EuropaBio response to the public consultation on the concept paper: European Commission Guideline on the Format and Content of Applications for Paediatric Investigation Plans

EuropaBio welcomes the opportunity to comment on the concept paper*: European Commission Guideline on the Format and Content of Applications for Paediatric Investigation Plans*.

Consultation item No 1: Do you have any comments on the format and content of applications for agreement on or modification of a paediatric investigation plan and requests for waivers or deferrals?

We support the paediatric regime in Europe. The Paediatric Regulation is a pioneering effort to address a European market failure.

As with many pioneering legal projects, many provisions of the Regulation have been left open to divergent interpretations. It is crucial that the Commission ensures that their efforts to implement the Paediatric Regulation do not have unintended consequences[1] and that the development of medicinal products for either adults or paediatrics is not deterred or delayed.

The inherent flexibility left by legislators in the Regulation's provisions should not be used to create a restrictive and inefficient regime. Such regimes are burdensome both on vital regulatory resources and market participants.

A proper reading of the legislative provisions, in light of the overall objectives, highlights a number of places where rules adopted by the Commission and the EMA are in our view going beyond the initial objective of the legislation. The PIP process has become bureaucratically broad, demanding and detailed.

A core aim of the Regulation, as set out in Recital 4, is "*to facilitate the development and accessibility of medicinal products for use in the paediatric population*". As the Commission notes in its 2013 Report, "Better Medicines for Children - From Concept to Reality" (COM (2013) 443), the objective must be achieved without "*the requirements delaying the authorisation of medicines for adults*"[2]. This is not necessarily a zero-sum game (where one ambition must suffer so that another can benefit): inefficiency harms both simultaneously.

As PIP requirements are often expensive or take very long (especially for SMEs), they may incur huge financial and operational risks for companies. The implementation has made it unnecessarily difficult for developers to benefit from deserved rewards available under European paediatric medicines legislation. (Ref: surveys conducted by the European Federation of the Pharmaceutical Industries and Associations (June 2011) and a white paper published by the European Vaccine Manufactures (January 2011)).

[1] Such unintended consequences already exist within the primary legislation itself. The Commission notes in its report, "Better Medicines for Children - From Concept to Reality" (COM (2013) 443): "*there are some concerns that the requirements under the Regulation may cause delays in the authorisation of products with paediatric-only indications, as they bring added complexity to the R&D and regulatory process for products that already directly target children.*"[1] This irony must be addressed, ideally before the next currently envisaged report date in 2017.

[2] "Better Medicines For Children - From Concept to Reality" (COM (2013) 443), s2

This is disproportionate, and could be contrary to the objective of the Regulation to avoid deterring the development of adult indications. The Commission's concept paper does not sufficiently reflect that concern.

EuropaBio would like to stress that any changes to the guideline must have the objective to provide a simplified and more flexible system that does not create unnecessary administrative burden[3]. In this context, it is specifically important to ensure that Small and Medium Size companies (SMEs) are not discouraged from innovation in Europe by burdensome requirements.[4]

Therefore, we clearly welcome a revision of these guidelines, which could significantly improve the functioning and application of the Regulation.

Scope

We submit that the requirement to target entire "conditions" in PIPs has been constructed on the basis of forced readings of the Regulation. This policy has been based on an assumption that a reference to "disease or condition" in Article 11(1) means that a PIP must necessarily cover at least one "disease or condition" for an application for marketing authorisation to be valid under Article 7 or 8. Yet the law does not actually state this. On the contrary, the scope of a PIP should reflect the intended therapeutic indication. This is clear for the following reasons:

Firstly, neither Article 7 nor 8 mention "conditions". Article 8, however, is firmly based on *indications*. When filing for a new indication, Article 8 stipulates that that documents to be submitted in connection with the Paediatric Regulation "*shall cover both the existing and the new indications*". Considering that nothing about Article 7 suggests a wider scope of PIP than in this Article 8, it therefore follows that both Article 7 and 8 only require an indication-based PIP.

Secondly, Article 2(2) defines 'paediatric investigation plan' by reference to 'conditions' in the sense of 'precondition' and/or 'circumstance' - not in the sense used to justify broad-scoped PIPs. That is absolutely clear from the German text of the Regulation, which speaks of "*der Voraussetzungen*".[5] From this we must conclude that Article 2(2) also does not support a 'condition'-based scope for PIPs.

Lastly, Article 11(1) only sets out the preconditions for waiver grants. It does not strictly define either the scope of a waiver *or* the scope of a PIP. Article 11(1) takes a gradual approach, which starts broadly, considering entire classes of medicinal products. It then considers specific medicinal products, a disease or condition, and then ends with a quite narrow catch-all (absence of significant therapeutic benefit over comparable treatments). If we are to follow the logic that because Article 11(1)(b) mentions diseases or conditions, it follows that a PIP should be so broad in scope as to ensure an exploration of an entire condition, then it should be equally true that Article 11(1)(c)

[3] As the Commission notes in COM (2013) 443, s5.7 "*There can be no doubt that the Paediatric Regulation places a considerable additional burden on pharmaceutical companies*"; and "*In terms of output, this entails some unnecessary effort in compiling and screening paediatric investigation plans*".

[4] Moreover, the burden-benefit ratio of the Paediatric Regulation is skewed against endeavours to explore niche therapeutic areas, and is most favourable for products which achieve significant market success regardless of the Paediatric Regulation's incentives: "*The economic value of the reward depends on the turnover of the product concerned. In the case of blockbuster products the amount may be considerable, while for niche products the effect is small.*" (COM (2013) 443, s5.7)

[5] This is also clear from the English text: medicines are authorised per indication, not per "condition". "*determining the conditions in which a medicinal product may be authorised*" therefore makes no sense unless talking about circumstances and/or preconditions.

mentions entire classes of medicinal products, so a PIP should require exploration of an entire class of medicinal products. That is clearly wrong.

In fact, the actual scope of a waiver is most directly defined in Article 11(2). That Article makes it clear that a PIP can be defined by reference to population subsets or to *specified therapeutic indications* (or a combination of both). If it is true that one can infer the scope of a PIP from the scope of a PIP waiver (despite the strained logic of doing so), then Article 11 clearly points to indication-focused PIPs.

There will be some who steadfastly cling to the argument that because Article 11(1)(b) talks about "diseases or conditions", therefore a PIP must have a condition-based scope. Yet even they must admit that it is Article 11(2), not Article 11(1), which most clearly defines the basis of a waiver, and that Article 11(2) talks about indications. For their theory to hold any water at all, one would need to treat "disease or condition" (in Article 11(1)(b)) and "specified therapeutic indication" (in Article 11(2)) as quasi-synonymous. As further discussed below, the concept paper proposes a change to the Guidance's definition of "condition". That change makes "condition" more synonymous with "indication", by including "specific use during specialised therapeutic or diagnostic procedures". This appears to be a recognition of the aforementioned flaw in the Article 11(1)(b)-based argument. If that is the approach taken, the Guidance at least needs to avoid retaining the flawed legacy definition, as this would lead to significant confusion.

However, as set out above, it would be better not to deal with "conditions" at all. We believe that a correct reading of the Paediatric Regulation conclusively shows that for the concrete assessment of the scope of a PIP, the focus should be on the proposed therapeutic indication. **On that basis, EuropaBio submits that it is imperative that the Commission amend the Guidance to make it clear that the scope of the PIP is determined by strict reference to an indication, not "conditions".**

A concern that was raised in the *Nycomed* case (in respect of diagnostics) was 'ease of circumvention'. Yet the court made it clear that this issue must be handled as straightforwardly as possible: unless there is "*no less restrictive alternative*" to an approach to this issue, the approach would be disproportionate and therefore unlawful.[6] We submit that at least in respect of therapeutics, it would be better to apply the 'medical plausibility' test, which is used with orphan medicines. It has the benefit, at least, that is already established, and would not need to rely on flawed legal reasoning.

Content

As the PIP is usually agreed long before the actual start of paediatric studies, a detailed review and discussion of these studies is premature. It may be better in some cases to discuss paediatric studies nearer to the time they will be run. At that point, more adult clinical efficacy data will be available; an adult dose will also have been determined, which may also help formulation development. Significant efforts are wasted due to high attrition rates in early phases of medicine development; a focus of the PIP discussion on the high level development strategy and timeline would be better for both for the authorities and for developers. The current situation warrants the processing of multiple modifications in advance of the start of the paediatric studies and often results in a substantial delay in gaining approval for a new product or indication.

It is our position that a PIP application should outline which paediatric work will be conducted as soon as the safety and efficacy of a medicine is sufficiently established to conduct paediatric research - but not before. At the very least, we believe that there is a clear legal basis for delaying agreement on a plan, because it is very often duly justified for health reasons to wait until development has

[6] Case T-52/09 *Nycomed Danmark ApS v European Medicines Agency (EMA)*, paragraph 93.

clarified the risks and potential of a product. This is described in more detail in our submission on consultation question number 5 below.

It is one thing if the requirement "*obliges companies to think about paediatric use early on*"[7]; quite another to require them to construct an exhaustive dossier right from the start. As the Commission recognises, unforeseeable challenges during research and development force repeated variation[8,9] and "*near-systematic*" deferral[10]. Wasted up-front investment of time and resources in the creation of detailed initial plans is one of the several problems which the Commission has recognised:

> "*The Regulation requires companies to submit paediatric investigation plans at an early stage of product development. However, research on some active substances may be discontinued at later stages should further studies fail to show potential with respect to the safety and efficacy of the product. For every successful authorised medicinal product there are many that fail to make the finishing line. (…) In terms of output, this entails some unnecessary effort in compiling and screening paediatric investigation plans. To what extent this is offset by the benefit of early submission, which ensures that the paediatric development fits smoothly into the overall product development, need further monitoring.*[11]"

We submit that this is clear evidence that there is little virtue in constructing detailed but ultimately inaccurate PIPs, rather than accepting that it is an iterative process and should be geared towards efficient evolution of plans.

Against this background, we believe that the content of a PIP should be strictly limited to defining an outline of the types of studies that are required to prove the quality, safety and efficacy of medicines when used in children - and not detailed protocol descriptions. Similarly, the various express requirements to submit certain information as part of the PIP application should be removed where possible; additional information can always be requested if it is deemed necessary.

Only a simple and general application should be filed at the beginning of the procedure. If necessary, an agreed plan could include milestones at which the PIP can be refined and added to.

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[7] COM (2013) 443, s2

[8] COM (2013) 443, s4.1: "*In order to take account of new information during medicine development, agreed paediatric investigation plans need to be modified. Statistics show that several requests for modification are submitted for each agreed plan (see Table 2). To date, the Committee has already adopted more opinions on modifications than on the initial agreement of the investigation plan.*"

[9] COM (2013) 443, s5.7: "*A further point of concern is the high number of modifications to paediatric investigation plans. Figures seem to suggest that nearly all plans have to be modified at least once. Conceptually though this does not come as a surprise, in view of the early submission of paediatric investigation plans, the length of adult and paediatric developments and the substantial deferrals granted. An R&D plan frequently has to be adapted or amended to take account of initial results. Recruitment problems or necessary design changes in the trials may also lead to modifications. While it is acknowledged that substantial amendments or modifications to the plan have to be subject to discussions with the Paediatric Committee, this is less obvious for minor changes. In this context, the level of detail required by the EMA has been repeatedly criticised. In the past five years, the EMA and its Paediatric Committee have made efforts to provide for some flexibility in the plan so to allow a margin of manoeuvre that takes account of uncertainties in relation to certain parameters of a trial."*

[10] COM (2013) 443, s5.1

[11] COM (2013) 443, s5.7 The Commission should not neglect, in this respect, the fact that companies will ultimately be compliance-checked; they already have every incentive to think early about paediatric aspects of development and to ensure it integrates appropriately into the overall process.

Definitions

Condition

As stated above, the essence of the scope of a PIP should be an indication. The Commission guidance should be amended to reflect this.

If nevertheless the concept of "condition" is used, it should be defined in a manner that is most closely aligned to the therapeutic indication.

The concept paper introduces the following into the definition of "condition":

> "*a condition may also be represented by a specific use during specialist therapeutic or diagnostic procedures (E.g. use in bone marrow transplantation, contraception). As the medicines development is different, diagnosis, prevention and treatment of a condition will be considered as separate"*

We believe that *the new sentence:* "*a condition may also be represented by a specific use during specialist therapeutic or diagnostic procedures (E.g. use in bone marrow transplantation, contraception*" should be explained or qualified, as it may introduce further ambiguity and confusion of the terms "condition" and "indication". The new text should only be applicable for those products whose use is not associated with a "distinct disease or syndrome".

In addition, we disagree with the second sentence. "*As the medicines development is different, diagnosis, prevention and treatment of a condition will be considered as separate"*. There might be cases in which the development is not different.

Lastly, the examples given ("*E.g. use in bone marrow transplantation (…)*") do not relate to the definition, because they are not "a specific use".

Accordingly and in this context, EuropaBio suggests the following definition of "condition":

> *Condition: a specific use during specialist therapeutic or diagnostic treatment or procedures.*

Other new definitions

The additional definitions of "key elements" and "extrapolation" are not necessary. Extrapolation, for example, is a well-defined scientific concept, not a legally defined term[12].

Additional comments on content and layout

Harmonisation

Development of paediatric medicines occurs in a global context, and EuropaBio believes that significant simplification could be achieved with a much greater alignment between the EU and the US requirements related to PIP and Paediatric Study Proposal documents. We find that the US guideline, which is currently being developed by the FDA[13], provides a good example for a potential

[12] EMA "Concept paper on extrapolation of efficacy and safety in medicine development - draft", 22 June 2012; copy available at http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129285.pdf

[13] Copy available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf

EU revision as its structure is clear and follows the logic of medicine development without frequent repetition of information.

Overly constrictive form design

We believe that Part A could be modified to clarify which sections of Part A form part of the decision.

Redundant or inflexible requirements

We would also like to stress that the requirement provided by line 181 (*"Applicants should provide a general justification of the application submitted, including the methodology chosen to identify potential conditions of paediatric need")* should be kept as flexible as possible in order to avoid unnecessary burden. There is no basis for this requirement in the Regulation, and so it is only justified if its benefits outweigh its burdens.

Consultation item No 2: Do you have any comments on the operation of the compliance check and/or the compliance statement?

In order to comply with the Regulation, all compliance checks capable of delaying a marketing authorisation should be conducted in accordance with Recital 4 to the Regulation, which states: "*These objectives should be achieved (…) without delaying the authorisation of medicinal products for other age populations*."

A process that requires PIP modifications and an interim detailed compliance check can be a serious logistical challenge in the run up to filing a new formulation or indication. It would be more effective to require only one detailed check after the paediatric investigation plan has been completed, at the point at which the reward is being claimed. All checks until that point should be as efficient as possible - i.e. as light-touch as the law allows.

In Article 23(1), the only type of application which must be checked for compliance with the plan is a PUMA (i.e. Article 30) application. For other applications, Article 23(1) only requires a competent authority to verify the filing's compliance with Articles 7 and 8.

That means that all that Article 23(1) strictly requires for such applications is a tick-box exercise to see whether all data generated so far has been submitted (which can be done by requiring a certification by the applicant) and/or whether the application includes waivers or deferrals.

Article 23(2) grants various entities a useful tool to be used in appropriate situations of doubt regarding compliance, but both 23(2) and 23(3) are clear that PDCO opinions are not mandatory (e.g. 23(3): "*If the Paediatric Committee is requested to give an opinion (…)*"). That is consistent with Recital 16. A similar conclusion can be drawn concerning Article 24, where in appropriate cases of doubt the competent authority can make use of the Article 23(2)(c) tool.

EuropaBio would like to add that the concept of "compliance" - at all stages - should be tolerant enough to (for example) recognise that a study may have altered sample sizes (or other key elements) but still present data necessary for "determining the conditions in which a medicinal product may be authorised to treat the paediatric population", which is the focus of the law.

Lastly, it should be pointed out that as they are currently performed, the annual reports on deferrals and the interim compliance check seem to be duplicative in their intent. We would suggest streamlining these to the fullest extent possible.

Consultation item No 4: Do you have any comments on the key elements of a paediatric investigation plan? Is it appropriate to list key elements in this guideline or should key elements

only be specified in the individual decision of the Agency agreeing a specific paediatric investigation plan?

We believe that it is important to maintain the list of key elements. At the same time, flexibility concerning those elements is essential and in many cases it is not possible to ensure that all of those elements are included or met.

Therefore, we believe that the document should not include any binding elements to provide some level of harmonisation across decisions.

Furthermore, it is worth keeping the list very slim, so that it lists only factors that it is strictly necessary (not merely "desirable") to determine in advance. Once a few lynchpins are agreed, the scientific advice procedure can be used by companies to make sure that they then design and implement their studies to make sure that they can generate the necessary data and meet the requirements for their reward.

Consultation item No 5: Please feel free to raise any other issues or make any comments which have not been addressed in the consultation items above.

Linking and splitting

We would like to stress that rules concerning merging or splitting PIP decisions should be clarified to enable simpler and faster solutions.

As medicine development is a very dynamic and iterative process, the concrete regulatory filing strategy is sometimes difficult to predict and any requirements to complete such additional administrative activities in advance of a submission can present a risk for a delay.

Article 7 states that an application would only be valid if it includes the results of a PIP. That does not mean that applications which contain the results of two PIPs are invalid. That is a contrived and overly literal interpretation that creates a strong disincentive to file for simultaneous approval of indications associated with different conditions ('A' and 'B'), because having to link the PIPs at that point results in a much larger and hard-to-reach PIP. An incentive is created to keep indication/condition 'B' on the back-burner, and file after. This is bizarre and nonsensical; it imposes a policy that penalizes parallel-track development programs and efficient approaches to filing for marketing authorisation, and disincentivises the expansion of the usefulness of medicines, across age groups.

It is also straightforward to understand why the literal approach to reading Article 7 is *legally* flawed. Firstly, the use of the word "a" cannot, under normal interpretative conventions, exclude two or more PIPs. Secondly, Article 7 states that the application should contain "one of the following:", then lists four items without saying whether these are linked by "or", "and", or "and/or".

Taking the inflexible approach that is being used to justify linking, the competent authority would logically also have to either adopt a policy of refusing applications that do not contain data + a product-specific waiver + a class waiver + a deferral; or a policy of refusing applications that contain more than one of those items. In addition, it is very relevant that Articles 7 and 8 do not refer to a *single* PIP.

Evidently, literal readings of Article 7 result in absurdity - the first hypothetical interpretation is clearly nonsensical, whilst the other would require the validation of all applications that (for example) contain a decision of the Agency granting a deferral - any deferral, for any condition, to any person, even if only covering one of multiple conditions covered by the application. That is not the

intent; nor is there any sign in the law (unless one unhelpfully takes an unhelpful, ultra-literal approach) that authorities should invalidate applications which relate to more than one PIP.

Therefore, we strongly suggest simplification of the rules.

Agreement timing

As discussed above, PIPs are generally being agreed too early, only to then require frequent modification. This challenge has been recognised by the FDA, which therefore only requires agreement of a paediatric plan at the end of Phase II. Any measure taken to align the European system with this timing would be beneficial, for a number of reasons:

- The later the plan is agreed, the more realistic, well-informed and relevant it can be;
- Harmonisation of the two systems will lead to reduced duplication of effort in creating and agreeing the plans; and
- Agreeing the plans in parallel will reduce the possibility that FDA and EMA requirements will diverge, avoiding the risk that redundant studies or protocol variations will be required.

The Commission should publish guidance on what constitutes “duly justified cases” justifying the delay of agreement of a PIP.

The Commission should therefore explore the full range of possible “due justifications”. The interests of public health are an obvious case, but so too is when the public interest (as represented by overall utility or cost-benefit) of agreeing a PIP at this stage (followed by resource-heavy deferral and modification steps) is negative.

Whether due justification exists should be a routine matter for companies to determine before each PIP process, guided by early dialogue with the Scientific Advice service. It is expected that in many cases the same reasoning that would justify a full PDCO deferral decision would also constitute due justification in the context of Article 16.