

Consultation in relation to the Paediatric Report
Ref. PCPM/16 – Paediatric Report

1. PART I - GENERAL INFORMATION ABOUT RESPONDENTS

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2. PART II – CONSULTATION ITEMS

2. EXPERIENCE ACQUIRED OVER THE LAST TEN YEARS

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?

EUCOPE agrees that specific legislation supporting the development of paediatric medicines is necessary to guarantee evidence-based paediatric medicines, in order to reduce treatment of children outside the actual approved indication.

EUCOPE believes that the Paediatric Regulation has created a movement towards better and more research and development in medicines for children which has positively impacted all stakeholders. For example, pharmaceutical companies created and staffed specialist paediatric departments working on specific paediatric development programs able to generate the best evidence. A growing body of knowledge is being assembled e.g. on paediatric physiology and new methodologies (modelling and simulation, extrapolation), which should facilitate and improve the efficiency of paediatric drug development.

EUCOPE maintains that the current Paediatric Regulation is well formulated whilst its application by regulators could be improved by amending the guidelines instead of changing the legislation.

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?

EUCOPE believes that the current Regulation has been successful in achieving its objectives to encourage the development of paediatric medicines and to improve the information available on the use of medicinal products for infants, children and adolescents. The EMA 10 Year Report indicates that by the end of 2015, the Paediatric Committee (PDCO) had adopted 859 opinions for PIP, which then generated 177 new paediatric medicinal products and indications.

Therefore, this legislative framework has contributed to the development of paediatric medicinal products, especially in areas such as respiratory, immunology and cardiovascular diseases. From EUCOPE's perspective, any new paediatric product or indication is important as it allows doctors and parents to no longer rely on off-label use of perhaps unsuited adult products.

Regarding the differences across therapeutic areas in terms of paediatric medicines available, there are a number of reasons why most PIPs are linked to adult development. The Paediatric Regulation seeks to reduce off-label use in children and, in practice, a medicinal product is more likely to be used off-label in the same indication as the one authorised for adults. Advances in the understanding of the molecular mechanism of disease, in particular in cancer, may help create new links between adult and paediatric conditions, and help the development of drugs for paediatric cancers.

The link adults-children is not the only explanation to the disparity of paediatric development among therapeutic areas. Few or no new paediatric products and indications are developed in certain therapeutic areas due to safety concerns -patient populations being too small or either commercial considerations. Because certain conditions addressed occur so infrequently that development costs are unlikely to be covered through sales, an incentive is needed to stimulate investment in areas with low potential for return on investment. This justifies the adoption of the Orphan Regulation and then the Paediatric Regulation within the framework. The effects of a statutory instrument such as the Orphan Regulation or the Paediatric Regulation, are better guaranteed if it proposes the right incentive, i.e. an incentive that is both certain to the investment. In the case of the Paediatric Regulation, incentives are uncertain as well as difficult and slow to obtain.

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?

The number of innovative new paediatric medicines approved in Member States has increased. Companies fulfil the obligation to market paediatric products within two years of their approval by actually placing paediatric products on national markets or by having them available upon request, depending on the size of the national paediatric patient population. However while the number of approval has increased, the ultimate availability of certain products depends on the local markets as pricing and reimbursement decisions are made by the local authorities.

With regard to off-patent medicinal products in particular, for which the concept of the Paediatric Use Marketing Authorisation (PUMA) was conceived, the number of new paediatric medicines available in the Member States has not substantially increased since the Paediatric Regulation came into effect because only three medicinal products were granted a PUMA. However it is important to note the marketing of such products faces many obstacles (see below, consultation item 12). In the case of Buccolam, for example, the UK failed to adequately enforce removal of a similar off-label medicine and perpetuated its use.

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?

As seen in the data gathered by the Commission, substantial additional investment and cost are incurred to implement agreed Paediatric Investigation Plans (PIPs). However, it is difficult to estimate the cost impact of the Paediatric Regulation due to a variety of factors in paediatric development programs and requirements in PIPs. Cost is highly dependent on a number of factors, such as the number of clinical studies, the number of patients enrolled, requirements for new formulation development, the length of safety follow-up, the method of monitoring etc. As regards the average costs reported by the Commission we have the following comments:

- The average aggregate cost invested annually by the industry in paediatric research (2 billion Euros per year, i.e. 16 billion Euros over 8 years (2007-2015)) is not overestimated but underestimated. Indeed, 88% of the PIPs have not yet been fully implemented and the final cost of implementation of a PIP is only known after completion.
- The average administrative cost to prepare and manage a PIP (720,000 Euros) is beyond anticipation and expectation, especially as a PIP could be a document relatively simpler to what it is. It represents a substantial amount of money, especially for SMEs. Efforts should be made to lower the administrative cost as much as possible so that money can be better invested in actual research. It is even more so that a fair number of PIPs are discontinued. PIPs are required to be proposed, negotiated and agreed upon at a time – after Pharmacokinetics studies (PK studies) in adults (commonly referred to as “end of Phase I”)- when companies do yet not know whether they will pursue the development of the substance, let alone in the condition targeted by the PIP. However, it is common knowledge that a substantial amount of all development is stopped during or after Phase II. In those cases, companies have invested financial and personal resources in preparing, negotiating and sometimes modifying a PIP relating to an active substances the development of which is abandoned. This alone justifies reducing the administrative cost.
- The average research cost (18.9 million Euros) can seem quite low for an entire paediatric development. Yet, it is five times more than the cost envisaged in the RAND Study (4 million Euro), which served as the impact assessment for the Paediatric Regulation. It is therefore fair to say that the Paediatric Regulation bears a financial and administration impact that was unanticipated by the industry.

One can only assess whether a cost is reasonable on a PIP by taking into account all relevant facts (characteristics of the product, nature of the disease, etc.). One may however wonder if such prices are reasonable in cases where no incentive is available to the company (insofar as the Paediatric Regulation is expressly based on an incentive system) or the paediatric data turn out to be unnecessary for demonstrating

the safety or efficacy of the medicinal product when used in the paediatric population.

Cost and effort reduction could be achieved via a better and earlier alignment, in particular between the U.S. (FDA) and the EU (EMA) in order to achieve a common development program suitable for both regions. For that reason EUCOPE welcomes the recently concluded collaboration agreement and is looking forward to work with the regulators to achieve successful implementation. Involvement of the sponsor in the EU-U.S. dialogue is crucial for its success. Reduction could also come from a better sequencing of paediatric development.

EUCOPE stresses the increasing demands of the PDCO with regard to paediatric studies which contributes to higher costs and may sometimes delay adult approvals (in the case of joint adults-children trials). Setting a very high standard with regard to the number of trial subjects is especially detrimental for rare diseases because of the scattered nature of the patient population which requires to open many more sites.

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?

EUCOPE believes that the reward system needs to be implemented in a better way. According to the EMA 10 Year Report, 44 rewards have been granted over 10 years, including 3 orphan market exclusivity extensions (4 since then) and 2 PUMAs (3 since then). This represents less than 50% of the completed PIPs (99), 5% of the agreed PIPs (859) and 25% of the new paediatric medicinal products and indications.

So far, the reward system has encouraged companies to fully integrate their paediatric development planning within the overall product development strategy. However, this early planning does not automatically result in companies receiving a reward. Paediatric programs may never receive any reward for the following reasons:

- there is no underlying summary of product characteristics (SPC) that can be extended
- the clinical development program will not be finished in time because of the length of the studies due to the difficulty to recruit sufficient trial participants within a reasonable amount of time
- upon expiration of the SPC the product is no longer in clinical use due to better performing follow-on innovations in the treatment area

The low number of rewards does not result from the decisions of the national patent office's either. To the contrary, it is the experience of EUCOPE members that overall the national patent office's properly implement and apply the Regulation, with due respect of its objectives.

The low number of rewards mainly results from (i) the Paediatric Regulation also covering products without patent or orphan designation and therefore ineligible for a reward and (ii) high demands with regards to content of PIPs that leads to extensive deferrals.

EUCOPE notes that the SPC extensions do not generally cover the average cost of a PIP (20 million Euros as per the European Commission) except perhaps for blockbusters, which remain in limited numbers. According to the Commission, the actual average cost of implementation of a PIP amounts to 20 million Euros instead of the expected 4 million by its impact assessment. Thus, in theory, the reward is five times lower than what it should have been to adequately compensate the investment in paediatric research.

2.6. The orphan reward

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

EUCOPE believes that the orphan reward is particularly valuable as it can incentivise research into rare

paediatric diseases. For example, it may encourage the development of re-purposed medicines that do not have patent protection. For companies that develop medicines for rare disease, the reward from the Orphan Regulation (10-year market exclusivity) and the reward from the Paediatric Regulation (market exclusivity 2-year extension) go hand in hand, and both incentives provide continued stimulus.

According to the EMA 10-Year Report, only 3 market exclusivity extensions have been granted since the entry into application of the Regulation, i.e. 50% of the 8 completed PIPs for orphans and 2% of the 150 PIPs for orphans (source: EMA 10-year to the EC; p. 84). This shows that numerous research initiatives are undertaken which do not result in a reward, demonstrating the complexity of the development of orphan paediatric products.

The decision on which a reward is chosen depends on the characteristics of the medicinal product concerned and can thus be determined on a case by case basis. Depending on the nature of product they develop (orphan/non orphan) and the conditions they have to meet, companies can't cumulate benefits (only for 2 exceptions) but opt for the most suited reward, enabling them to reinvest into areas of high unmet medical needs.

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?

At the beginning, the implementation of the Paediatric Regulation resulted into heavy bureaucratic processes. EUCOPE believes that the implementation of the Paediatric Regulation has improved recently. The Guideline on PIPs was amended at the end of 2014 and the early 'paediatric interactions' started mid-2015. Still, more efficiency could be reached, for example by taking the medicine development process operations into account, further streamlining the administrative burden or encouraging dialogue between interested parties (companies, PDCO, SWAP, etc.). In particular, the procedures set forth by the Paediatric Regulation as implemented by the EMA should be reduced and shortened whenever possible. PIP protracted process leads to longer time to marketing authorisation, which ultimately results in delayed patient access to important life-saving therapies. Timing is therefore a crucial element to be taken into account. In particular:

- In 2014, the Commission has agreed to limit the mandatory content of the PIP to the key binding elements. This change has facilitated the partial compliance check and reduced the number of modification procedures. A next step should be a 'lean PIP', i.e. a PIP that lists the basic studies and their essential features and obliges the company to detail each study when the right time comes, i.e. when the company has enough scientific knowledge to propose a realistic and doable detailed study, through a PIP modification. Such a lean PIP would reduce the time of 'negotiation' of the PIP and the number of modification procedures. It would also make 'discontinued PIPs' less of a waste of valuable resource. Finally, the successive partial compliance checks could be stopped as a full compliance check after completion of the PIP would be sufficient.
- The implication of the PIP modification process should be improved and streamlined to distinguish between minor and major modifications. Minor modifications could be submitted anytime (no agency deadline or validation) and approved within a 15-30 day window, provided that they fulfil the criteria predefined by the PDCO. For major modifications, companies could follow the existing procedure unless the product has a PRIME status or is in the Adaptive Pathways scheme, in which cases the window for approval would remain 15-30 days. Moreover, the use of registries and Real World Evidence (RWE) could help reduce development and access timelines. Greater extrapolation flexibility, especially in rare diseases studies or where severe recruitment challenges have been experienced (for novel products treating unmet medical needs) should be developed.
- Scientific advice should be encouraged in order to ensure that rare disease companies are not overwhelmed by additional and sometimes premature requirements.
- Agreement to modifications of key binding elements during scientific advice procedure should overcome the need for a specific modification procedure.
- Flexibility would also be welcome during the compliance check. The objective of the Paediatric Regulation is to generate paediatric data to prove that the medicinal product is safe and efficacious in the

paediatric population. This justifies flexibility when assessing compliance with the PIP.

- EUCOPE highly appreciates the level of knowledge of the PDCO on specific paediatric issues and acknowledges the CHMP recommendations and decisions with regard to paediatrics. In order to gain efficiency and avoid duplication of work, a high level of reliance and recognition of each other's competences by both committees, is essential. Clear roles and responsibilities as well as accountability should be defined for CHMP, PDCO and PRAC to avoid overlap or conflict. Regulatory accountabilities need to be better clarified within the respective committees remit. The PDCO should seek input from key opinion leaders, registries and patient organisations during the assessments of initial PIPs and their potential modifications. This is particularly important with regard to the number of trial subjects required for the paediatric studies, as the PDCO often disagrees with the numbers stemming from clinical sites, companies feasibility studies and national registry databases.

More generally, one could have expected the EMA/Commission to be more reasonable when applying the rules to orphan medicinal products and ATMPs. The (heavy) burden imposed by the Paediatric Regulation on companies involved is heavier in rare diseases or advanced therapies.

With regard to orphan products, the PDCO needs to ensure that the unique nature and challenges associated with rare diseases are taken into account. Companies developing products in rare diseases are already committed to conducting trials in children as a large proportion of rare diseases are childhood diseases. However the PDCO does not always consider this fact and applies an approach to paediatric development that makes pharmaceutical development even harder for companies working in rare diseases. Furthermore, the PDCO has increased its expectations from year to year, which has directly impacted the ability of companies to develop orphan medicinal products.

More flexibility and understanding of the industry's concerns and constraints would be welcomed in the future, especially for SMEs as well as for companies committed to rare diseases and ATMPs.

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?

EUCOPE believes that the waiver requirements in the Paediatric Regulation are appropriate to avoid unsafe, unnecessary or unethical research in children. However, in its members' experience, waivers are difficult to obtain despite the evidence provided by companies related to operational feasibility issues conducting clinical trials, gaps in basic research, established paediatric off-label use and other challenges faced in the development of products for paediatric use.

EUCOPE recommends granting of waivers when adequately justified by developers. Moreover, further guidance needs to be developed with multi-stakeholder input that will weigh the paediatric needs as identified by epidemiology against operational research, development and financial risks to achieve an appropriate balance.

The Commission's suggestion that opportunities have been missed is surprising. First of all, the PDCO has never granted product-specific waivers lightly. To the contrary, it has adopted a restrictive interpretation of the grounds of waiver and has become increasingly demanding on the evidence thereof. Waivers have been granted very carefully, on scientific or ethical grounds. Secondly, the EMA has been recommending that the scope of the PIP be determined on the basis of the mechanism of action since 2012, i.e. for four years. The missed 'opportunities' therefore are probably very few. Only a few voluntary PIPs have been submitted due to the combination of the PDCO's high demands on paediatric development, its lack of flexibility and the ineffective incentive system.

The proposal to rely on the mechanism of action rather than the adult condition is not comprehensible because the EMA does rely on the mechanism of action since 2012, at least for oncology products (see above). Reliance on the mechanism of action however should remain the exception rather than the rule. Indeed, reliance on the mechanism of action means that the company may have to make a paediatric development in a disease that is different from the adult disease. Such paediatric development would thus become more

dangerous unless the company may and do undertake a (new) adult development in that disease as well. In addition, new indications may present specific safety aspects that require additional investment. Therefore, such paediatric development would be more time consuming and impacting the financial ability of companies to re-invest in the development of new medicines. As such, they must remain at the company's entire discretion except in exceptional cases and subject to both more EMA's flexibility with regard to the paediatric studies and eligibility for a reward.

2.9. Deferrals

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

Deferrals are an essential feature of the Paediatric Regulation. They are useful instruments to ensure that the paediatric development takes place when it is appropriate to do so, specifically for safety reasons. Without deferrals, the approval of many adult medicinal products would be delayed by years, and obviously, the development of paediatric medicines could not occur to the detriment of adult medicines.

Like waivers, deferrals are not granted lightly by the EMA; timelines need to be well justified by companies. In that regard, more flexibility is needed when companies want to postpone the deferrals due to development issues or changes in research focus.

Timelines are usually not lengthy. Extensive deferrals result from the combination of the time of submission of the PIP (often after Phase I) the scope of the PIP and the paediatric studies required by the EMA. Deferrals would be shorter if the PIPs were submitted later in the development of the product and/or related to the adult indication and/or included less complex studies.

Deferrals could be used as effective instruments to prioritise the best in class paediatric medicine development in areas with fast therapeutic advances. For example in the HIV or HCV area, breakthrough therapeutic options are available that make earlier treatment obsolete even before patent expiry (e.g. Boceprevir, Sofosbuvir).

EUCOPE notes that extensive deferrals do not affect the enforceability of the PIP but do affect the effectiveness of the rewards as the company only becomes eligible for the reward after the PIP is completed, including the deferred studies..

2.10. Voluntary paediatric investigation plans

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

EUCOPE would welcome a global alignment between FDA and EMA practices. It would be appreciated if the EMA were to consider a system similar to the U.S. 'written request', subject to a same level of flexibility as the FDA. The Paediatric Regulation is built on the recognition that incentives are needed to convince companies to invest in paediatric research. Interestingly, the EMA 10 Year Report shows that over a same period of time (2007-2015), more new paediatric products have been authorised in the U.S. (249) than in the EU (221), hinting that 'written requests' are an effective paediatric tool.

2.11. Biosimilars

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

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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?

EUCOPE acknowledges positively the efforts being made by the EU Commission to reduce the off label use and the amount of clinical trials in the paediatric population creating the PUMA concept. EUCOPE encourages the EU Commission to maintain the concept and to improve it.

With this regard, EUCOPE would like to focus on the following aspects, where improvements would be appreciated:

- Data and marketing protection in connection with a PUMA does not prevent medicinal products with the same active substances which have been approved for adults from being marketed and prescribed for children and adolescents. Off-label use of these medicinal products has often become established practice in paediatric medicine. Consequently, both physicians and patients have become "accustomed" to off-label use of certain products.
- The paediatric studies which are conducted for obtaining the PUMA may, in some cases, confirm and support the off-label use of competing medicinal products.
- Because of the studies which have to be conducted for completing the PIP and obtaining the PUMA, PUMA medicinal products are hardly able to compete in terms of price with medicinal products with established off-label use, which are usually available as generics, preparations, and the likes ('specials in the UK').
- Physicians are likely to have little interest in abandoning proven off-label use of inexpensive medicinal products in favour of medicinal products which have the same active ingredients but are more expensive.

These aspects, especially the problem of off-label use, are cited as decisive for the lack of success of the PUMA in publications of the EMA and the European Commission and in opinions of European associations. The resulting disadvantages for the manufacturers are not offset by the data and marketing protection periods. Data exclusivity is an ineffective instrument in a market characterised by substitution. This protection merely prevents competitors from marketing generics/hybrids of the paediatric medicinal product, but does not hinder the presence in the market of medicinal products for adults with the same active ingredient and their off-label use in children. Moreover, national reimbursement systems sometimes favour (or even require) off-label use. In a generic competitive environment, off-label use can therefore be seen as a key factor in the lack of success of the PUMA.

The Commission is well aware of the issues for the PUMA' lack of success. While those reasons may be linked to downstream decision-making at national level, the Commission can still limit their effect, either directly or with the assistance of the Member States. For example, the presence of an added benefit should be acknowledged for all PUMA products given that products in off-label use have been converted into approved paediatric medicinal products. A prohibition on substitution should be introduced for paediatric medicinal products; otherwise approved paediatric medications will continue to be replaced by standard medications which are not approved for the use in children. More generally, the Commission must ensure that all relevant agencies (e.g. EMA, national regulatory agencies and national health services) have a coordinated approach to combat, and actually do combat, off-label use in cases paediatric medicinal products are authorised for that use.

Companies are willing to invest in the development of age-adopted formulations of old medicinal products in order to improve the paediatric patients' treatments, i.e. despite the lack of return of investment. However they

need some assurance that their efforts and investment would not be in vain.

Another factor that contributes to the lack of success of the PUMA being granted, is the PDCO's demands with regard to the paediatric studies. According to the EMA 10 Year Report, 22 PIPs for PUMA have been agreed by the PDCO over the 46 PIP proposed by companies, i.e. less than 50%. In practice, companies propose a PIP for PUMA, start negotiating it and withdraw it when the PDCO becomes too demanding in terms of paediatric studies. Insofar as PIPs for PUMA are voluntary and the PUMA is an inefficient reward, any PIP for PUMA brings somewhat unexpected paediatric data and the withdrawal of such PIP is a loss for society. The PDCO could therefore show more flexibility in the paediatric studies it requires from companies.

During the discussions on the adoption of the Paediatric Regulation, it appeared that innovative companies would probably not invest much in paediatric research for off-patent medicinal products. This led to the creation of a PUMA system that was also designed for generic companies (PUMA can be applied for hybrid applications). The idea was that generic companies would want to develop paediatric versions of their generic adult products in order to benefit from some exclusivity. No generics' company has however invested in paediatric research so far. It also led to Article 40 of the Paediatric Regulation, which envisages the funding of research in off-patent medicinal products by the EU, through the MICE. The MICE however was never created; instead the Commission relied on FP7 and then H2020. An EU fund exclusively dedicated to paediatric research could promote the development of PUMAs.

EUCOPE notes that according to the Commission, one of the reasons for so few PUMAs is that companies may choose marketing authorisations with orphan designation rather than the PUMA. This choice however is imposed by the Commission as it considers that companies may not benefit at the same time from the PUMA and from orphan designation. This restriction, which arguably has no legal basis (a medicinal product with an orphan designation may be granted a marketing authorisation under Regulation 726/2004 and a PUMA may be granted under Regulation 726/2004), reduces even more the relevance of the PUMA as an incentive to paediatric research.

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?

EUCOPE welcomes the Commission's efforts to limit the challenges faced by developers in carrying out paediatric clinical trials. Nevertheless, these challenges remain an issue, especially for rare diseases studies involving children given additional associated complexities (such as rarity of patients, lack of knowledge on natural history, difference between genotype and phenotype, etc.).

EUCOPE would like to highlight a few issues:

- The level of required details of paediatric studies should better match the development phase. Especially for orphan indications, early Phase I/II studies often need to be conducted in paediatric patients (thus, neither in healthy volunteers or adult patients). In early stage (FTIM/PoC/Ph II), essential knowledge on PK, PD and safety is obtained, which significantly impact on the design of subsequent studies (e.g., modifications of endpoints, study population, dosing frequency etc.). The requirement of having PDCO approval of very specific details of the late-phase design/development prior to entering early-phase development, (i) increases the hurdle to enter the clinical phase and the risk of substantial delays during development; and (ii) results in lengthy PIP modification procedures. The overall outcome is not necessarily safer treatments for children, but certainly more costly and time-consuming drug development. A 'lean PIP', as suggested under consultation item 7, would resolve the problem.
- For orphan drugs, a more frequent use of deferral for a number of age subgroups would be useful since patient recruitment can be quite time consuming due to the limited number of patients. The Paediatric Regulation is clear that it should not block or delay the authorisation of medicinal product for other populations
- EUCOPE is in favour of expanding the FDA-EMA paediatric cluster work including more information on common decisions and recommendations

Recruitment of subjects for clinical trials: Recruitment of paediatric subjects for clinical trials is difficult for SMEs (including e.g. orphan drugs as product group) when big pharmaceutical companies have already approved PIPs in the same indication. In such cases, the big pharmaceutical companies organise large studies that the PDCO then considers as the standard. Example: A global acting company performed a clinical trial in 82 study centers worldwide, 123 subjects. Such a number of centers for a paediatric trial with e.g. an ATMP is not affordable for an SME and providing investigational medicinal products to centers distributed worldwide cannot be performed due to manufacturing reasons. However, PDCO requested comparable study designs (randomised controlled studies) as those performed by big pharmaceutical companies with already approved PIPs in this indication.

Currently, the main issue with regard to paediatric clinical trials is feasibility, which primarily concerns products of a same class. Feasibility is a very important problem because companies are prevented from implementing their PIPs for reasons beyond their control. The development of paediatric networks helps but is probably not sufficient. The solution proposed by the Commission, i.e. collaboration between companies, is not realistic for an industry based on intellectual property rights. Grouping products also significantly complicates trial designs and does not necessarily allow for smaller total numbers of trial subjects. In addition, the time lines of the development programs will often not be sufficiently aligned.

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?

EUCOPE is not in favour of a new fee system on the PIP process as the financial impact would hit SMEs in particular and thereby discourage further innovation. Similar to scientific advice/protocol assistance, SMEs should benefit from waivers.

EUCOPE recognises the significant investment made by the Member States in the paediatric system. A not less significant investment is also made by the industry.

The Commission has indicated that the average administrative cost of a PIP is 720,000 Euros. Adding a fee for a scientific assessment of the PIP proposal would increase that cost and make the European paediatric system even more deterrent for any company. Certainly, it would not favour more PUMAs.

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?

EUCOPE believes the Paediatric Regulation has had positive effects on paediatrics research. Nevertheless, challenges, in particular with regard to clinical trials, remain and tend to slow down the R&D in the paediatric field. Therefore, stressed throughout the document, we call for a better implementation of the regulation via soft law (e.g. guidelines).

When Brexit will happen, EUCOPE would strongly call for keeping the UK research institutions involved in paediatric studies.

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?

EUCOPE would welcome developments on PK/PD, adaptive design and Bayesian design. The various initiatives relating to early access to medicines and GCP Renovation, may have an impact on the development of paediatric medicines. Indeed, they may impact the time of submission of the PIP (end of PK studies in adults). When envisaging a new scheme or initiative, the Commission should always consider the Paediatric Regulation and invite all stakeholders involved to provide their input thereon.

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?

Given the time and efforts involved in drafting a PIP and then 'negotiating' it with the PDCO (the PIP procedure takes about a year), the Paediatric Regulation has added complexity to the R&D and regulatory process with however little demonstrated results/benefit.

1. *Application form (Part A) of PIP* is not appropriate for advanced therapy medicinal products, e.g. dosages. Amount of cells per dosage should be possible. Further issues arise when submitting information regarding strength and excipients.

EUCOPE suggests that the application form be adjusted, taking into consideration the particularities of ATMPs (e.g. by giving the possibility to add free text for the dosage).

2. *Point in time of PIP-submission:* According to Article 16 of the Paediatric Regulation, the PIP or the application for waiver shall be submitted with a request for agreement, except in duly justified cases, not later than upon completion of the human pharmaco-kinetic studies in adults. However, this requirement is too early as not even data from proof-of-concept studies in adults can be provided at this stage. Submission of PIP should not be required before data of a planned Phase II are available.

3. *Line extensions for patent-protected products:* In practice, it is not sufficient to submit a PIP for the extensions (e.g. new dosage form or indication) only. Such a PIP should also comprise already approved dosage forms, which results in a multitude of clinical studies even though the products already have a marketing authorisation, at least in parts.

EUCOPE is in favour of the option to submit a PIP for the line extension only.

More generally, EUCOPE members expected the Paediatric Regulation to be implemented differently from the way the EMA/Commission did. First of all, the Paediatric Regulation was written with the adult indication in mind (see the RAND Study), but was applied on the basis of the adult condition and then the mechanism of action. Secondly, the PDCO has been very – and increasingly – demanding with regard to the paediatric studies in the PIPs, both in terms of number and content. Finally, while the Paediatric Regulation simply sought to generate paediatric data in order to avoid off-label use, the EMA has turned it into a series of administrative processes that became more and more burdensome and costly. At the same time, one could have expected the EMA/Commission to be more understanding when applying the rules to orphan medicinal products, ATMPs or to SMEs. The (heavy) burden imposed by the Paediatric Regulation on companies, is even heavier for those products or those companies.

EUCOPE would welcome more flexibility and understanding of industry's concerns and constraints, the need to address off-label use and a greater FDA/EMA alignment.

CONCLUSION: In a context of the Commission's efforts toward Better Regulation, EUCOPE strongly believes the various issues identified can be addressed via soft law (e.g. guidance documents) and do not need a reopening of the current Regulation.