SUBMISSION OF COMMENTS ON < GUIDELINE TITLE: Commission Guideline on the Format and Content of Applications for Agreement or Modification of a Paediatric Investigation Plan and Requests for Waivers or Deferrals and Concerning the Operation of the Compliance Check and on Criteria for Assessing Significant Studies> <DOCUMENT REFERENCE: Version January 2007>

COMMENTS FROM <<These comments are submitted by Francis P. Crawley (fpc@gcpalliance.org) on behalf of the following organisations and contact persons:

- **Good Clinical Practice Alliance - Europe: Francis P. Crawley, Executive Director, Contact Person;**
- **Ethics Working Group, Confederation of European Specialists in Paediatrics (CESP): Francis P. Crawley, Member, Contact Person;**
- **Working Group on Paediatrics, Institute of Clinical Research (ICR), Pippa Williams, Head of Membership, Contact Person;**
- **European Network for Alternating Hemiphlagia in Childhood (ENRAH) [FP6 funded project]: Tsveta Schyns, Director, Contact Person;**
- **European Federation of Allergy and Airways Diseases Patients' Organisation (EFA): Susanna Palkonen, Executive Officer, Contact Person;**
- **Research Committee, International Primary Care Respiratory Group (IPCRG): David Price, Chairman, Contact Person.>**

These organisations have jointly pooled their comments. The aim has been to achieve a carefully reviewed and harmonised submission of comments representative of paediatricians, researchers, and patient groups in Europe.

GENERAL COMMENTS

The draft '**Commission Guideline on the Format and Content of Applications for Agreement or Modification of a Paediatric Investigation Plan and Requests for Waivers or Deferrals and Concerning the Operation of the Compliance Check and on Criteria for Assessing Significant Studies**' (Version January 2007) represents a major contribution by the European Community to the promotion of improved healthcare for Europe's children. The paediatric investigation plan represents the heart of '**Regulation (EC) No 1901/2006** of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use' whose entry into force on 26 January 2007 provides a strong legal framework for promoting clinical trials performed in children in order to improve the knowledge and practice of medicines involved in the treatment of children. The undersigners of these comments have had the privilege to work with the European Commission, EMEA, European Parliament, and Member State Competent Authorities in the promotion of both an ethical and legal framework as well as regulatory structures that will improve the study and labelling of medicinal products for use in children. This draft guideline represents a welcomed step forward.

The draft guideline provides a detailed outline of requirements and expectations by Competent Authorities and the EMEA paediatric committee for sponsors engaged in the development of medicinal products for marketing authorisation in the Community. Our specific comments below are intended to assist the European Commission in providing a child-centred regulatory approach to medicinal products development within the European Union, cognizant of the needs of researchers and sponsors of medicinal products. The comments here are informed by a patient-oriented and ethical standpoint.

The commentators provide in annex a copy of the draft guideline that includes specific grammatical and textual considerations. These considerations were considered too numerous and cumbersome to be included in the list below of specific comments.

Finally, the draft guideline provided here will need to be further supported by specific operational guidance in informed consent and ethical review of clinical trials performed in children. The commentators have wide practical and formal experience with drafting and implementing guidance at the European and Member State levels, as well as at the international level. Following on the initiative and finalisation of this guidance, the commentators propose to prepare **specific operational guidance for informed consent and ethical review**, based on the previously prepared CESP guidelines referred to in this guidance. This will be complimented by the development of **education programmes for researchers and ethics committees** engaged with clinical trials performed in children in order that they better understand and appreciate the requirements, expectations, and role of the paediatric investigation plan in Community medicinal product development. The development of the guidelines and education programmes will be open to interested parties across Europe, including the Ad Hoc Group and the EMEA.

SPECIFIC COMMENTS ON TEXT		
GUIDELINE SECTION TITLE		
Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
p. 3, para 2	Awkward phrasing.	Rewrite the first sentence as follows: 'To meet these objectives the paediatric regulation creates a number of requirements on the pharmaceutical industry for developing medicinal products for paediatric use as well as rewards for the pharmaceutical industry for complying fully with the requirements for studies in children.'
p. 3, para 2, footnotes 2 & 3	The Commission should clarify the manner(s) in which 'other interested parties' are to be consulted. In particular, it should indicate how parties other than the pharmaceutical industry and its Forum are to be included, for example, patient organisations, academic institutions, NGOs, ethics committees, paediatric organisations. It appears that the requirements of both Article 10 and Article 45(4) are being addressed in this draft guideline, though the consultation processes foreseen by the Parliament and Council differ. The Commission should clarify how these consultation requirements are being met.	
p. 3, 2nd to last paragraph	The definition of 'condition' here would appear to include 'disease'. Nonetheless, throughout the draft guidance reference is made to disease(s)/condition(s) (even to 'disease or condition' and 'disease' or 'condition' alone) suggesting a difference. If definitions are given or created, they should be used consequently.	
p. 3, last paragraph	rewrite with 'and/or' for greater inclusion, similarly in p. 6, 1.2 Part A, A.8.	Rewrite as follows: '(b) **Paediatric investigation plan indication:** the proposed indication(s) in the paediatric population for the purpose of a paediatric investigation plan, and at the time of paediatric investigation plan submission. It should specify if the

[1] Where available

		medicinal product is intended for diagnosis, prevention and/or treatment of a condition.'
p. 4, para 2	Clarification required. There is a general confusion throughout the draft guideline. At times the draft guideline addresses the development of medicinal products only in terms of 'therapy' (as here). At other times the guideline takes a wider consideration regarding the (potential) 'therapeutic, diagnostic, and/or preventive use' of an investigational medicinal product. It would seem the latter is more correct. The guideline provides no indication for the variances in consideration. If such a reason exists, this should be clarified in the guideline and consequently carried through the entire document.	Rewrite as follows: '(d) **Granted Therapeutic Indication:** The therapeutic indication in adults and/or paediatric populations for which a product has already received marketing authorisation. This authorisation has been the result of (a) previous positive assessment(s) of quality, safety, and efficacy data submitted to a European Competent Authority in a marketing authorisation application.'
p. 4, para 3	Clarification required	Rewrite as follows: '(e) **Measures:** (see the use in Article 15(2) of the paediatric regulation) include the studies, trials, data and pharmaceutical development necessary in a paediatric investigation plan to obtain a marketing authorization for a paediatric indication with an age appropriate formulation in all subsets of the paediatric population affected by the condition, as specified in a paediatric investigation plan.'
p. 4, 1.1, para 3	As somewhat clarified in section 1.5 Part D, D.1.2 on page 11, the ICH E11 reference should perhaps be taken only as a reference, not as definitive. Different paediatric diseases, populations, and studies may require differing age groupings. (It should be kept in mind that the ICH E11 is an industry and regulatory standard. It was not developed in cooperation with independent paediatric expertise.) An example of where this does not apply is in asthma where the age groups might be more appropriately defined as 0 to 27 days, 1 month to 4 years, and five years +. This is consistent with current guidelines and evidence on the differential effect of medicines. It should be made explicit that the 'subsets' referred to here (and in the following) are 'age-related subsets'. Other paediatric population subsets may be further defined (within specific studies) according to disease, genetic, pubertal stages, or other differentiations. Correct	Rewrite as follows: 'The paediatric population encompasses several age-related subsets, as defined for example in ICH guideline E11[4]:'

	further throughout the text.	
p. 5, 1.1, para 6	Not only the 'details' of studies already conducted should be included but also publications concerning or related to the investigational product. One thinks of the failure in the TGN 1412 study to provide a sufficient literature background when such was possible.	Rewrite as follows: 'In particular, all relevant details should be given of any incomplete or discontinued pharmaco-toxicological test or clinical study or trial relating to the medicinal product, and/or completed trials concerning indications not covered by the application. A full list of references of publications concerning, or related to, the product should also be provided in the application.'
p. 5, 1.2 Part A	Rewrite for clarity. Information not provided early on should be provided at some foreseen point at a later time.	Rewrite as follows: 'At an early stage of product development it may not be possible for an applicant to provide comprehensive responses to all sections of the application; however, applicants should always complete all sections of Part A using the forms annexed to this guideline. Where information is not available, this should be stated as well as at what point the missing information will be provided.'
p. 5, 1.2 Part A, A.1	This paragraph appears rather remarkable considering that Directive 2001/20/EC clearly requires the identification of a sponsor for each clinical trial carried out in the EU, and that the Directive further clearly defines the role and responsibilities of a sponsor in a clinical trial. It would appear that only a sponsor could possibly be authorised for carrying out a Paediatric Investigation Plan (PIP) and, thus, only a sponsor could take on the responsibility of submitting an application for a PIP, waiver, or deferral. Certainly a sponsor may engage the assistance of any party the sponsor may wish to develop the application, but it would seem that the application may only be received by the Agency from the sponsor or a designated representative of the sponsor. It would further appear inappropriate on the part of the Agency to accept an application from, and thus provide a decision to, a party not responsible for the exercise of the decision. Thus, only than the sponsor or its (legally) designated representative should be defined as 'applicant'. This, without exception, including so-called 'academic studies'. Considering the legal responsibilities of a sponsor, it would not appear possible that a sponsor should remain anonymous to the	Rewrite as follows: '***A.1 Definition of, and contact information for, an applicant*** The application for a Paediatric Investigation Plan, waiver, or deferral must be submitted by the sponsor (the legal person responsible for the research and development of the product) or its representative, following the definition of a sponsor as provided in Directive 2001/20/EC. The name and address of the applicant should be provided. The name(s) and contact information of the person(s) authorised to communicate with the Agency on behalf of the applicant during the procedure, and after the Agency's decision (if different), should be provided. In view of the fact that Agency decisions will be made public, the applicant is required to provide a contact point (address, telephone, fax, e-mail) for enquiries from interested parties that the Agency will then make public with the decisions.'

	public. The sponsor should not be 'encouraged' but rather 'required' to make public its name and contact information, including name, address, telephone, fax, and e-mail. (As a legal entity, a sponsor must have a physical address. Why should this not be disclosed?)	
p. 5, 1.2 Part A, A.2	Considering that the Regulation concerns 'medicinal products', one is confused as to what role '(if available)' could play here. If this refers somehow to the first paragraph of 1.2 Part A, this would appear rather strange: to submit somehow an application for PIP, waiver, or deferment for a medicinal product that does not (fully) exist? It would appear difficult for the Agency to act on, or even accept information on, a medicinal product not fully identified and existent. We suggest deleting '(if available)'.	Rewrite as follows: 'The name(s) and full contact information of the manufacturer(s) and site(s) of manufacture of the active substance(s) and of the medicinal product should be provided.'
p. 6 1.2 Part A, A.3, para 2	Same query as above. In addition, why 'might be' and 'it is suggested' instead of 'required'? It would appear that the Agency would find it difficult to provide evaluate, consider, and even receive information on a medicinal product not fully specified. Being well-disposed to the competitive interests of the pharmaceutical industry should not hinder good regulatory practice.	
p. 6, 1.2 Part A, A.4	Rewrite for clarity.	Rewrite as follows: 'The applicant should specify the type of product for which the application is submitted (for example, a new chemical entity, a new biological product, a vaccine, a gene therapy product, somatic cell therapy medicinal product). In addition, the applicant should specify the product's target and mechanism of action.'
p. 6, 1.2 Part A, A.5	As above, delete 'If available,'	
p. 6, 1.2 Part A, A.6 & A.7	It is not clear as to why this section refers variously to 'Member States', 'Community', and 'EEA'. Further, it is suggested that the information in p. 6, 1.2 Part A, A.7 be presented in the same (or similar) manner to A.6.	
p. 6, 1.2 Part A,	The decisions of ethics committees regarding the product, from	Add the bullet points:

A.6	within or outside the Community, should be included in this listing. The Agency should similarly be informed of all current applications for ethical review.	• 'copies of all decisions (negative or positive) received on applications for ethical review concerning the product from within or outside the Community,' • 'information on all current applications for ethical review, inside or outside the Community,'
p. 6, 1.2 Part A, A.8	The phrase 'at the time of submission' seems questionable here. One might prefer from a medical perspective to focus in the PIP on the indications addressed rather than the product itself: should the indications addressed change, one might reasonable expect that a new application should be submitted.	
p. 7, 1.3 Part B, B.1	In the first of the last two sentences of this section, it would seem that 'in the paediatric subsets is redundant here, given the two previous bullet points the sentence modifies. We suggest including 'and described in terms of the specific populations in which the medicinal product is intended for research.' The reason for this is that researchers need to take into account the specificities of the research populations their studies include.	Rewrite as follows: 'Emphasis should put on the seriousness of the disease, aetiology, clinical manifestations, and prognosis as well as variability in terms of genetic backgrounds. This may be based on published references or standard textbooks and described in terms of the specific populations in which the medicinal product is intended for research.'
p. 7, 1.3 Part B, B.2	We suggest substituting 'effect' with 'anticipated safety and efficacy profile' in this section.	
p. 7, 1.3 Part B, B.3	Why only on the prevalence and incidence 'within the Community'? European industry and academics (with EU monies) are engaged in medicinal products developments intended to treat diseases primarily prevalent in Third Countries (for example, malaria). Currently, sponsors (industry and academic) tend to register such products with the US FDA, this includes European sponsors using European public monies (and studies specifically carried out in paediatric populations. The Agency should develop a manner to address registration of European medicinal products intended for use in primarily Third Countries. Here prevalence and incidence outside the Community would be of interest. There may also be an interest in prevalence and incidence in Third Countries for evaluating medicinal products primarily intended for use in Europe. Similarly in p. 8, 1.2 Part B, B.4 regarding 'the diagnosis,	

	prevention, and/or treatment interventions' The Commission should clarify the meaning of 'Community' in this document. It appears to be used interchangeably with European Union (including Member States) and EFA.	
p. 8, 1.3 Part B, B.4, para 1	Rewrite for clarity. The use of the term 'methods' is not correct here. It is more correct to state 'interventions'. (See the confused use of the term 'methods' in the *Declaration of Helsinki*, paragraphs 6, 29, 30.)	Rewrite as follows: 'For each disease or condition already authorised by the medicinal product, as well as for each disease or condition addressed by a new medicinal product in development (that is, for new medicinal products or for new indications for authorised medicinal products) the applicant should identify the diagnosis, prevention, and/or treatment interventions available, making reference to the relevant scientific and medical literature as well as any other relevant information. This should include unauthorised treatment interventions, if they represent the standard of care. If no current standard of care exists, this should be stated.'
p. 8, 1.3 Part B, B.4, para 2	Revise for clarity. 'if applicable' appears questionable. What listed here in the case of authorised medicinal products would not be (in some or any cases) applicable?	Rewrite as follows: 'In the case of authorised medicinal products, the list should include those authorised nationally in at least one Member State and by the Community. This can be presented as an overview table containing the invented names(s), active substance, Member State(s) where authorised, holder of the authorisation, and the authorised indication.
p. 9, 1.3 Part B, B.5, para 3	The reason for the following sentence appears unclear: 'If significant therapeutic benefit cannot be fully justified at that early stage of the development of a medicinal product, the paediatric committee may consider a waiver or deferral, as appropriate.' It does not appear necessary to state in advance conditions for the judgments made by the paediatric committee. We suggest deleting this sentence.	
p. 9, 1.3 Part B, B.5	It does not appear appropriate to limit the medicinal needs to 'therapeutic'. 'Diagnostic and/or preventive needs' should be included.	
p. 11, 1.5 Part D, D.1.3	This paragraph appears to be particularly important for the evaluation of a PIP. The first sentence is particularly unclear and confusing regarding just what is required. It would seem that the	Rewrite the first sentence as follows: 'The applicant should outline the previous development of the medicinal product and indicate its relevance for the paediatric development of the medicinal product.

	Agency and, in particular, the paediatric committee, would not be satisfied simply an 'outline' of previous studies, non-clinical and clinical. It would seem to be in the public (and potential child's) interest that the full set of results is submitted with the application. The full study reports of previous studies would appear to be necessary to a critical application of the PIP. Relying simply on the sponsor's outline and (selected?) reporting of results in not in the public's interest (nor in the interest of children). The title of this section also appears confusing. It refers both to 'quality' and 'data' without establishing a link between the two. The paragraph itself seems to be more interested in the 'availability' of results without making any reference to 'quality'.	The reports of all pre-clinical and clinical research should be submitted with the application.'
p. 11, 1.5 Part D, D.1.4	The term 'highlighted' appears less than appropriate here. We suggest replacing it with 'outlined and explained'.	Rewrite as follows: 'The interrelation (in terms of common studies, data, and timelines) between development in adults and paediatric populations should be outlined and explained.'
p. 12, 1.5 Part D, D.2 and following	The introduction and use of the term 'strategy' is not defined in this section. Does 'strategy' differ in some significant ways from 'plan'? Considering that this guideline concerns a 'plan', the introduction and use of the term 'strategy' should be explained in its more specific meaning (if such a meaning exists). Otherwise the term 'plan' might be more appropriate here.	
p. 13, 1.5 Part D, D.4, para 4	The use of the term 'information appears imprecise in this sentence.	Rewrite as follows: 'o The possibility to support pharmacokinetics in certain age groups using existing chemical, pharmaceutical, and/or biological data, or to extrapolate pharmacokinetics from other populations.'
p. 13, 1.5 Part D, D.4, last paragraph/bullet point	It appears confusing as to why 'long-term safety studies' may not be required as part of the PIP, yet required for marketing authorisation. Please clarify.	
p. 14, 1.5 Part D, D.4, para 1	The 'Agency' tends to prefer the term 'Data Monitoring Committee (DMC)' to 'Data and Safety Monitoring Board (DSMB)'. See the CHMP EMEA Guideline on DMCs from July 2005. We suggest using the term DMC here for consistency.	

p. 14, 1.5 Part D, D.5.2, para 2	A footnote number (4) is provided, but there is no reference indicated.	
p. 15, 1.5 Part D, D.5.4, bullet point 2	A justification for the foreseen control should be provided.	Rewrite as follows: '• Type of control (placebo or active control with dose to be used) and justification for the control'
p. 16, 1.7 Part F: Annexes	As suggested above in the comment on p. 6, 1.2 Part A, A.6, include the decisions of ethics committees.	Add the bullet point: • 'copies of all decisions (negative or positive) received on applications for ethical review concerning the product from within or outside the Community,'
p. 18, Section 2, bullet point 4	It would seem that 'the grounds for accepting compliance' (more simply put, 'the grounds for compliance') would not need to be stated. It would be sufficient for the Competent Authority to state that compliance was achieved.	

Please feel free to add more rows if needed.

These comments and the identity of the sender will be made public.