

Stakeholder consultation on the experience acquired with the Paediatric Regulation

Novartis' answers to the European Commission Consultation

Novartis is a global healthcare company based in Switzerland that provides solutions to address the evolving needs of patients worldwide. Our work is driven by a strong scientific understanding of diseases and awareness of unmet medical needs. We believe in using evolving science and innovation in product development to identify effective treatment options for childhood diseases.

Novartis has a long-standing and sustained commitment regarding the development of paediatric medicines and our portfolio includes a number of medicines that are indicated for use in children [Exjade (deferasirox), Glivec (imatinib), Ilaris (canakinumab), Miflasone (beclometasone), Miflonil (budesonide), Revolade (eltrombopag), Riamet (artemether/lumefantrine), Ritaline (methylphenidate), Tegretol (carbamazepine), Tobi and Tobi Podhaler (tobramycin), Trileptal (oxcarbazepine), Xolair (omalizumab)], many of them have been developed before the entry into force of the Paediatric Regulation.

Our active R&D portfolio has led us to a total of 103 PIP/waivers negotiations with the PDCO (as of 15 January 2017), since the implementation of the Regulation covering over 60 compounds and combinations. This represents about 8% of all agreed PIPs/waivers as reported by EMA in the same period.

We thank the Commission for this opportunity to submit responses to the consultation based on our experience of the Regulation and its implementation, using examples from our portfolio as appropriate.

We believe that the legislation does not require an amendment for it to achieve its intended objective. However, we have concerns on the way it has been interpreted and implemented. Our experience of the system that has been put in place to implement the regulation is that it is overly prescriptive. Even more importantly, it lacks prioritization, resulting in a waste of resources and a shift of focus away from unmet medical need in children. As a result, patients are being enrolled in studies that cannot be feasibly completed, become redundant and waste resources for industry, investigators and regulators alike. In our responses to the consultation questions, we will provide evidence on the inefficiencies and recommend more pragmatic application of the law to facilitate a more efficient development of medicines for children. We would like to encourage a thoughtful assessment of how the regulation has been interpreted and implemented, which we are confident will lead to a better use of all stakeholders' resources with the possible creation of a "Notice to Applicant" that would bring together all the necessary guidance and the interpretations of the Paediatric Regulation. Importantly, we believe that a more pragmatic application of the law will also facilitate a more efficient development of medicines for children.

1. More medicines for children

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Figures show that the Paediatric Regulation has had a substantial impact on the development of paediatric medicines in the EU. Pharmaceutical companies now consider paediatric development as an integral part of the overall development of medicinal products, even if some of them continue to perceive paediatric research as regulatory-driven rather than company-driven.

The number of agreed paediatric investigation plans will soon surpass 1 000. In the 2007-2015 period, 99 paediatric investigation plans were completed and over 230 new medicines for use by children (new marketing authorisations and new indications) were authorised, most of them linked to the Paediatric Regulation's requirements. In addition, competent authorities' assessments of paediatric studies undertaken prior to the Paediatric Regulation (Article 45 of the Regulation) have helped collect already known evidence and to complement product information with paediatric data.

A comparison of the situation before and after the Regulation demonstrates a clear positive effect of the Regulation in terms of new authorised medicines. The same is true for international-level comparisons between regions with paediatric-specific legislation and those without: regions with legislative provisions in place have a significantly higher number of new paediatric medicines.

However, it is unlikely that the Paediatric Regulation would ever be able to create a self-sustaining system that could maintain such results without the external support of a specific legal framework for paediatric medicines.

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

Novartis' response

Novartis has a long-standing and sustained commitment regarding the development of paediatric medicines and our portfolio includes a number of medicines that are indicated for use in children, including many that have been developed before the entry into force of the Paediatric Regulation. Therefore, we believe that regulations that incorporate obligations and rewards should be considered as a complement, facilitating the development of medicines that innovation in science and innovation in drug development alone may not be able to sustain.

The Paediatric Regulation has created a movement towards better research in medicines for children that impacts all stakeholders. Many pharmaceutical companies, including ours, have created and staffed specialist paediatric departments that work with individual teams to design and implement paediatric development programs that can generate the best evidence. Further, a growing body of knowledge is being assembled on paediatric physiology or on new methodologies (modelling and simulation, extrapolation) that can help further improve paediatric drug development.

Finally, we believe that while the paediatric regulation created a movement towards better research in medicines for children, its implementation has not led to an efficient and sustainable infrastructure to support paediatric drug development research, nor has it addressed the need to focus on priority projects when limited patient numbers and resources are available (e.g., diabetes mellitus and melanoma). We believe that all of this can be accomplished through a more pragmatic interpretation and implementation of the existing Regulation via non-legislative measures (e.g. via guidelines). Responses provided in later Consultation Responses will detail our proposals related to interpretation and implementation.

2. Mirroring paediatric needs

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The starting point for most paediatric investigation plans is a research & development programme for adults. Under Articles 7 and 8 of the Paediatric Regulation, adult developments have to be screened for their potential use in children. A consequence of this approach is that progress in paediatric medicines is dependent on companies' adult product pipeline, i.e. on advances in the therapeutic areas and conditions in which there is a need or a market in the adult population. Where the adult needs overlap with paediatric needs, children will benefit directly. However, there is a considerable number of diseases that are biologically different in adults and children, where the disease burden differs, or that only exist in children.

Achievements of the Paediatric Regulation are therefore not the same across all therapeutic areas, even if agreed paediatric investigation plans cover a large variety of conditions. Some therapeutic areas have seen considerable progress over the past ten years, while for others the availability of new therapies is limited or has not yet materialised. It could be argued that the qualitative effect of the Paediatric Regulation does not really differ from other statutory instruments, which intend to redirect private investment towards previously neglected areas, such as for example the EU legislation on rare diseases. They are an important enabler, but as far as their effect is concerned, they are partly dependant on factors that can hardly be influenced by legislation.

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?

Novartis' response

Paediatric development does not mirror paediatric needs because these needs have not been defined as the essential starting point for implementation of the Regulation. Currently industry is doing its own assessment of the unmet needs but would welcome a multi stakeholder agreement on the most relevant needs so that it can target those.

Defining real and unmet paediatric needs will better guide industry in considering opportunities for innovation and prioritizing their resources. One way to define the paediatric need would be to better implement Article 43 of the Regulation (inventory of therapeutic needs) with the view of creating a list of disease priorities for paediatric medicines to allow PDCO and companies to identify areas of unmet medical needs on which development should be focused. The process for drafting the list should include all stakeholders.

EMA also supports this, as seen in its 10-year report in section 6 "Lessons learned": *"An EU structured, scientific, prospective and agreed identification of paediatric needs could provide predictability to the pharmaceutical industry."*

In the implementation of the Regulation there has been a blurred understanding that needs for paediatric research may not identically "mirror" the need and feasibility of paediatric drug development. We have encountered requests from PDCO that went beyond what was necessary to provide meaningful information for use in a paediatric population.

Novartis believes that PIPs should reflect what is needed to bring a product to the market, and should not include studies that are of limited value in the assessment of benefit/risk of the potential paediatric medicine. It is our assertion that incorporation of a well-vetted paediatric drug development needs list, in tandem with focus of the PDCO on agreeing to meaningful paediatric drug development programs, will both increase feasibility of conducting a paediatric drug development program as well as the feasibilities of conducting studies that are agreed as part of the PIP. This should enable a more efficient paediatric drug development across therapeutic areas in order to bring medicine to children faster, without unnecessary trials.

3. Availability of paediatric medicines in the EU

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The Regulation includes several instruments to ensure that, once a paediatric investigation plan is completed and the paediatric medicine is authorised, the product is placed on the market and available in the entire EU. For example, the SPC reward under Article 36 will only be granted if the product is authorised in all Member States. Moreover, Article 33 contains an obligation to place the product on the market within two years of the date on which a new paediatric indication is authorised.

These are complementary measures to ensure the availability of new paediatric medicines to all patients in the EU and to allow physicians and clinicians to use them in their daily work. At the same time, certain inertia in the system is reported, where physicians may not immediately switch treatment habits to newly authorised products.

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?

Novartis' response

As a company, we cannot comment in general on the number of new medicines available in Member States. However, we consider that "availability" is not solely about a company placing a product on the market and a doctor prescribing it, but it is also affected by decisions regarding re-imburement.

As a company, we have concerns that we may be required via the Regulation to develop products that we will place on the market where they will not be used, either because there was limited (no) unmet need, because reimbursement limits a products usage, or because prescribers do not change their practice habits. Over the last decade paediatric development has improved and the quality of paediatric development is expected to continue to increase in the next years, which should lead to the availability of labelled medicinal products for paediatric use. However the effort and resource committed to this (by all stakeholder groups) will be wasted if there are no initiatives at the level of the member states to support switching from off-label use to labelled paediatric medicinal products. In line with the spirit of the Regulation, the availability of paediatric medicines to all patients should be supported by all stakeholders, including by the national health authorities through granting fast access to new licensed therapies.

A high quality research plan leading to an appropriately authorised medicinal product for use in the paediatric population is of no value if the product is not used.

This is supported by EMA in its 10-year report in 6.2. "Availability of paediatric medicines" : *"Even when a medicine is authorised for use in children this does not necessarily imply that children have access to the medicinal product, despite specific obligations being imposed on marketing authorisation holders which have benefited from the paediatric rewards (Article 33 of Regulation (EC) No 1901/2006). This is an important issue which requires consideration from all stakeholders in order to make appropriately studied and authorised medicines available to children. Actual availability and accessibility depend on further arrangements for placing on the market such as reimbursement and sufficient pricing, which have to be agreed in each Member State."*

4. Reasonable costs

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The Paediatric Regulation places an additional burden on pharmaceutical companies by requesting them to carry out additional paediatric research which they might not have undertaken otherwise.

An evaluation of paediatric investigation plans agreed over the last ten years, based on an external study ordered by the European Commission, shows that the total R&D costs per plan on average amount to € 18.9 million, with each plan including an average of three clinical studies. On top of this, companies incur administrative costs of around € 720 000 in relation to filing of the initial submission of a paediatric investigation plan and for subsequent modifications. In total, the estimated average incurred costs per paediatric investigation plan is therefore just below € 20 million. Based on the average number of new plans agreed per year (107 in 2008-2015), this amounts to total annual costs of € 2.1 billion incurred by the industry. At the same time, this may be an overestimate given that not all agreed paediatric investigation plans will be completed as some are discontinued, for example if the company decides to shelve the adult development programme.

The above figures suggest that the additional costs incurred by industry as a consequence of the Paediatric Regulation are reasonable and that they lead to only a limited increase in the total costs of medicine development.

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

Novartis' response

As paediatric development is global, its overall cost is impacted by the extent of the global development program. The lack of effective alignment between US and EU programs, amongst other regional Health Authority requests, can have substantial impact on the overall cost of a program.

In our company's experience, costs also vary greatly from one product to the next reflecting that each PIP is unique. An average cost may not be able to reflect these complexities:

- The first PIP for a compound is usually more expensive as more measures (technical, nonclinical and clinical) are requested.
- While some of the Novartis PIPs only require one clinical study to be performed¹, we have examples of much more complex plans, including one for which we have been requested to carry out 5 non-clinical studies and 11 clinical studies, and to develop a paediatric formulation²; in such cases the cost will significantly differ.
- We have a high proportion of compounds (20%) that have several agreed PIPs (the highest number is four PIPs, for canakinumab). For such compounds, the cumulative cost of all PIPs for one program can be high.
- Some medicines are developed only for paediatric patients, in such case the full cost of development is the cost of paediatric development.
- The overall cost of a program also extends beyond the conduct of the studies committed to in a PIP: post-marketing commitments resulting from approval of the paediatric indication such as registries, Post Authorization Safety Study (PASS) and long-term follow-up studies need also to be taken into account.

Additionally, we have noted that, as we have moved towards having PIPs conducted outside of the intended adult condition (e.g., by mechanism of action), the ability to bridge scientifically to previously generated data for foundational proof of efficacy may be diminished, therefore requiring a higher number of non-clinical and clinical proof of efficacy studies and mechanistic, biomarker measures to support the unlinked paediatric indication for the medicinal product. This can substantially increase the cost of some agreed PIPs.

Finally, it is important to consider that there are some "hidden costs" that should also be factored, such as the cost related to manufacturing a paediatric formulation and maintaining it

¹ PIPs with only one clinical measure are for compound that already have a PIP approved in another condition

² EMEA-001003-PIP01-10-M02

268 on the market (Article 35), especially in the case the medicine has limited (or even no) paediatric
269 commercial use as better or safer medicines have become available.
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5. Functioning reward system

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The objective of the reward system introduced by the Paediatric Regulation (6-month SPC prolongation or orphan-specific reward) is to allow companies to recuperate the additional costs incurred as a result of the Paediatric Regulation through prolonged protection periods.

An analysis of the paediatric investigation plans completed so far shows that not all companies were able to obtain a reward. Figures show that at least 55 % of the completed plans benefitted from a reward, however. Most rewards took the form of a prolongation of the SPC certificate; in a few cases (four), the market exclusivity period of an orphan medicinal product was extended. In several instances, companies waived the product's orphan status shortly before marketing authorisation in order to make the product eligible for the SPC reward rather than the orphan reward, as the former is often considered to be economically more attractive.

There are various reasons for why not all completed paediatric investigation plans benefitted from a reward. In some cases, companies were not able to complete the paediatric development before the deadline for submitting a request to prolong the SPC expired (two years in advance). In others, products that fell under the scope of Article 7 of the Paediatric Regulation were not protected by a patent and/or SPC and were therefore not eligible for a reward despite being subject to the obligations. It is however, expected that over time the ratio of products that benefit from a reward will increase, as companies start to plan better and earlier to complete more paediatric investigation plans before the SPC expires.

Another factor that complicates the reward system is linked to the fact that SPCs have to be obtained from the national patent office in each Member State in which an SPC exists. However, the number of SPC prolongations granted in the last ten years (nearly 500) shows that companies regularly receive the reward from the national patent office in which they apply.

The monetary value of the SPC reward depends largely on the overall revenue that a particular product brings in during the period in which it is protected by an SPC. Typically, this period corresponds with the peak in sales. In most cases, the reward's value is likely to surpass the average paediatric investigation plan compliance costs discussed under point 2.4, in some cases significantly. However, this surplus may be used to cover the costs of discontinued paediatric investigation plans or ones that did not receive a reward.

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?

Novartis' response

The rewards provided by the Regulation are to balance the significant investment required, both financial and in personnel, in order to deliver meaningful information for use in the paediatric population. It is Novartis' position that a more pragmatic implementation of the Regulation would do much more to facilitate efficient paediatric product development and securing of Reward.

In our experience, it is difficult to complete a PIP, and completing it on time to be able to claim the 6-month SPC extension reward is even more difficult. In addition, the reward itself is difficult to secure, as the process for obtaining the SPC extension once a product has received positive compliance check is complex and unduly burdensome, highlighting the uncertainty of whether a compliant PIP will attract a reward. This is supported by EMA data: by the end of 2015 only 44 medicines benefited from a paediatric reward (39 SPC extensions, 3 orphan rewards and 2 PUMAs): this is only 5% of the agreed PIPs and less than 45% of the completed PIPs³.

³ According to EMA report by the end of 2015:

- The PDCO had adopted 860 opinions on the agreement of a PIP
- The PDCO had adopted opinions on final/full compliance for 99 agreed PIPs : **only 12% of the agreed PIPs**
- A compliance statement was added to the marketing authorisation for 30 centralised medicines and 35 nationally authorised medicines: **only 8% of the agreed PIPs**
- 44 medicines benefited from a paediatric "reward": this is **only 5% of the agreed PIPs and less than 45% of the completed PIPs**
 - The SPC extension reward was granted for 39 medicines
 - 3 orphan rewards and 2 PUMAs were granted

324 Furthermore, it is important to note that no reward is possible when product development is
325 quick (when it takes fewer than 5 years from the date the basic patent was filed to the date of
326 the first MA in the EU) as the product has no SPC to which the reward can be attached;
327 nevertheless still a PIP has to be agreed as per Article 7 of the Regulation.
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329 This is further supported by EMA in its 10-year report, section 6.1.2. “Rewards and incentives“:
330 *“For certain medicines the obligations of the Regulation, i.e. to obtain a PIP or waiver apply*
331 *without the opportunity to obtain the reward (for example active substances which are not*
332 *eligible for an SPC/patent that qualifies for an SPC, such as some vaccines). In addition,*
333 *requesting the reward is cumbersome in comparison to other rewards in the regulatory field*
334 *(e.g. data protection or market exclusivity, which are automatically applied), as applications*
335 *must be made in each Member State where an SPC exists.*
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337 *Moreover, some completed PIPs did not lead to a reward if the paediatric development was*
338 *completed after the two-year advance notice period which is required to apply for the SPC*
339 *extension. The two-year notice is intended to provide due warning to manufacturers of generic*
340 *medicinal products, but it effectively prevents the possibility of granting the reward to the*
341 *company having performed the development in some cases.”*
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343 Importantly, SPC extensions allow companies to fund future research in follow-up indications
344 or for other compounds, thus helping to develop more products and indications for paediatric
345 use.
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347 In response to the Consultation question regarding the role of “early, strategic planning” in
348 achieving reward, Novartis is unclear on which data the EC is basing its statement *“It is*
349 *however, expected that over time the ratio of products that benefit from a reward will increase,*
350 *as companies start to plan better and earlier to complete more paediatric investigation plans*
351 *before the SPC expires”*. The EMA 10-year Report does not provide any analysis on whether
352 the timing of PIP agreement impacts the ability of a company to secure a paediatric reward.
353 Indeed, in our experience, an early planning and agreement of a PIP is not always a guarantee
354 for success. On the contrary, agreement of PIP measures early in the development of the
355 product, at a time when only limited knowledge on the product is available, can lead the
356 applicant to agree to inappropriate and unfeasible commitments that will have to be modified
357 over time and create more work and unnecessary delays. We have filed over 100 Requests for
358 Modification with the PDCO for our PIPs, including a PIP where the total number of requests
359 for modification, including those we had to withdraw, is now reaching 8.
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361 As stated in the introductory statement, the rewards provided by the Regulation are to balance
362 the significant investment required, both financial and in personnel, in order to deliver
363 meaningful information for use in the paediatric population. However, it has been our experience
364 that agreeing to, implementing and completing a PIP does not equate to a future reward. It is
365 Novartis’ position that a more pragmatic implementation of the Regulation, including phased
366 agreement on PIP components, diminishing the extensive resource drain of multiple
367 modification requests, would do much more to facilitate efficient paediatric product development
368 and availability of medicinal product for patient, than earlier submission and agreement of a
369 detailed end-to-end PIP.
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6. The orphan reward

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When the legal proposal for the Paediatric Regulation was discussed, about 60 % of orphan-designated products were off-patent. This was the beginning of the implementation of the Orphan Regulation, and a few of older substances had been transformed into pharmaceutical quality-medicinal products. This was one of the reasons for why the legislature decided to introduce an orphan-specific reward in the Paediatric Regulation, in the form of a two-year extension of market exclusivity.

However, currently, more than 90 % of newly authorised orphan medicines are on-patent. The SPC reward may be economically more attractive for them, but orphan-designated products are only eligible for the orphan reward (Article 37).

In some instances, especially for medicines that have both common and rare conditions, companies voluntarily waived the orphan designation in order to make the product eligible for the SPC reward. This can be considered as 'playing the system' or as showing that the orphan reward has only a limited impact. At the same time, however, most of the products that received the orphan reward belong to the category of 'orphan blockbusters', i.e. they generate substantial revenue in a niche market for the companies concerned.

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

Novartis' response

The orphan reward is meant for products which are not protected by a patent. It can be very valuable in such cases as well as if the development of an orphan product was fast (i.e. if it takes fewer than 5 years to get a marketing authorisation from the date the basic patent was filed, and the product has no SPC to which the reward can be attached). However the SPC reward may be preferred for patented orphan medicinal products depending on the duration of the SPC. Industry needs the flexibility to be able to choose between the two rewards on a product-by-product basis to facilitate product development and it is our understanding that regulations allow this possibility based on voluntary withdrawal of the orphan designation. Ultimately, rewards allow companies to fund future research, thus helping to develop more products and indications for paediatric use.

This is supported by EMA in its 10-year report

- In section 6. "Lessons learned": *"The principles underpinning the definition of rewards for orphan medicines do not foresee the circumstances where the orphan medicinal product is patent protected. This creates the need for companies to choose between rewards derived from the PIP or Orphan designation, many times to the detriment of the framework created for orphan medicinal products."*
- In section 6.1.2. "Rewards and incentives": *"The paediatric legislation was developed when about 60% of the orphan-designated products were off-patent (2003-2004). However, over time this has substantially changed, and in the years 2013 to 2016 (September) 95% of the orphan-designated products which obtained marketing authorisation are covered by a patent (41/43). As a consequence, the orphan reward (2 additional years of market exclusivity) appears less interesting to developers, unless there is no SPC, or it cannot be extended. The fact that the two rewards are mutually incompatible can be seen as unfair, as developing for a rare disease in children is doubly difficult. Considering this change of paradigm that a substantial number of orphan medicinal products are covered by a patent the adequacy and the proportionality of the reward for orphan medicinal products might be discussed."*

The paediatric orphan reward does not appear to always be commensurate with the extent of work that is being applied to paediatric orphan drug development. Indeed, orphan drug development is very complex and specifically paediatric orphan drug development and PIPs may bind companies to agree to additional measures outside of what was necessary to determine the benefit/risk profile of a compound (e.g., EMEA-000060-PIP01-07: The marketing authorisation for canakinumab to treat a very rare disease Cryopyrin Associated Periodic

432 Syndromes (CAPS) was obtained on 24 January 2013, and however, it took over two more
433 years to complete the PIP, and full compliance check was granted on 19 June 2015).
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7. Improved implementation

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The Paediatric Regulation gives the EMA and its Paediatric Committee primary responsibility for handling paediatric investigation plans, deferrals and waivers. Hence, the EMA plays a key role in the Regulation's implementation. Efforts have been made to learn from the first years of implementation and to simplify paediatric investigation plan opinions to reduce the need for modification if there are non-significant changes to the paediatric investigation plan programme. These efforts have helped to decrease the overall ratio of changes to paediatric investigation plans.

Additionally, the revision of the Commission's guidelines on the format and content of paediatric investigation plans in September 2014 introduced measures to streamline the process of agreeing the plans. Moreover, in 2015 the EMA introduced early interaction meetings with companies to encourage them to consider paediatric needs in the early phases of medicine development. These early meetings also make it possible to determine the appropriate timing, and integration of paediatric measures in the context of the overall medicine development.

To facilitate paediatric development across regions, in 2013 the EMA and its US counterpart the FDA launched so-called 'common commentaries' on paediatric development plans that have been submitted to both the EMA and FDA and that must be reviewed by both agencies. While informal and non-binding, these commentaries and discussions between the two agencies have helped to align views and to avoid contradictory requirements with regard to the paediatric development programme.

However, it remains a challenge for the EMA and its Paediatric Committee, as well as for companies, to consider key aspects of medicine development when certain information is not yet known and when discussions are still based on assumptions and scarce data. This is true especially as one of the objectives of paediatric development plans is to create legal certainty about regulatory authorities' expectations towards companies. On the other hand, only early interaction makes it possible for paediatric development to be seamlessly integrated into overall product development instead of being an afterthought. In principle, it should also lead to more (cost-)efficient R&D, as it makes it possible to consider integrating adolescents into adult trials thereby reducing overall study costs.

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

Novartis' response

Novartis agrees that, since 2007, as the complexity of implementing the Regulation became apparent, some PIP-related processes have been clarified over time. However, there has been only limited attempts to address the complexity of the PIP content and our experience with over 100 unique regulatory procedures related to paediatric drug development under the Regulation, tells us that this area could benefit from a more pragmatic and simplified implementation. Improvements should go beyond the procedural aspects associated with the Regulation (e.g., PIP application, compliance check), and should importantly address the scientific content of the plans. This can only be done with a significant increase in scientific expertise and with a more efficient integration of existing expertise at the EMA in the assessment of scientific components of paediatric investigation plans.

There is room for the implementation to be further improved, striving for more pragmatism and less administrative burden. The system that has been put in place to implement the regulation is overly prescriptive and lacks prioritization.

Some of the efforts made are not delivering what was expected. For example, EMA put in place in 2015 an 'early interaction' meeting. As a company, we were very hopeful about the prospect of such an opportunity to engage the PDCO and EMA in a non-binding and informal manner on our pipeline programs that have the ability to integrate paediatric development very early in development, potentially hastening multiple paediatric development programs. However, we were disappointed that the new early interaction meeting that we participated in added limited value as our team required engagement on key scientific questions and not an administrative advice. Furthermore, as a company we need to be able to reach out to the experts when we

497 have scientific questions that need to be discussed, this is currently not possible within the early
498 interaction meeting as this is only a selective process (in term of project but also in term of
499 development timing). Additionally, PDCO has a restricted interpretation and considers the early
500 consultation as applicable only to the first PIP for a compound and not for PIPs that are
501 developed later, as we extend the use of the product to new indications (Article 8 PIPs). In our
502 experience, the PDCO refused some of our meeting requests because we were seeking
503 informal guidance on potential paediatric interests and initial PIP development for follow-on
504 indications for drugs already in later stages of development or even already approved for an
505 adult indication. [EMA's 10-year report is highlighting the fact that the new early interaction
506 meetings are not really about the science but more about timely submission: "*The EMA / PDCO
507 have recently launched early interaction meetings to assist with timely submission of the PIPs
508 and appropriate development according to paediatric needs.*" EMA's 10-year report, page 68].
509 To better facilitate paediatric drug development, EMA and PDCO need to find the means of
510 bringing together the scientific expertise available at the agency to provide meaningful advice
511 on programs well in advance of adult development, and to allow for more efficient and
512 constructive pathways forward for development that are not mired in administrative procedure.

513
514 Another example concerns the commission guideline on paediatric investigation plans
515 published on 27 September 2014. The guideline deleted the study initiation date from the key
516 elements to simplify the PIP process. However EMA is still requiring study initiation dates in its
517 key element form preventing industry from benefitting from the simplification suggested by the
518 EC.

519
520 Additional suggestions to facilitate implementation via non-legislative measures (e.g.
521 guidelines) include:

- 522
523 - Introduction of a paediatric parallel scientific advice procedure
524 To construct a rigorous science based program where the availability of affected
525 paediatric patients is limited, there is a clear need for convergence of research
526 approaches in order to successfully execute on a global drug development program.
527 When regulators diverge on their requirements for study, sponsors require a pathway
528 whereby they can engage with regulators across agencies in a single interaction to
529 discuss the science, complexity of research and identify a meaningful pathway forward
530 in order to bring the best quality medicinal products more efficiently to market. It should
531 be a quick procedure in respect to development plans and should not have too strict
532 entry criteria that would prevent most of the projects to benefit from it at an appropriate
533 time.

534
535 We have in our portfolio a bisphosphonate⁴ where the PDCO has requested a clinical
536 study while the FDA has granted a waiver on the grounds of safety. The study was
537 started in 2009, and has been ongoing since, it will not be completed as currently
538 planned as it is not possible to recruit the patients. If parallel advice had been possible,
539 we would have been able to have a global agreement on what would have been
540 feasible, and avoided to have an unfinishable study, to the detriment of the children
541 enrolled in the study, and of the scientific community.

542
543 We note that the commission is referring to the 'common commentary process', which
544 is a useful tool used by the health authorities to discuss common topics in paediatrics.
545 However, it does not involve the applicants and by the numbers has been rarely used
546 to provide follow-up guidance to impacted companies: as of May 2015 only 15 Common
547 Commentaries have been sent to sponsors, which is less than 2% of the 860 PIPs
548 agreed by EMA.

- 549
550 - Streamlining the application for CHMP decisions/ Scientific Advice output and their
551 integration into the PIP
552 There should be a possibility to integrate the outcome of a paediatric SA procedure into
553 the PIP without having to submit another Request for Modification to integrate it.
554 Currently two separate procedures are required where experts often discuss the same
555 question, and at times, do not reach the same conclusion. This is not an optimal use of
556 the CHMP and PDCO resources as well as sponsor resources, and it lengthens the
557 timeline for development of paediatric programs.

⁴ EMEA-000057-PIP01-07-M05

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We have a case in 2016 of a PIP Request for Modification regarding a change to some of the parameters of an ongoing clinical study. The conclusion of the PDCO was that we should obtain a Scientific Advice to address a statistical point, as the committee did not have the required expertise. Once we received the requested advice, procedurally we had to file for a further Request for Modification to bring this advice back to the PDCO. Taking into account the procedural times for the initial Request for Modification followed by a Scientific Advice followed by a second Request for Modification, a total of 10 months had elapsed before being able to submit the changes to the study centers.

- Better balance between timing and content of the PIP
PDCO should allow flexibility on the timing of submission of the PIP or on the content of the PIP.

The Regulation requires a PIP to be submitted at an early time point in the drug development process. At this early stage, detailed paediatric plans may not easily be determined and the company will not know whether the product will successfully transition into later phase development.

- Flexibility on the content of the PIP: If the PIP has to be submitted at an early time in the drug development process, the PDCO should adopt a pragmatic approach on the level of detail that should be included in a PIP application (high-level or staged application more appropriately reflecting the actual knowledge/data that is available at that time-point). In doing so more feasible PIPs would be agreed and a high number of Requests for Modification could be avoided decreasing the respective workload for PDCO and sponsors. This is supported by EMA in its 10-year report: *“excess level of details in PIP opinions may result in lack of flexibility”* (section 6.7. “PIPs and their life-cycle”)
- Flexibility on the timing of submission: A more flexible and pragmatic interpretation of the timing of PIP submission could avoid a high number of Requests for Modification. Furthermore greater flexibility could also avoid some unnecessary clinical trials in children (e.g. when the development of a product is terminated in early phase, or when data extrapolation could be considered once more adult data becomes available).

This is supported by EMA in its 10-year report: *“it is challenging to consider all aspects of medicine development for children at a time when important characteristics even of the adult development are not yet known. PIP opinions which are too detailed at such an early stage can be difficult to agree and counterproductive because emerging data will inevitably lead to changes”* (page 8).

- Transparency of paediatric studies results (6-month reporting requirement in Article 46 and posting to EudraCT under Article 41)

The timeline for submitting paediatric study results under Article 46 and posting them to EudraCT under Article 41 is 6 months from completion of the study, which is defined as Last Patient Last Visit (LPLV). Compliance with these timelines is very challenging for marketing authorisation holders, particularly for large and/or complex studies, when translation are required or when LPLV occurs quite some time from data-base lock. There is no compelling scientific or ethical reason why the result submission and posting requirements for paediatric studies should differ from those for all other studies (which are within 12 months of completion).

Furthermore, the Regulation does not specify the scope of Article 46. There is a need for the development of a concise EC guidance that includes the procedural submission elements, but also provides clarity on scope. As a company, we have experience of filing about 100 Article 46 submissions, and in the absence of a clear scope of what is needed, we have had to submit both interventional and non-interventional study results. It is quite possible that some of these studies also have or will be resubmitted at a later date as we apply for the corresponding paediatric indication. This is a duplication of work for both the applicant and the health authorities. Further, we believe that there is the need to establish a clear definition of what is ‘study completion’ that more adequately reflects trial completion (e.g., last data collected or database lock) and a suitable means to cross-reference previous study results submission. For Article 41, clarification is required on what third country interventional studies are required to be posted.

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- PIP revocation process

There is currently no possibility for an applicant to apply for revocation of a PIP when development has been abandoned because of lack of efficacy or safety signals (PDCO and EMA cannot revoke a PIP, either). EMA has introduced a process for applicants to notify the Agency of the termination of a paediatric development, however, this notification has no legal consequences, and the PIP decision remains in the public domain and paediatric obligations remain. This is a concern in particular when the development that is stopped is a further development of a product that already holds a marketing authorization in another indication. We have such examples from our portfolio, and can provide details on request.

8. Waivers and the ‘mechanism of action’ principle

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The Paediatric Regulation establishes a system which waives the requirement of a paediatric research programme for specific products or for classes of products (Article 11). This happens if a product is likely to be ineffective or unsafe for children or if it does not have a significant therapeutic benefit over existing treatments. The obligation is also waived if the disease or condition for which the product is intended occurs only in adults.

The waiver aims to avoid unnecessary research and to correctly frame the scope of the obligations. However, as simple and straightforward as the waiver concept seems to be, it has been criticised over its effects, especially in cases where the obligation is waived because the adult disease does not exist in children. One particular example is paediatric oncology, where many paediatric cancers share biological similarities with adult cancers, but occur in different organs and therefore are usually considered as different conditions. Consequently, a company may be entitled to a waiver even if the mechanism of action of the adult product under development may potentially also be effective in treating certain paediatric cancers.

This has led to missed opportunities in the past, even though some companies decided not to apply the waiver and to carry out paediatric research on a voluntary basis and based on the ‘mechanism of action’ principle. These companies understood that doing so would make them eligible for a reward under the Paediatric Regulation, so the voluntary research serves not only a public health purpose, but may also prove economically beneficial to them. The EMA’s 2015 review of class waiver decisions may help to engage in a dialogue with applicants regarding voluntary research. However, some parties consider that the voluntary approach will fall short and advocate for a stronger reliance on the ‘mechanism of action’ principle. Others argue that changes to the waiver concept risk endangering the objective of disease-agnostic statutory rules as well as the predictability of paediatric investigation plan decisions with regard to the expected scope of paediatric research.

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?

Novartis’ response

Novartis has already used ‘mechanism of action’ (MoA) principles when evaluating its compounds for specific paediatric need (e.g. the bisphosphonate zoledronic acid (Zometa) was evaluated for its potential use in osteogenesis imperfecta [an indication which was not granted in the EU/EEA due to lack of efficacy] and the protein kinase inhibitor imatinib (Glivec) for childhood acute lymphoblastic leukaemia). In fact 60% of Novartis’ oncology compounds have agreed PIPs of which the majority have paediatric development being pursued based on mechanism of action.

Novartis acknowledges the points raised by the Commission in the final paragraph and agrees that “missed opportunities” (for all therapeutic areas and all age subsets) are part of innovative product development. While it seems simple to evoke the principle of using the MoA to drive paediatric development and address so called missed opportunities, the MoA principle is a poorly defined concept that may have limited scientific tractability if a MoA has not been validated as being an actionable target in a defined paediatric disease. There is currently no regulatory guidance provided in the EU to guide decision-making.

When a company invests in a drug development program, it decides all aspects of its development program, using available scientific platforms that have been validated, utilizing regulatory guidelines and requesting scientific advice if needed. However, the Paediatric Regulation compels companies to evaluate all of its compounds for paediatric opportunities, even when there is limited foundational science to support the understanding of disease or existing professional society and regulatory guidance on how to best consider a product’s development.

Therefore, when discussing how a MoA principle could be implemented, we believe that such a concept requires clear gating components to be considered: (1) the system should be transparent, (2) consistent, and (3) predictable.

695 It should also be noted that the fact that a need exists does not mean that the opportunity will
696 be realised (e.g. the need will be fulfilled). If a need can be addressed in a scientifically-sound
697 manner that is also feasible, as a company, we will do it. However, in paediatric drug
698 development the number of available patients often does not allow for robustly-powered
699 confirmatory studies and companies face feasibility issues when several PIPs, for different
700 medicinal products, for the same indication/condition, have to be run in parallel. It is unethical
701 to start study/enrol children in a study that has a low probability of completing successfully (e.g.,
702 enrolling the study as intended per protocol) or of generating enough data to yield a meaningful
703 conclusion. Therefore, there is a need to include feasibility (and the lack thereof) as a key
704 criterion in determining the appropriate path of development for a medicine (e.g., traditional vs.
705 alternative approaches [Modelling and simulation, extrapolation]) which may include a request
706 for waiver.

707

708 Further, when considering possible paediatric indications, it is critical that policy-makers and
709 regulators recognize the capacity and capability of the company to construct drug development
710 programs that may go outside of their area of knowledge and expertise. Going well beyond the
711 condition that encompasses the adult indication may result in disproportionate and extensive
712 PIPs which ultimately discourage or even halt drug development of new products and
713 indications, not only in the paediatric population, but also in the intended adult population. This
714 is aligned with the EMA 10-year report: *“In cases where the paediatric need differs from that in
715 adults, the additional requirements for companies may create difficulties and result in the need
716 for additional scientific and financial resources that in the absence of additional incentives may
717 be a burden on drug development.”* (section 6.6. “Scope of PIPs and waivers”)

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719 More generally, Novartis would like to emphasize that waivers are not at the sole discretion of
720 a sponsor, they are granted by the PDCO once they have been scrutinized through a regulatory
721 procedure and if supported by sound scientific rationale.

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9. Deferrals

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The Paediatric Regulation includes provisions for deferring the initiation or completion of some or all measures contained in a paediatric investigation plan (Article 20), with a view to ensuring that research is carried out only when safe and ethical. It also includes measures to avoid that the requirement of completing a paediatric investigation plan blocks or delays the authorisation of adult products. Experience shows that deferral is a widely used instrument and there is no evidence that the paediatric requirements have delayed the processing of adult application, with the exception of those rare cases where companies submitted the paediatric investigation plan late, i.e. only shortly before they planned to submit the adult application.

The concept of deferral is in some instances also useful to delay the initiation of a paediatric trial until further information from adult trials is available, especially regarding the safety of potentially toxic compounds. At the same time, deferrals that delay the initiation of the paediatric trial until after the adult authorisation can create problems, as in these instances recruitment for paediatric studies can become more difficult once the product is available on the market. Parents often fail to see the added value of agreeing that their child participates in clinical research if the adult product can already be used (off-label) in children.

Extensive deferrals may also cause frustration among clinicians and patients, especially if they mean that the paediatric product to treat a life-threatening disease will only be available to children years after the adult authorisation comes through. Moreover, long deferrals may undermine the enforceability of paediatric requirements, and the availability of the reward, especially if the deferral ends after protection periods for the product have expired.

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

Novartis' response

Novartis does not agree with the above assessment of deferrals.

Deferrals are an essential tool to allow the Paediatric Regulation to meet its objectives of a safe and ethical study of a drug in children without delaying authorization for adults. No deferred timeline is ever at the sole discretion of a sponsor, to be "rubberstamped" by the PDCO. Deferrals are granted by the PDCO only when fully justified, and when the applicant has a sound scientific rationale. Furthermore there is an efficient mechanism to monitor their use via the required submission of Annual Reports on Deferrals.

Looking at our portfolio, we note that we have only two products with no deferrals and no waiver. These two products had been in use for a number of years at the time of entry into force of the Paediatric Regulation. In both cases, they were enough data on the safety of the product to allow an immediate start in children.

In our experience, the number of Novartis PIPs with a full deferral, where the paediatric development only started once the adult development has been completed, is low (9, 20% of all deferrals). The majority of the deferrals granted by the PDCO for Novartis PIPs were partial deferrals (35, 80% of all deferrals), where development in paediatric starts while the adult development is ongoing. A common example of a partial deferral that has been agreed has been for the deferred start of one age group (e.g. toddlers and infants) while additional data is being generated for other populations to inform on key safety or clinical pharmacology components.

We consider that deferrals are necessary tools to ethically study drugs in children as we often do not know enough about the safety and efficacy of the compound to initiate paediatric programs at the end of phase 1 of drug development. We endorse the ICH position that "Information that can be obtained in a less vulnerable, consenting population should not be obtained in a more vulnerable population or one in which the patients are unable to provide individual consent."⁵ This is of critical importance in particular when we are evaluating new molecular entities to which there is limited data to inform on safe application in the paediatric

⁵ ICH E11 Clinical investigation of medicinal products in the pediatric population

782 population. We cannot think of any alternative measure to deferrals that could be used to
783 guaranty ethical clinical research in children.
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785 In its 10-year report, EMA accuses industry of using repeated deferrals as a way of avoiding
786 finishing PIPs⁶, however the agency did not provide data on the number of PIPs that are thus
787 delayed by this means.
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789 Deferrals may also be used to mitigate the difficulties stemming from the extensive requests
790 from PDCO. When faced with a complicated and extensive PIP, deferrals are often required to
791 gather a maximum of data before safely initiating the paediatric development. If the PIP process
792 would allow a more staggered (phased) approach, sponsors could reasonably agree to conduct
793 earlier phase measures (e.g., nonclinical development and dose-finding/exposure-response
794 studies) prior to agreeing to extensive clinical measures. Sponsors could also very reasonably
795 be given a measure binding them to return to the PDCO for agreement on the clinical measures
796 once earlier phase development has been completed. This serves two valuable purposes:
797 firstly, a reduction in the number of time-consuming and inefficient Request for Modification
798 procedures; secondly, it provides a reasonable forum to address emerging science or data
799 within the class of product or in understanding of disease progression within the more detailed
800 clinical development measures.
801

802 Long deferrals can also mean that over-complicated and unfeasible study(ies) have been
803 requested by the PDCO. In such cases, applicants are forced to defer repeatedly the completion
804 dates of studies as they are not able to reach the target recruitment figures that they must
805 comply with.
806

807 We note, however, that as a sponsor we will always prefer finishing agreed commitments rather
808 than having to provide public annual updates on the status of its agreed PIP commitments that
809 have been deferred. As long as a PIP is not completed, we are accruing costs related to
810 resourcing open commitments. Furthermore, a completed PIP could allow us to secure a
811 reward.
812

813 Finally, Novartis would like to query the basis for the statement “*there is no evidence that the*
814 *paediatric requirements have delayed the processing of adult application*” as in our experience,
815 the EMA has no means to substantiate it. We are not aware of any requirement to inform the
816 EMA of a company’s internal strategic decisions not to pursue product development or
817 supplemental indications.
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⁶ “Once the marketing authorisation for adults is granted, deferred paediatric studies may be delayed or not initiated. This is due to the fact that once the product becomes authorised, the most significant deterrent of the Regulation, non-validation of the marketing authorisation application, is not applicable. This leaves the regulatory network without the means to enforce the PIP completion once the product is authorised.” (EMA 10-year report page 82)

“For example, measures and studies whose completion is not deferred and need to be completed before marketing authorisation application tend to be completed in time and in compliance with the agreed PIP. This is ensured by checking compliance at the time of the marketing authorisation application as non-compliance would prevent validating the application. On the contrary, once the marketing authorisation for adults is approved, deferred studies may be delayed. The PDCO sees many requests to postpone completion, or requests for changes of critical elements of the studies that substantially reduce the scope and quality of the development in children. Once the product becomes authorised, the most significant deterrent of the Regulation, i.e. non-validation of the marketing authorisation application, is not applicable.” (EMA 10-year report page 84)

10. Voluntary paediatric investigation plans

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The EU was not the first region to introduce specific legislation in order to tackle the absence of medicines that are tested and authorised for use by children. In fact, the United States passed paediatric-specific legislation already in 1997. While the general goal is similar, there are certain differences in scope and nature. For example, with the so-called ‘written request’ US legislation includes an instrument that allows its Food and Drug Administration to submit to companies a paediatric research proposal, which, if honoured, makes the company eligible for an incentive.

Some argue that EU legislation lacks the tools to invite and incentivise companies to voluntarily carry out paediatric research in the form of a voluntary paediatric investigation plan. However, although the Paediatric Regulation is geared towards obligations, it also includes the possibility to submit voluntary paediatric investigation plans. Nothing prevents a company from submitting a paediatric investigation plan request for a paediatric-only development or to complement an adult development with a paediatric investigation plan, even if it is entitled to a waiver (under Article 11(1)(b)). In these circumstances, the company in question is able to benefit from rewards under the Regulation and these serve as an incentive. Some companies fully realise the potential of voluntary paediatric investigation plans and consider paediatric research projects beyond the obligations of the Paediatric Regulation, while others are less forthcoming.

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

Novartis’ response

We understand that what the EC calls a ‘voluntary PIP’ covers a PIP agreed in the absence of an adult indication, or a PIP agreed that is outside its adult indication (the company could even have a waiver for its adult indication). Regardless, in all cases, even if the creation of such a PIP is voluntary, once the PIP is agreed with the PDCO the company is fully obligated to carry out the agreed development, and compliance will be checked at time of MA submission.

Note that “voluntary PIPs” are more likely to be pursued if a reward is possible. Currently, companies can only secure reward for the PIP that is attached to the first regulatory submission attracting a PIP. Sponsors will run several paediatric development programs but in the best situation they will be rewarded by only one reward. The EMA’s policy to limit reward to the first regulatory submission has an important impact on companies’ decisions to pursue voluntary PIPs.

Paediatric-only product

Regarding the case of a PIP agreed that is outside its adult indication, it is our understanding that when a company decides to develop a product purely for a paediatric population, a PIP is mandatory. However, Novartis is of the opinion that the application of the Paediatric Regulation to the development of treatments for diseases that occur only in children should be made optional/voluntary or studies included in the Marketing Authorisation Application dossier should automatically be considered as the PIP studies and granting of a Marketing Authorisation should trigger a PIP completion. When a company is willingly developing medicines for children, there is no need to impose on them paediatric obligations. Paediatric research is already complex, adding the burden of a lengthy procedure with the PDCO and ending with a PIP that may not be pertinent to the actual requirements for determination of benefit/risk required by the CHMP is disincentivising paediatric-only research.

For paediatric-only development, the PDCO input on a PIP offers limited to no added value. Interaction with the PDCO requires a separate lengthy procedure to agree the PIP. This adds additional time to the paediatric development process, and as it is separate from the CHMP, may not be aligned with what is required to demonstrate the benefit/risk for the medicinal product authorisation. For this companies rely on the CHMP’s scientific input (to which 3 PDCO members are participating).

While this seems counter intuitive, making the application of the Paediatric Regulation optional to developments that target a disease occurring only in children would indeed incentivize paediatric research as it would not bind a sponsor to the complex procedural burden of agreeing and modifying a PIP. In such cases, a PIP could still be entered into voluntarily by the applicant,

880 in which case all of the obligations (and potential for rewards) would apply, or the PIP could be
881 automatically aligned with the development plan agreed with CHMP.

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883 The same argument can also be made for orphan paediatric medicines. Making the application
884 of the Paediatric Regulation to Orphan Medicines optional/voluntary or linking it into the
885 marketing authorisation procedure would decrease the procedural burden of orphan paediatric
886 drug development, it would make it simpler to study drugs for orphan disease in paediatric
887 patients. Rare diseases are inherently more difficult, expensive and time-consuming to study,
888 and this challenge is still greater for clinical trials involving children. With many rare diseases
889 still having sub-optimal or no therapy options, research and development these conditions
890 should be further encouraged by the relaxation of the regulatory requirements in this specific,
891 limited context.

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11. Biosimilars

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Under Article 9 of the Paediatric Regulation, certain product categories are exempt from the obligations introduced. This is for example the case for generic medicines and biosimilars and is justified by the fact that the relevant knowledge for using the active substance in children was already obtained through clinical research with the originator product (at least, for those products which were authorised after the Regulation entered into application). It is therefore not justified to repeat paediatric trials for these product categories.

At the same time, some originator products are authorised with specific age-appropriate paediatric formulations. Some argue that biosimilars copying the originator product may not necessarily include these paediatric formulations, which may lead to products entering the market without being adapted to paediatric use. This could potentially exclude children from benefitting from these products. At the same time, in the case of biosimilars, it is likely that the originator product will remain on the market despite direct competition from biosimilars. A product that is adapted for use in children will therefore remain available.

Moreover, if the company holding the marketing authorisation for the originator product would intend to discontinue marketing the product, it may be obliged to transfer the marketing authorisation to a third party in accordance with Article 35 of the Regulation. This rule was introduced to ensure that important paediatric products do not disappear once regulatory protection periods and patent protection expire.

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

Novartis' response

The guiding principle of a biosimilar development program is to establish similarity between the biosimilar and the reference product based on a comprehensive comparability exercise on the analytical, nonclinical and clinical level (Directive 2001/83/EC). Based on the overall biosimilarity demonstrated between the biosimilar and the reference product, an approved biosimilar is allowed to refer to the safety and efficacy data established for the reference product. The same scientific principle should apply for the paediatric information from the reference product. It is likely that the innovator product would already be subject to, or have completed a PIP or being granted a waiver, and therefore has gathered relevant information on the use of the medicine for children, if appropriate.

Hence, no additional studies in any paediatric patient group are deemed necessary for a biosimilar medicine to avoid unnecessary clinical studies in this vulnerable population. This is also in line with the Paediatric Regulation that aims to improve the availability of information on the use of medicines for children without subjecting children to unnecessary trials.

We therefore agree that it is scientifically and ethically not justified repeating or conducting paediatric studies with biosimilar medicines.

The situation is more complex regarding specific age-appropriate presentations. In general, biosimilar developers may deviate from the reference product as regards to strength, pharmaceutical form, formulation, excipients or presentation – if justified (CHMP/437/04 Rev 1); this includes specific paediatric formulations or presentations. Consequently, some biosimilar sponsors may skip the paediatric presentation/formulation due to additional development efforts. However, this comes with the trade-off to be not eligible to claim the associated paediatric indication, and therefore with a potential disadvantage for the biosimilar sponsor on the market. On the other side, this “carve-out strategy” of paediatric indications may also invite off-label use with not suitable presentations/formulations.

As an innovator company, we therefore expect that biosimilar and generic sponsors are requested to register and market presentations and/or formulations that allow paediatric use (if approved for the reference product) and therefore enable access to all patient groups. However, the paediatric presentation of the biosimilar medicine does not necessarily have to be identical to the portfolio of the reference product – it only has to be suitable to ensure treatment of all paediatric patient groups approved for the reference product and it should comply with available biosimilar guidelines.

955 We realize that in some cases the additional development efforts for paediatric
956 presentations/formulations may delay access of biosimilar medicines in the adult population.
957 Therefore, one should consider allowing biosimilar sponsors a deferral; also in light of the fact,
958 that 1) deferrals are common practice for innovator drugs and, that 2) the biosimilar sponsor is
959 likely to face some disadvantages on the (tender) market due to the restricted label. A
960 commitment by the biosimilar applicant to market paediatric presentations after a certain time
961 following approval or after a certain time as agreed with the Agency could be a potential option
962 to ensure access of biosimilar medicines to all (paediatric) patient groups and caregivers.
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964 Since biosimilars are exempt from the obligations of the Paediatric Regulation, the innovator
965 companies do not only have the burden of clinical research in children, but also the obligation
966 to market the paediatric product (Article 33) and in case of a planned discontinuation of
967 marketing, the obligation to transfer the marketing authorisation (Article 35). Hence, innovators
968 must maintain products on the market despite the fact that better, safer or more affordable
969 medicines may have become available in the meantime and that there may be no residual
970 demand for the innovator product. Manufacturing and proper maintenance of marketed
971 products is resource intensive on many levels (technical, regulatory, pharmacovigilance, etc.).
972 Companies are wasting resource to maintain obsolete products on the market that are ultimately
973 not benefitting the paediatric population. None of this currently applies to biosimilar applicants.
974

975 If there was the same marketing responsibility for all marketing authorisation holders with the
976 same version of an active substance, also Article 35 (which is currently punishing innovators)
977 might not even have to be enforced.
978

979 Biosimilars (and generic or hybrid medicines alike) should continue to be exempted from the
980 obligations of the Paediatric Regulation based on the scientific justifications as described above;
981 in particular, since there is no scientific need and to repeat paediatric studies would be
982 unethical. However, there is a need for a shared responsibility to ensure access of medicines
983 for children and we see the necessity that biosimilar applicants should be encouraged or even
984 obliged to develop and market suitable paediatric formulations/presentations. This could for
985 example be achieved by a respective approval commitment. With such a regulatory measure,
986 there should also be no need for a formal PIP (as required by the Paediatric Regulation), which
987 would be an unnecessary administrative burden for the biosimilar applicants and the Agency.
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12. PUMA - Paediatric-use marketing authorisation

The paediatric-use marketing authorisation (PUMA) introduces an incentive to carry out research into the potential paediatric use of off-patent medicinal products that have been authorised for adults. The main goal of the PUMA concept is to stimulate research in existing products and to help transform known off-label use into authorised use that is safer and better circumscribed.

To date, only three PUMAs have been authorised, which is disappointing. The PUMA concept struggles with similar problems as any scheme meant to encourage companies to invest in additional research for known compounds that have been available on the market for decades. Medicine developers fear that a PUMA will not necessarily prevent physicians from continuing to use competitor products with the same active ingredient off-label, at lower costs, nor substitution for cheaper forms at the level of pharmacies. Moreover, national health care payers are often hesitant to agree to a premium price for such products. These are complex factors that can hardly be addressed at EU level, through the Paediatric Regulation. They concern downstream decision-making at national level, which is outside the scope of EU law.

In 2014, the Commission and the EMA clarified that a paediatric investigation plan for a PUMA does not have to necessarily address all age groups. However, this measure does not seem to have stimulated interest. This being said, in the case of rare diseases orphan marketing authorisations may have been chosen over PUMAs.

It is often argued that the PUMA concept would require additional funding from public sources. However, the Commission provided funding for off-patent medicines projects for several years and only some of these projects led to an authorised product.

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?

Novartis' response

The fundamental issue with the PUMA concept is that even after a PUMA is granted, off-label use continues as medicinal products with the same active ingredient are available at a cheaper price and used off label in children. Critical to this issue is that there has been no effort at national level in term of pricing/reimbursement for on-label paediatric medicinal products.

No reward will be of any value if the product is not prescribed and used. Therefore, future activities should explore other avenues that could not only add efficiency by enhancing the access of new therapies to paediatric patients, but also could be attractive for industry, such as guaranteed access to the market (e.g. new therapeutic uses in children being granted automatic inclusion in paediatric formularies, automatic guarantee of reimbursement).

The PUMA is a new MA for an old product. A new MA means additional burden for an old product (new Periodic Safety Update Reports (PSUR) cycle, need for a Risk Management Plan for a product that otherwise does not have this obligation, price negotiations that will be difficult as generics are already on the market). Novartis has an example of a product that was already approved for paediatric use⁷ and qualifies for a PUMA. However, as previously noted the separate PUMA comes with post-market obligations and a new negotiated price. While the PIP was completed and a positive opinion on full compliance check was received, there was no value from the reward. As the product is already labelled and available for paediatric use, the company has chosen to not pursue the PUMA filing.

The European Paediatric Regulation mandated the European Commission to fund research on off-patent medicines with demonstrated therapeutic interest for children. Responding to this mandate, five FP7 project calls were launched and 20 projects were granted. The funded projects investigated 24 medicines, covering 10 therapeutic areas in all paediatric age groups, for which 15 PIPs were agreed with the PDCO (including 71 studies of whom 29 paediatric

⁷ EMEA-000184-PIP02-14

1049 clinical trials, leading to a total of 7,300 children to be recruited in more than 380 investigational
1050 centres). A 2015 publication by L. Ruggieri⁸ highlighted “critical aspects” pertaining to PIPs.
1051 “...the challenging issue for FP7 paediatric projects is to respond to different requirements
1052 imposed by the Research Programmes framework (deadline, limited resources, scientific
1053 publications, etc.) and by the Paediatric Regulation (PIP should be agreed, all the paediatric
1054 population should be covered, unmet paediatric needs prevail over scientific interest). The
1055 recommendations of the PDCO mean that relevant differences can be created from the original
1056 project mainly in term of (a) number of studies, (b) patients populations, (c) paediatric
1057 indications and (d) studies design. For these reasons, the implementation of PIPs has
1058 represented a critical point in the framework of these projects causing prolongation of the
1059 contractual procedures with the EC and often, delays in the start of the studies.”

1060
1061 It’s interesting to note that these companies are reporting issues aligned with Novartis’
1062 perspective that a more pragmatic implementation to allow for greater flexibility as it relates to
1063 procedural elements and program design also applies the PUMA process. Addressing these
1064 may better facilitate the development of paediatric medicines through the PUMA process.
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⁸ Ruggieri, L., Giannuzzi, V., Baiardi, P. et al. *Successful private–public funding of paediatric medicines research: lessons from the EU programme to fund research into off-patent medicines* Eur J Pediatr (2015) 174: 481.
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13. Scientifically valid and ethically sound — Clinical trials with children

The Paediatric Regulation aims to ensure that evidence of the quality, safety and efficacy of medicinal products is generated before the product is used by children. This means more clinical research carried out with children prior to authorising medicines. However, so far the exact impact on the number of paediatric trials and study participants is difficult to quantify due to some shortcomings in the available databases with regard to mandatory data.

Generally speaking, EU legislation is well equipped to ensure that paediatric research is scientifically valid and ethically sound. These aspects are considered not only by the EMA's Paediatric Committee in its assessment of paediatric investigation plans, but also by the ethics committees and regulatory authorities that are responsible for authorising individual clinical trials. It is important that everything possible is done to make sure that the specific vulnerability of child patients is fully considered and that the children's best interests are taken into account.

The Regulation has fostered and stimulated expert discussion about the optimal design of paediatric trials. This includes initiatives related to the exchange of good practices, development of new scientific guidelines, and modelling and simulation, with the aim of reducing the number of necessary study participants. Additionally, it brought attention to the debate about the role that children should play in research decisions and about the proper protection of children taking part in research. Initiatives range from the creation of young people advisory groups to discussion of appropriate information about clinical studies for patients and parents, to practical issues, such as forms and other paperwork.

Still, paediatric trials pose particular challenges. For example, recruitment difficulties frequently lead to delays in conducting and completing them. Paediatric trials also tend to be multi-centre trials, sometimes with just a few patients per site, which can create operational challenges, including with maintaining the necessary staff and expertise on-site.

Moreover, sometimes there are waves of development, with a peak in activities carried out by multiple companies in parallel, for the same adult disease. A recent example is type II diabetes. Such waves lead to an increase in paediatric research programmes, even if — when seen from the perspective of therapeutic needs — not all of them would have been necessary. They may also lead to feasibility problems with regard to the conducting of trials, as companies may target the same patients and the same sites around the same time. The EMA and its Paediatric Committee have made efforts to alleviate the problem by trying to convince stakeholders to engage in collaborative research, but experience shows that companies are hesitant to engage in this way, as they are not used to collaborative projects for new developments, especially if they may potentially reach blockbuster status in adults.

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?

Novartis' response

The EC question regarding 'ethically sound' clinical trials raises the important question of feasibility. Currently, minimal attention is paid by the EMA and PDCO to the complexity that feasibility places on trials committed to under an agreed PIP. In our experience, feasibility is not a word that EMA has used in its communications. However, the impact of feasibility is clearly linked to the ethics of clinical research in vulnerable populations.

Currently sponsors are asked to initiate paediatric programmes that include clinical studies whose initiation could be questioned ethically despite the fact that there may be scientifically valid reason to perform such trial. The type-II-diabetes programmes described by EMA in its

1121 10-year report⁹ are a good example. Is it ethical to initiate studies that will never finish and will
1122 never provide usable data to the patients and the physician? In such cases, the children enrolled
1123 in the studies are only facing risk and cannot expect any benefit from their participation.
1124
1125 Agencies, industry, and clinical investigators need to start thinking more constructively and we
1126 need to be more imaginative: affixing traditional drug development approaches to paediatric
1127 drug development is not going to address the gap in available knowledge. We should be actively
1128 engaging on the applicability of alternative study design and data analysis approaches. While
1129 the Regulation is written with individual products in mind, there is no restriction within the
1130 Regulation to building disease-specific solutions to address unmet need. EMA could entertain
1131 the use of master protocols (where appropriate) with experts where any new class of drug
1132 targeting the disease could automatically be considered for inclusion in the master protocol.
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1134 We fully support the actions of the EMA and PDCO to alleviate these issues, including through
1135 collaborative partnerships where possible. However companies operate in a competitive
1136 setting, innovator companies do not share confidential information amongst each other in early
1137 phases of development. Nevertheless, there are other pathways. We consider that the IMI
1138 Projects are an example where collaboration across companies may address scientific
1139 questions in well-defined frameworks. These types of well-structured research projects that are
1140 responsive to need and call are a model for how stakeholder groups could work to foster joint
1141 paediatric development projects. In addition, these types of collaboration may generate
1142 meaningful information that will improve upon the quality of the clinical trials that are conducted
1143 under the Regulation and the quality of the data generated ultimately providing greater benefit
1144 to patients.
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⁹ EMA report section 3.2 “Modifications of agreed PIPs”: *“Another example is diabetes mellitus, where many medicines are being developed for adult patients, due to the high prevalence of the disease and the relevance of the market. In particular for type 2 diabetes, many PIPs have been agreed despite the low number of children and adolescents with type 2 diabetes mellitus, because none of the products in the newer classes is authorised yet for children. This has exacerbated recruitment difficulties, due to many competing developments. At the same time, it is difficult for the PDCO to prioritise which medicines should be developed in children in such cases, given the limited information available on the potential safety and efficacy at the time the PIP is agreed, and the potential legal challenges associated with comparative evaluations. To address these issues, EMA has organised two workshops with invited experts, where innovative approaches were discussed, such as the use of non-competitive (platform) trials, where several products are compared to a single placebo (or standard treatment) group (see section 3.16.).”*

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14. The question of financial sustainability

Implementation of the Paediatric Regulation presupposes a significant investment (of resources) by Member States, e.g. by appointing members to the Paediatric Committee and by contributing to the assessment of paediatric investigation plans and providing free-of-charge paediatric scientific advice, thereby supporting the activities of the EMA.

As the assessment of paediatric investigation plans does not involve any fees, the EMA does not reimburse national experts for doing this work. There are some concerns that this could potentially have a long-term impact on the proper functioning of the system.

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?

Novartis' response

Novartis notes that the EC is currently in the process of reviewing the fee structure of EMA, and we recommend that the discussion initiated in this consultation question is completed as part of that global review. To this end, we would like to provide some comment for consideration as a part of that discussion.

One of the objectives of the Paediatric Regulation is “*to facilitate the development and accessibility of medicinal products for use in the paediatric population*” but at present, the procedural review process is unpredictable, uncertain, and inefficient, often times as a direct result of which EMA Paediatric Coordinator is assigned to a project. This harms both patients, whose access to life-saving drugs may be unnecessarily delayed, and the companies that research and develop these products.

Fees for service could be considered for paediatrics if the use of the fees will ensure that significant progress is made in improving the efficiency and scientific added value of the system. We could be willing to accept fees if we would have certainty that we would have better expertise at PDCO (e.g. possibility to discuss new clinical trial design, statistical expertise) and more scientific support generally (increased involvement of the Rapporteur and the Co-Rapporteur). At present, the best quality of scientific input on our paediatric projects comes from the CHMP. It is a common occurrence that we are directed to Scientific Advice by the PDCO in order to address key scientific questions that are pivotal to the efficient and effective implementation of our paediatric plans. Novartis would also be more willing to accept fees if it leads to faster services (e.g. the ability to have quicker compliance check process thus avoiding delaying Marketing Authorisation Application or putting a Marketing Authorisation Application at risk).

Therefore, if fees are introduced, it should ensure for the sponsors that agreed PIPs do not require excessive numbers of modification due to ill-timed requirements for submission and overly detailed commitments at early stages of development. Additionally, fees should ensure for a sponsor that agreed commitments will ultimately result in information that can be used by the CHMP to assess the benefit/risk of a medicinal product for use in the paediatric population, and not an academic wish list for data that is of limited use in the labelling of a product for its safe and efficacious use.

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15. Positive impact on paediatric research in Europe

The Paediatric Regulation has had a positive effect on paediatric research. It is however, recognised that such research is geared towards product development. For some diseases or therapeutic areas, a good understanding of the underlying disease is still lacking. Additional basic research on the diseases themselves would therefore be beneficial to facilitate and inform appropriate product development. This cannot be guaranteed through the Regulation, but requires additional efforts and funding from public and private sources.

In addition, the Regulation is generally beneficial for research infrastructure due to the increase in research projects that intend to comply with paediatric investigation plans. This includes a positive spill-over effect in terms of additional jobs, growth and innovative activity across the EU that would not have happened if it were not for the R&D investment made in relation to the Regulation.

In anticipation of an increase in paediatric trials, several Member States have increased the capabilities of existing research networks or have established networks specifically dedicated to paediatric medicines. In addition, the European Network for Paediatric Research at the EMA (Enpr-EMA) was established in 2009 as a 'network of networks' to provide efficient inter-network and stakeholder collaboration. To date, nearly 40 networks are part of Enpr-EMA and share good practices on common quality standards.

Despite these recognised efforts in recent years, the paediatric research infrastructure needed to conduct paediatric studies did not develop at the same pace to meet the growing need and to ensure consistent long-term availability beyond single trials. This is one of the reasons for why the IMI public-private partnership ('innovative medicines initiative') is currently considering to facilitate the establishment of an EU paediatric clinical trial network.

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

Novartis' response

Novartis agrees that the work that has been done to date has had a positive effect, however, areas for improvement remain. Those should be addressed via a better implementation of the current regulation via non-legislative means (e.g. guidelines).

An obligation imposing research to be done does not necessarily improve the quality of research. Nevertheless, ensuring the expansion of knowledge about pathophysiologic basis of paediatric disease, natural history of disease, and expansion of paediatric developmental physiology will enhance paediatric drug development. This is particularly important as innovation has been demonstrated to be driven by a strong scientific basis for disease and the scientific tractability for the application of a mechanism of action in the paediatric population (e.g., juvenile idiopathic arthritis, cystic fibrosis).

There is a difference between quantity and quality of research: more research and too many studies is not always a positive sign, it can also be a waste of resources, which could have been used for more targeted research instead, and it can expose children to unnecessary trials. For example, a high number of melanoma studies are planned or ongoing; however, due to the rarity of the disease process in paediatric subjects, they are unlikely to complete thus leading to no improvement for the children. This allocation of resource to these types of scenarios prevents other useful programmes to be sponsored.

As an industry, we want to design the best programmes to bring meaningful therapies to patients across multiple marketplaces. As a global company we conduct paediatric research globally, and looking at Europe and European needs in isolation is detrimental. Paediatric research is complex and to construct a rigorous science-based programme, especially where the availability of affected paediatric patients is limited, requires global drug development considerations. Therefore, infrastructure needs should take into consideration, as much as

1255 possible, the flexibility to address regional variations in practice and an inter-operability of
1256 research infrastructures to allow for efficient and seamless research practice. At this point in
1257 time, the European research infrastructure is not optimal and will need to be further enhanced
1258 to facilitate the pace of industry research. This includes *inter alia* efficient ethics review, better
1259 harmonization of medical and research practice, and intensive commitment to training.

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1261 Finally, we believe that societally, there is an important role for both public and private funding
1262 in advancing paediatric research needs. In the US, there are many more paediatric oncology
1263 studies funded in relation to the EU. This is because paediatric academic groups in the US have
1264 a more sustainable public and/or privately funded infrastructure. In Europe, the lack of public
1265 funding for these groups is an important limitation that clearly impacts the ability to support
1266 paediatric medicinal product development and general paediatric research. The innovative drug
1267 development industry cannot be expected to compensate for this lack of appropriate public
1268 funding on its own. Relying on an IMI project to build a clinical trial network¹⁰ is a start, but it will
1269 have to deliver if it is to be sustainable. As the call has only just been extended, it will be at least
1270 5 years until we see any potential metrics on the added value.
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<https://ec.europa.eu/research/participants/portal/desktop/en/opportunities/h2020/topics/imi2-2016-10-04.html>

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16. “Mirror, mirror on the wall” - Emerging trends and the future of paediatric medicines

The way pharmaceuticals are developed may change over time due to scientific advances and technological developments. For example, small chemical molecules dominated the market for authorised medicines for a long time, while in recent years there has been an increasing shift towards large, biological molecules.

Other trends include the stratified development of medicines (adaptive pathways) or the concept of personalised medicine (or ‘precision medicine’), which aims to optimise the use of medicines by targeting them to patients’ individual genes to ensure that they will be truly responsive to treatments.

These new (emerging) development paradigms may be perfectly compatible with the mechanism introduced by the Paediatric Regulation. At the same time, however, it cannot be neglected that the Regulation was developed at a time when the traditional, classical way of pharmaceutical development was still pre-dominant; hence the idea of linking the obligations introduced under the Regulation to broad adult medicine development.

Furthermore, the Paediatric Regulation builds on pharmacological differences between patients based on age. However, concepts such as precision medicine may have the effect of prioritising other distinguishing features in the future, potentially rendering age less relevant. In order to ensure the continued relevance and impact of the Paediatric Regulation it is therefore important to understand the extent of such future trends and their effect on paediatric medicines.

At the same time, it is important to ensure that children fully benefit from new emerging concepts, such as for example precision medicine.

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?

Novartis’ response

We agree that children should be able to fully benefit from new emerging concepts and the paediatric regulation should aim to facilitate this process.

Alternative approaches such as extrapolation, modelling and simulation have been at the forefront of discussion in 2016. EMA engaged across regions to discuss the topic in several forum including workshops that they sponsored in late 2015 and early 2016 and publication of ‘Reflection paper on extrapolation of efficacy and safety in paediatric medicine development (EMA/199678/2016)’. We would like to congratulate and thank EMA for these initiatives that we believe will increase efficiency and pragmatic approaches to paediatric drug development.

Innovation should be applicable to more than just industry. The PDCO should also encourage innovative design for studies and paediatric development plans. Looking in section 3.11 “Innovation in PIPs” in the EMA 10-year report, one would expect to see descriptions of innovative ways of carrying out paediatric studies, but the chapter mainly reflects industry-driven product innovation in paediatric drug development. PDCO should facilitate the use of, or recommend alternative program development approaches to facilitate a more efficient programme that uses the minimum number of paediatric patients and limits unnecessary exposure.

In the current framework, we already face difficulties regarding alignment between CHMP and PDCO. We can only imagine that the difficulties will increase for ATMPs as CAT alignment will also be needed. To avoid divergence and duplication, a reflection should be done on existing regulatory pathways to assess whether there is opportunity to incorporate alternative merged pathways or parallel pathways to facilitate alignment between committees and facilitate review timelines.

New models of development often lead companies to investigate follow-up indications. Each new indication triggers a new PIP (Article 8 PIP), leading to the compound having multiple PIPs.

1333 Handling multiple PIPs and having to complete them in the absence of a reward may
1334 disincentivise companies who wish to develop new indications.
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1336 Finally, emerging thought supports broader consideration of specific paediatric subsets
1337 (adolescents) within the construct and design of traditional adult registration programs. As
1338 much as possible the EMA and PDCO should be encouraged to promote the incorporation of
1339 relevant subsets into these programs to facilitate the faster authorisation of medicinal products
1340 for the population. This is particularly relevant to life-threatening diseases where unnecessary
1341 delay of paediatric authorisation has a significant impact on paediatric patients and their
1342 families.
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17. Other issues to be considered

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*The Paediatric Regulation has to be seen in the context of other EU legislation regulating and encouraging the development of medicines. For example, as far as rare diseases are concerned, the objective of stimulating research and development is also fostered by Regulation No 141/2000 on orphan medicinal products. The complementary effect of those instruments may need to be considered.*⁹

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?

Novartis' response

In many ways the regulation's implementation reflects our initial expectations, but in some areas the implementation did not go as we expected. A more pragmatic implementation via non-legislative means should be considered to address the majority of these issues. Below are some suggestions for consideration:

- EMA/PDCO balance
Currently the PDCO Rapporteur and Peer Reviewer play a limited role in the PIP evaluation (application & life-cycle management). The EMA paediatric coordinator writes the summary report and the PDCO relies heavily on the opinion of the paediatric coordinator in the scientific contribution to the review of the PIP. In other regulatory procedures e.g. for a centralised marketing authorisation, the Rapporteur and co-Rapporteur are responsible for these tasks.
- Lack of alignment between committees
A lack of alignment on paediatric programme development has occasionally been observed between the PDCO and working parties of the CHMP (regarding endpoints, patient populations, or methodologies). A PIP is not agreed with the CHMP, but with the PDCO and if paediatric studies lead to a new indication for use in the paediatric population it will be review by the CHMP. The CHMP may support use of alternative statistical and methodological approaches, endpoints, comparators, and designs to those requested by the PDCO. This leads to numerous back-and-forth discussions across working parties, committees, and working groups to obtain alignment on a path forward. This is particularly concerning for paediatric only indication.
We have the case of a product for which we submitted to FDA an amendment to the Written Request to change some of the parameters of an ongoing clinical study in order to finish the study earlier, the amendment was accepted. In parallel, we filled a PIP Request for Modification in EU. We were asked by the PDCO to seek Scientific Advice as they did not have the required expertise to assess our request. After a Scientific Advice that supported the proposed changes, we had to file another Request for Modification to implement the outcome of the Scientific Advice into the PIP. The PDCO is now not accepting the outcome of the Scientific Advice, and requests that the parameters stay unchanged. In the end after 10 months we still are not able to implement the changes and speed up access to the paediatric medicine. As the same change was approved by the FDA this is jeopardizing the ongoing global clinical trial.
- Lack of alignment at other levels
There are instances where national Health Authorities (NCAs)/Ethics committees (ECs) do not agree with the decisions of the PDCO impacting Clinical Trial Applications (CTAs). This is very inefficient for companies and can dramatically impact development timelines.
This is supported by the EMA 10-year report: Figure 10 (page 43) lists the reported difficulties in conducted PIP studies: 9% are due to refusals/problems with NCA(s) and 7% to refusals/ problems with EC. And in section 3.9. "Interactions with ethics committees" EMA state that "an analysis of EudraCT data has identified 98 instances of clinical trial applications for studies including children, which have received a refusal from an ethics committee in the EU. Fifteen of these were reported as being included in a PIP; however, for 48 instances no information about inclusion in a PIP was available."

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- Member states responsibilities

The paediatric regulation was driven by the will to reduce off-label use, however the status of off-label use in the paediatric population is not covered by this consultation. This is indeed a Member States responsibility and NCAs should take measure to reduce this practice, especially when newly labelled products for paediatric use are approved and made available in the commercial marketplace.

- Transparency

EMA has built an extensive paediatric database, however very little usable information is released publicly on their website. Further, we have noted the content of the PDCO minutes have become less informative over the past few years. In particular, the report on activities of sub-committees or Working Parties can be of great utility to companies in understanding emerging trends that may enhance the efficiency of our strategic planning in paediatric product development. But at the same time EMA is increasing suggesting more transparency and disclosure of more and more paediatric information from the applicant (for example: opinion Annex I key element, 3rd country study results in EudraCT). We believe that transparency efforts will best inform paediatric needs when they are bi-directional, and its principles should not only be relegated to industry and industry-sponsored studies.