EuropaBio comments on
GENERAL REPORT ON EXPERIENCE ACQUIRED AS A RESULT OF THE APPLICATION OF THE PAEDIATRIC REGULATION

General comments

EuropaBio welcomes that the Regulation has paved the way to encourage paediatric development. EuropaBio also welcomes the rewards and incentives provided by the legislation. At the same time, we would like to stress that the requirements should not create an unnecessary negative impact on the development of adult indications and impair timely access to medicinal products targeted at adult population.

We would also like to highlight that the Regulation might create a significant administrative and financial burden on Small and Medium Size Enterprises (SMEs). It is important to note that more than 70% of biotech and pharmaceutical companies in the EU-27 have less than 50 employees. Biotech SMEs deliver innovation and provide the high value-added jobs that will help the EU achieve its goal of becoming the foremost knowledge-based economy in the world.

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?

In general, we agree that the Paediatric Regulation has increased focus on paediatric medicine development. EuropaBio welcomes and supports the rewards and incentives encouraging paediatric development provided by the legislation. However, at the same time, the legislation has created a significant administrative burden for the innovative industry and increased further the already complex regulatory environment in the European Union. Specifically the time period leading to a successful marketing application filing with many competing regulatory activities has to be managed diligently to avoid any unintentional delays.

We would also like to note that development of paediatric medicines was already undertaken by our member companies prior to the application of the Paediatric Regulation to address unmet medical needs.

EuropaBio would like to point out one requirement for paediatric trials that is not in line with requirements related to adult clinical trials:

- Reporting of clinical trial study reports within 6 months instead of 12 months.

We fail to fully understand the necessity for this difference from a paediatric public health perspective and would like to encourage that this requirement is brought in line with the rules for adult clinical trials to facilitate the implementation of a robust company compliance process for **all** clinical trials.

Consultation item No 2: Do you agree that it is too early to judge whether the Regulation has delivered in terms of outputs, namely to reduce the off-label use of medicinal products in the paediatric population and to increase the number of products that have been researched, developed and authorised for use in children.

Yes, we agree that it is too early to judge whether the Regulation has delivered in terms of outputs as the drug development process takes comparatively long. However, we do not believe that the legislation will subsequently result in the desired reduction of the off-label use of medicinal products. In order to achieve this objective, it is necessary to establish appropriate national/local measures and programs that which would reach the treating physicians and be effective in national medical practice.

Consultation item No 3: Do you agree that the PUMA concept has been a disappointment? 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?

We agree that the PUMA concept has not been successful. From an innovative industry perspective, we find this concept not to be attractive enough to encourage innovation. The available incentives to conduct additional development in off-patented medicines are not sufficient to provide a positive return on investment to developers as the current expectations and requirements are too strict to make the concept viable from a business perspective.

We would welcome a discussion with stakeholders which other incentive mechanisms could potentially encourage innovation in this area. Some interesting proposals have been made in the context of antimicrobial policy option development[1].

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.

We would like to stress that the paediatric obligations have significantly increased administrative burden on companies and the additional regulatory complexities provide a substantial risk for delays of adult development and new product filings as well as filings for new adult indications. These complexities need to be managed not only within a European, but also within a global context.

As development data emerges over time during the development process each new set has to be assessed for impact on subsequent regulatory strategy and existing regulatory documents. The time period leading up to a MA application is usually very busy and requires the availability of many different documents in a very short timeline. Any document or additional regulatory process interfering with this critical path will necessarily have potential to create a delay of the MA filing.

For example, the change management process for PIPs is very complex and not quick enough to react with sufficient speed on changed facts. The partial compliance checks **before** the validation of adult MA applications are unnecessary long and require detailed clinical trial study reports to be available well in advance of the filing for a line by line comparison with the approved text in the PIP decisions. Availability of these documents is usually determining the filing date for a specific product as they are one of the last components of a new MA dossier.

[1] OHE – New drugs to tackle antimicrobial resistance; http://www.ohe.org/publications/article/new-drugs-to-tackle-antimicrobial-resistance-5.cfm

The EMA policy on splitting and merging of PIP Decisions to be congruent with the adult indication before the actual compliance check creates further potential delays. Article 7 of the Regulation does not explicitly provide for this "congruence" requirement nor does the Regulation foresee a "partial" compliance check beyond the usual validation.

In addition, the obligations from imposed additional paediatric investigations result in substantial associated costs. As companies' research and development budgets are limited, the additional obligations are likely to divert resources form other on-going development programs and have as such a negative impact on medicines development for adult indications. In general, it is important to focus on pragmatic and flexible solutions.

Consultation item No 5: Do you have any comments on the statement that the purpose of the Paediatric Regulation is not to replace an established system of medicinal product development by a new regulatory system, but to ensure that every new product is screened for its potential use in children so that over time there will be a significant increase in the number of products for which specific paediatric data is available.

In general, EuropaBio believes that there should be more focus on specifically targeting paediatric indications rather than on screening all adult indications.

We currently observe an over-emphasis on the paediatric needs element while ignoring other important factors like practical feasibility of the trials or economic impact on drug development programs. However, all these elements need to be carefully balanced to avoid unintended negative consequences.

In general, we support the increased focus and screening of potential paediatric uses, but are seriously concerned by the obligations that are mandatorily imposed on our members. The Regulatory system has usually been reactive to applicant's proposals, while the implementation of this Regulation has the set the rules in a different manner.

Consultation item No 6: Do you agree that the legislation provides for a balance approach between a burden and a reward for the pharmaceutical industry?

EuropaBio welcomes the rewards and incentives provided by the legislation.

However, EuropaBio believes that the administrative and financial burden of the legislation on the industry outweighs the actual value of the rewards in many instances, particularly with regard to strict interpretation of the SPC extension rules, document requirements and timelines at EU and national level. We also feel that the incentives are not encouraging enough for the development of complex, innovative medicines, such as biotechnology medicines. Therefore, there is room for improvement.

EuropaBio would welcome a review of the Commission guidance on paediatric investigation plan (PIP) in order to make the requirements more proportionate and flexible. In line with the EU principles of better regulation, EuropaBio would also welcome a review of the provisions of the Regulation to explore whether it could be made easier to understand and accessible, without fundamentally changing its content and in particular the possibility of obtaining the rewards.

Unnecessary regulatory obstacles that obstruct the smooth development and regulatory approval process of new medicines and new indications need to be removed.

Specifically the great level of details required for very early PIP submissions, the arbitrary definitions of conditions and indications and the "partial" compliance checks should be re-thought to achieve a more proportionate system.

Consultation item No 7: 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?

We agree that Articles 45 have a positive impact on compiling existing paediatric data. At the same time, EuropaBio believes that progress related to the evaluation of existing paediatric data submitted in 2007 according to Article 45 has been rather slow so far, but that these reviews actually will have the greatest potential to include additional paediatric indications or dosage recommendations for off-patented products into product information.

We fully understand that the system can only absorb a limited number of additional procedures from this Article per year. However, the current speed will make this a long-term activity. Some time limit should be set. Data from these studies may also be available in the scientific literature and as such be already used by the physician to treat their patients.

We strongly encourage that the regulatory context which was applicable at the time when the data was generated needs to be taken into consideration to achieve a pragmatic implementation.

The regulatory evaluations carried out on submitted paediatric trials under Article 46 has not yet led to a big outcome for paediatric patients.

Many of those studies that actually have a regulatory impact on the labelling of a product are anyway submitted via appropriate variation procedures and in compliance with MAH responsibilities under Directive 201/83/EC as amended.

Hence the added value of regulatory resources spend on this activity are rather questionable.

We generally welcome the work sharing procedures as a pragmatic way to work with limited regulatory resources and would encourage a full harmonisation of the submission and evaluation processes for CAPs, MRP and national products.

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?

We agree that this problem needs to be primarily addressed at national level.

Healthcare professionals could be further encouraged through engagement and dialogue with various relevant learned societies and medical associations at national level. Increased attention in physicians' study curricular or continuous update of treatment guidelines may be necessary.

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation?

We believe that the Regulation has not had a positive impact on the research infrastructure or practical feasibility of clinical trials with children. Prior to the adoption of the Regulation, there have been already many challenges making it very difficult to conduct clinical trials with children, such as for example problems with informed consent or slow recruitment due to practical aspects. Many ethical questions have not been solved or harmonised due to the strict national competence of Ethics Committees and their independence from the Regulatory system. Experience also shows that it is particularly difficult to recruit for single dose PK trials which may not have any direct benefit to children.

Consultation item No 10: Non-completed paediatric investigation plans

EuropaBio believes that there is a need for a more flexible and pragmatic approach. For example with regard to timelines when the paediatric investigation plans should be submitted, we would welcome flexibility allowing the industry to decide on case-by-case approach at which stage it is most practical and efficient to submit the plans. This decision has to take many factors into account such as available data, probability of success of the overall development program, targeted adult indications, availability of pharmaceutical formulations and economic and practical feasibility.

A PIP should be a high level strategy document that is agreed by Regulators once there is sufficient evidence that the product will eventually reach the market.

There remains a need for a mechanism to revoke an approved PIP when the development of the adult dose/formulation of a product is terminated. Currently, one can only propose a modification to either extend the deadlines - with retention of the annual reporting requirement - to infinity or obtain a deferral.

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?

Yes, we agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union.

Consultation item No 12: 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?

EuropaBio welcomes that the Regulation has paved a way to encourage paediatric development. At the same time, we should be mindful that the requirements do not create an

unnecessary negative economic impact on the development of adult indications and impair timely access to medicines targeted at the adult population.

EuropaBio would welcome a comprehensive discussion with stakeholders to ensure a more proportionate and balanced implementation of the Regulation considering the broader innovation in healthcare context.

The Paediatric Regulation should not be seen as the only tool to solve the huge unmet medical needs while placing disproportionate burden on innovative Industry.