Losartan which failed to meet all requirements for a complete file.[13]

## 8. Articles 45/46: The hidden gem of the Paediatric Regulation

*Consultation item No 7: Do you agree that Articles 45/46 have paved 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?*

EGA has no comments.

## 9. 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?*

**EGA comments**:

In addition, to encourage healthcare professionals in paediatric clinical research, it is important to highlight that paediatric indications rely on studies submitted by the Marketing Authorisation Holder (MAH). Healthcare professionals who publish observational studies of paediatric indication do not have an impact on the product information and rely upon a company to submit the dossiers for paediatric indication, although there is already a lot of experience from off- label use by health care professionals. This knowledge shall not be lost. There should be a mechanism in place to use already existing knowledge and to amend the SmPC without performing/ repeating the studies by the MAH. Elaboration of some therapeutic guidelines (new role of PDCO?) covering some recommendations coming from observational studies shall be considered as an additional source of information for paediatric treatment.

[13] European Union: Paediatric Extensions – A European initiative to encourage research into medicines for children, October 2009, Mondaq, http://www.mondaq.com/article.asp?articleid=88498

### 10. 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?*

**EGA comments**:
Overall, the proportion of paediatric trials as a percentage of all clinical trials was only considered to have increased to a modest extent, although it was suggested that this might be because more than 80% of paediatric trials had been deferred until after adult medicine development.[14]

It is crucial to ensure that clinical trials on children are a "last resort" and that all other alternatives should first be exhausted – such as the assessment of current off-label use and the results of existing trials outside the EU. In certain cases paediatric needs may not require new child formulations but the adaption of current dosage regimes, smaller dosages of current products or simply better information for child use. The role of independent research in this area should also be recognised.

### 11. Unnecessary efforts? Non-completed paedatric investigation plans

*Consultation item 10: Do you have any comments on this point?*

EGA has no comments.

### 12. 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?*

EGA has no comments.

[14] Regulatory Intervention in Paediatric Medicines, September 2012, T.M. Olski et al. Eur. J. Clin. Pharmacol. 67 (3), 245-52 (2011) in http://www.pharmtech.com/pharmtech/article/articleDetail.jsp?id=786307