SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE
COMMENTS FROM VOISIN CONSULTING
GENERAL COMMENTS
Voisin Consulting welcomes the opportunity to comment on this draft guideline, as we believe it will be helpful for the industry in terms of implementing the Paediatric regulation. We would however have appreciated the possibility of reviewing the Annexes to the guideline at the same time.
Voisin Consulting believes that the EMEA should explain the "spirit" of this draft guideline. It is important to make clear that the Paediatric Investigationnal Plan (PIP) is a living document and that not all sections have to be filled in after the phase I clinical studies.
Voisin Consulting believes that a clarification on the timing of the first PIP submission for a medicinal product would be helpful. The Paediatric Regulation explains that it is "no later than upon completion of the human pharmacokinetic studies in adults", however this timing is not straightforward for all products.
A specific guideline detailing the requirements to obtain the incentives described in the paediatric regulation would be welcomed. In particular, clarification would be useful on the requirement that the product should be authorised in *all* Member States: In practice, will this imply that the only concerned products are the ones approved through the centralised procedure? Also, what about a product approved in all Member States but owned by various MAHs?

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE		
Section. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
Introduction **§ (b) (p.3) & § (c) (p.4)**	The difference between the paediatric investigation plan indication and the proposed therapeutic indication is difficult to understand.	Examples of PIP indication and PT indication would help.
Section 1.1	Voisin Consulting acknowledges and welcomes the fact that one unique PIP should be submitted independently of the number of indications	

Date of transmission:

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	being developed in parallel for the same medicinal product.	
Section 1.1 – Paragraph 3/8	A cross-reference to the existing EMEA guidelines on organ maturity would be appreciated.	
Section 1.1 – Paragraph 4/8		Replace "When drafting paediatric investigation plans for paediatric use marketing authorisations, applicants are encouraged to consider whether there may be a therapeutic need for the medicinal product in each paediatric subset." By "When drafting a paediatric investigation plan, applicants are encouraged to consider whether there may be a therapeutic need for the medicinal product in each paediatric subset."
Section 1.1 – Paragraph 8/8	Voisin Consulting would welcome a clarification of the eventuality that the PDCO spontaneously requests an update of a specific PIP based on internal/confidential knowledge or publicly available/published information.	
Section 1.2 – Part A.1	Voisin Consulting welcomes the possibility for a CRO (or, by extension, a regulatory consulting company) to submit a PIP on behalf of a company developing a medicinal product. However, we would welcome a confirmation that, as long as the applicant is EU-based, the company in charge of the development of the medicinal product does not need to be based in the EU. Also, we would welcome a clarification concerning the necessity for the applicant to be EU-based. Voisin Consulting would also welcome clarifications on the possibility of transferring a PIP from one legal entity to another, and if so, the practical aspects to be considered.	
Section 1.2 – Part A.3	The Guideline states that "Substances not having an exact scientific designation should be described by a statement of how and from what they were prepared." As this statement is likely to change with time, we would welcome a clarification on the impact of such change on the validity of the PIP. This comment is based on our experience with orphan designations, where the description of the product for which	

	designation is sought needs to be determined and is not meant to change over time, otherwise the designation is no longer legally valid. From our experience, a regulatory classification with the Innovation Task Force is required for orphan products not having an exact scientific designation before any central procedure, such as orphan designation, is initiated. Could the Commission clarify why this section states that "Where the active ingredient is of herbal origin, the NfG on Quality of Herbal Medicinal Products should be taken into account" whereas Art. 9 of Regulation 1901/2006 states that Herbal Medicinal Products as mentioned in Art. 16 of Directive 2001/83/EC are exempt from the obligations referred to in Art.7 and 8 of this Regulation?	
Section 1.2 – Part A.4	Voisin Consulting understands that the Paediatric Regulation and by extrapolation this draft guideline, is applicable to medicinal products only. Voisin Consulting would like to draw the European Commission's attention to the case of borderline products, for which no clear regulatory framework exists. Should these products undergo a so-called "classification" procedure within the EMEA's Innovation Task Force (ITF) before submitting a PIP? Voisin Consulting would welcome clarification on this critical point.	
Section 1.2 – Part A.5	Could the Commission clarify whether information on the medicinal product (e.g. strength, pharmaceutical form and route of administration) should be specific to the paediatric development or cover both the adult and paediatric products?	Proposed wording: "If available, the proposed invented name, strength, pharmaceutical form and route of administration for both the adult and paediatric populations should be provided."
Section 1.2 – Part A.6		Last bullet point should read: "Details of any regulatory decision to restrict the use of the medicinal product in any EEA country."
Section 1.2 – Part A.8	Voisin Consulting would welcome a more detailed list of examples of agreed classification systems, as well as a clarification in the case that the envisaged indication is new and therefore not referenced yet.	
Section 1.2 – Part A.9	Voisin Consulting would welcome a confirmation or a clarification that a simple statement indicating whether products belonging to the same	

	class exist or not is expected, or if those products should be listed. Also, the guideline should specify whether "authorised" refers to the EU only, or if products authorised outside the Community should be listed.	Proposed rewording for the last sentence of Part A.9: "If there are authorised medicinal products belonging to that class, *this* should be stated."
Section 1.3 – Part B.1		Voisin Consulting proposes the following rewording for the first sentence of this section: "For each disease or condition *in which* the medicinal product is already authorised, as well as for each disease or condition *for* which *it* is the subject of new development […]".
Section 1.3 – Part B.3		Voisin Consulting suggests "The applicant should provide information of the prevalence and incidence of the diseases/conditions in the paediatric population in the Community (and in the different Member States) if available".
Section 1.3 – Part B.4	Based on our experience (with orphan designation applications), we believe it is not realistic to try to compile a complete list of authorised products belonging to the same class. We would therefore welcome clarification on the possibility of providing an overview of the major existing/authorised medicinal products, to set the therapeutic strategy background. Similarly, regarding medical devices approved for the same therapeutic use, it does not seem realistic to request this type of list. If possible, please indicate from which database such information could be extracted.	Voisin Consulting proposes the following rewording for the first sentence of this section: "For each disease or condition *in which* the medicinal product is already authorised, as well as for each disease or condition *for* which *it* is the subject of new development […]".
Section 1.3 – Part B.5 Paragraph 5/10 **Paragraph 6/10**	Voisin Consulting would welcome clarification as to what extent case f) is different from cases a) and b). Voisin Consulting would welcome clarification on the sentence "As experience with the use of the medicinal product in the paediatric population might not be available or might be very limited at an early stage of the development of a medicinal product, significant therapeutic	

Paragraph 7/10 **Paragraph 10/10**	benefit might also be based on well-justified and plausible assumptions". Voisin Consulting would welcome clarification on the sentence "if significant therapeutic benefit cannot be justified at that early stage of development of a medicinal product, the paediatric committee may consider a waiver or deferral, if appropriate". According to which criteria is significant benefit considered as not justified? Voisin Consulting would welcome clarification on what would be the grounds for considering a waiver in this instance. Voisin Consulting would welcome clarification on the sentence "Where the applicant considers the proposed paediatric development to fulfil a therapeutic need and this therapeutic need is not yet included in the inventory as established by the paediatric committee, *sufficient information* to explain this assumption should be provided". What is meant by "sufficient information": statistics, bibliography?	
Section 1.4 – Part C.1	Voisin Consulting would welcome a clarification on whether a request for a waiver for the full paediatric indication excuses the sponsor from submitting a PIP (Section D), i.e. that the sponsor may submit only Sections A, B, C and F. We anticipate that if a planned indication or a subset is not concerned by the waiver, a PIP (Section D) is required.	
Section 1.4 – Part C.2.2	The heading of this sub-section is "Grounds based on the disease or condition only occurring in adults". A rewording should be considered, as it is possible that the prevalence of a condition in the paediatric population is very low but not null and still a product specific waiver may be considered.	Voisin Consulting suggests "Grounds based on the disease or condition not occurring in the paediatric population or only in a specific subset".
Section 1.5 – Part D.1.2	A cross reference to the existing EMEA guidelines on organ maturity would be appreciated.	
Section 1.5 – Part D.1.3	The title of this section does not seem to be coherent with its content.	Voisin Consulting suggests "Outline of the quality, nonclinical and clinical data and development plan in adults"
Section 1.5 – Part D.1.6	Could the Commission please clarify the goal of this section, as the guideline states specifically that the information should actually be included in Section 1.3 – Part B.5.	

Section 1.5 – Part D.4 (last paragraph)	Voisin Consulting anticipates that feasibility issues, as mentioned in the last paragraph, will play an important role, and therefore, should be addressed more substantially in this guideline.	
Section 1.5 – Part D.5.1	Voisin Consulting would welcome a template of the summary table to obtain a standardised section; this table should be inspired from the CTD 2.6. In relation to the fourth bullet point, could the Commission clarify how, in practice, it will be possible to take into consideration the different European food cultures?	
Section 1.5 – Part D.5.2	Footnote (4) is missing at the bottom of the page.	
Section 1.5 – Part D.5.3	Since the formulation in the paediatric population could be different from the adult formulation, Voisin Consulting believes that the product administered should be included in the list.	
Section 1.5 – Part D.6	Could the Commission clarify which criteria will be considered by the Paediatric Committee to assess the "reasonable amount of time for unforeseen circumstances" which applicants should include in their proposal?	The first sentence should read "The section should present the detailed timelines of the measures included in the paediatric investigation plan".
Section 1.6 – Part E	Voisin Consulting believes that a reminder of the definition of the deferrals would be useful in this section.	
Section 1.7 – Part F	Please clarify whether full text articles are required or if a list of references is sufficient (full text articles could be provided upon request). Last bullet point: Could the Commission clarify whether it will be sufficient to include the English version of the latest approved product information.	

Section 1.8	Please clarify whether Part D along with the application form are the only documents required in the case of the submission of a modification of an agreed PIP. We understand that an agreed PIP may be modified if new products are available or if the prevalence of the disease evolves for example, as a consequence, on a case-by-case basis, other sections than section D could be important as well. Part E requesting deferrals should be useful as well.	
Section 2	This section explains that the compliance check that will be performed at the time of validation of an MAA. Are further compliance checks planned after the MAA is granted for products with approved deferrals?	
Section 2 – Paragraph 3/14	Voisin Consulting would appreciate clarification on how the compliance check will take into account the possibility of "unforeseen events" as mentioned in Section D6.	
Section 2 – Paragraph 3/14	Voisin Consulting would welcome a clarification on the possibility of obtaining a validated application while being non-compliant with the PIP. This statement seems contradictory.	
Section 2 – Paragraph 10/14	A clarification on whether publication of a guideline outlining the format and content of the so-called "compliance report" is planned would be appreciated.	
Section 3	It is Voisin Consulting's opinion that this section would deserve a stand-alone detailed guideline.	