# Paediatric Research Consultancy

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**SUBMISSION OF COMMENTS ON DRAFT COMMISSION PAEDIATRICS GUIDELINE FOR PAEDIATRIC INVESTIGATION PLANS**

**COMMENTS FROM : Jane Lamprill RN RSCN FICR, Independent Paediatric Research Consultant (PRC) Oxford UK**

## GENERAL COMMENTS

- PRC thanks the Commission for the opportunity to comment and welcomes the PIP guidance. Once it is slightly more "user friendly" this will be a valuable document to help companies provide better medicines for the children of Europe.
- Suggest that introduction contains sub-headings are re-classified into: 1) New or on-patent 2) Off-patent 3) Orphan & make it clear which guidance applies to which authorisation and which guidance applies to all three. Anecdotal evidence suggests that companies are very confused about PIP requirements in relation to generics and new formulations. Available guidance suggests that a PIP is not compulsory. However some companies don't realise that without a PIP there will be no PUMA reward .
- A major concern is that according to the EMEA FAQ of January 2007, the Paediatric Committee (PDCO) can meet with a cohort of 27 but does not make clear if an expert representing the child subjects' **ethical** needs should also be present. This in my humble opinion is absolutely essential to protect the interests of children and engender public confidence in the PDCO and EMEA.
- It would be helpful to state at the beginning of the guidance that the PIP should show evidence of how the company has taken steps in each proposed trial to consider ethical implications, minimise risk and distress to the child and keep inconvenience to the family to a minimum. Patient and parent groups will be concerned about this, but if it is not mentioned in the guidance, companies may not feel under obligation to provide this information.
- I also wonder how workable the PDCO will be, bearing in mind the huge amount of documentation to be read and discussed!
- Demands on companies are extremely onerous, especially information about treatment of disease in each member state as this will vary widely. E.g. UK where despite "NICE" we appear to still have a "post code lottery" about what treatment is allowed where.
- Companies are telling me that if the demands are too onerous or expensive, they will not bother to do the work, They do not appreciate that some studies (as I understand it) may be compulsory. Perhaps this could be made clear at the beginning of the guidance?
- Hearsay suggests that the PDCO will review PIPs on a first come first served basis rather than in date order of upcoming MAAs. How will the PDCO ensure that those drugs coming to MAA e.g. at the beginning of August 2008 will have a PIP in place, otherwise would there be a risk that a good paediatric medicine could be lost, due to bureaucratic delay?

Date of transmission:

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| • I may have misunderstood this but with consultation upcoming on the Orphan regulation, "Guideline on aspects of the application of Article 8(2) of Regulation (EC) No 141/2000: Review of the period of market exclusivity of orphan medicinal products" reducing the reward to 6 years in certain circumstances, it would be helpful if the EMEA or PDCO could kindly clarify how this may apply to the Paediatric Regulation and if there will be different and less stringent requirements for the Orphan product PIP if the reward is less. |
| • It would be helpful if the PDCO /EMEA could issue guidance for companies who are also applying to licence the same product in the United States as to whether paediatric trials performed for FDA authorisation may also be used e.g. for an MAA or PUMA to save the unnecessary replication of studies in children and clarify if the reward would apply both sides of the Atlantic |
| • There is some confusion as to whether the PIP is per indication or per compound as company may have > 1 product being developed for same disease or indication |
| • Detailed comments below – suggested changes in bold for clarity – Kind regards Jane. |

**SPECIFIC COMMENTS ON TEXT**

| Section. + paragraph no. | Comment and Rationale | Proposed change (if applicable) |
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| A6 and A7<br>Page 6 | Details of the medicinal product:<br>• How much detail do you need as you request this info from every MS and all non-EU countries where drug is used. The PDCO will not be able to cope!<br>• Are you including new drug delivery devices here or just drug? | Further guidance please |
| 1.3 Part B<br>Para 1<br>Page 7 | Would you need to know differences as well as you mention them in the next paragraph? | This part should also include details on the diseases/conditions in the paediatric population including their **similarities and differences** between adult and paediatric populations and within the different paediatric subsets, prevalence, incidence, diagnosis and treatment methods, and alternative treatments. This information can be provided in tabulated format for ease of reference. |
| B1<br>Page 7 | Clarification would be helpful here as the quality of publication may vary widely? | Emphasis should put on the seriousness of the disease, aetiology, clinical manifestations and prognosis, and variability in terms of genetic background, in the paediatric |

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| | | subsets. This may be based on **peer reviewed** published references, or standard textbooks **from reputable medical publishers.** |
| B3<br>Page 7 | A lot of information is required here which may be difficult to obtain. | The applicant should provide the **most recent available** information from **referenced reliable sources** of the prevalence and incidence of the diseases/conditions in the Community (and in the different Member States) if available. If **data available** ~~possible~~, this could be broken down by paediatric subsets. |
| B4<br>Para 1<br>Page 8 | Suggest that extemporaneous medicines should be included if this is normal standard of care? | This should include unauthorised **and extemporaneous** treatment methods if they represent the standard of care. If no methods exist, this should be stated. |
| B5<br>Para 1<br>Page 8 | Perhaps an extra sentence for clarification? | Whether the use of the medicinal product either through use as an authorised product or through the conduct of clinical trials in children is expected to be of significant therapeutic benefit to children or fulfil a therapeutic need in children should be judged by the paediatric committee and will determine whether a paediatric investigation plan receives a positive opinion or whether a waiver is granted. **Where significant other benefit is anticipated but yet unproven, a deferral may be granted.** |
| B5<br>Para 5<br>Page 9 | Suggest clarity needed at section c) to ensure product child friendly? | c) Improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration) leading to improved safety, efficacy or compliance **including improved taste and acceptability to children and care givers.** |
| B5 | PRC is worried about this paragraph as it could give the impression to the general public that just because there is | Particularly early in product development when data to substantiate significant therapeutic benefit may be scarce, |

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| Para 9<br>Page 9 | no paediatric medicine available, it is safe to test medicines in children at an earlier phase than is safe.<br>I may have misunderstood but I am not sure what you mean by the last sentence because if the drug could be used as an authorised product there would be no need to do a trial?? | studies in children may be justified **in severe or life threatening disease and with great caution. This is where** there is a therapeutic need of the paediatric population which may be fulfilled either through inclusion of children in clinical trials or through the availability of the medicine as an authorised medicinal product **for adults that have been adapted for children. Where medicines are extemporaneous, sponsor should make every effort to ensure uniformity of quality and accuracy of dosing.** |
| C2.1<br>Waivers<br>Page 10 | Presumably you need to know at what dose the medicine may be toxic as well? | In accordance with Article 11(1)(a) of the paediatric regulation a request for a waiver based on lack of efficacy **or known toxicity** in the paediatric population(s) should take account, for the different paediatric subsets, of the seriousness of the condition/disease and ….etc |
| C 2.2<br>Para 1 | Disease only occurring in adults: this is complex as e.g. I understand from the USA that an Alzheimer's drug may help paediatric brain injury. Thalidomide is very useful in paediatric skin disease etc<br>There is also no mention of disease severity here. | In accordance with Article 11(1)(b) of the paediatric regulation justification may be based on detailed information on the incidence or prevalence of the disease in different populations. **Where the same drug has different indications for adult and paediatric disease, this should be clearly stated** For waivers covering the totality of the paediatric population the justification should particularly focus on the earliest age of onset of the condition/disease. For waivers for specific subsets the justification should focus on the incidence or prevalence **and potential disease severity** in the different paediatric subsets delineated in Part B. |
| D1.2 | Tanner staging required by regulators in non endocrine studies usually leads to poor or zero recruitment! Great sensitivity is required. Suggest that orchidometer or unltrasound testicular volume technique is not used unless absolutely necessary to the disease being studied. | However, these age classes are wide and may include different maturation levels. In addition to age, the classification of the paediatric population may be based on other variables such as gestational age, pubertal stage(s), and renal function. **Where Tanner staging is used to define pubertal stages in non-endocrine disease,(e.g. epilepsy)** |

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| | | **sponsors must respect the young person's dignity and privacy. Company could e.g provide investigator with a validated pictorial reference chart showing Tanner stages for comparison after the discrete physical exam and when the child has left the room. An unnecessary physical measurement of developing genitalia is intrusive, a potential source of humiliation and is likely to lead to poor or zero recruitment.** |
| D2<br>Strategy<br>Para 1<br>Page 12 | Companies in their haste to be first to market may not realise that paediatric trials are usually much, much slower to recruit than adult studies | • Availability / **estimated** timeframe for the development of an age appropriate dosage form |
| | Medicines need to be child and parent friendly if compliance and improved treatment is to be obtained. | Potential issues in relation to the formulation (e.g. **safety and** appropriateness of excipients for the paediatric population **and acceptability to children and care givers)** |
| | Care for neonates as gastric acid production immature so formulations for these babies need | Stability of oral formulation given nasogastrically in different pH were drug used in premature babies |
| D.2<br>Para 3 | Child friendly again | The addition of a paediatric indication may result in the need for a new pharmaceutical form for example a liquid rather than a tablet or a tablet of a new strength, because the existing<br>pharmaceutical form may be unsuitable for use in all or part of the paediatric population. This means that the suitability of existing pharmaceutical forms should always be discussed in the<br>paediatric investigation plan, **with advice from medicine end-user healthcare professionals, children and parents.** |
| D3<br>Non clinical | Suggest juvenile animal studies will need to be carried out with the utmost care, to avoid public anger and distress. | o Specific studies justifying the most relevant species for potential<br>juvenile animal studies should be carried out **at last resort where the information is not available by any other means. As with paediatric studies, care should be taken to minimise animal risk and distress** |

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| D4<br>Para 1<br>Page 13 | May need to bridge between different age subsets as well as formulations? | Details of the formulation to be used should be given and plans for bridging between the different formulations **and age subsets where appropriate** should be addressed. |
| D4<br>Para 3<br>P13 | Justification of use of paediatric subjects:<br>Suggest that public will need reassurance | The applicant should justify that the subjects intended for inclusion in the trials are representative of the population in which the product will be used. **This is particularly important where research is performed in areas where families may be poor or illiterate and health careis not free of charge at point of delivery.** |
| D5.4<br>Page 15 | Bullet points – suggest add | • **Duration of trial**<br>• **Acceptability of trial to children and parents**<br>• **Evidence for minimisation of risk and distress**<br>• **Plan in case of positive pregnancy test in pubertal children** |
| 1.6. PART E<br>Para 1<br>Page 15 | Some studies may be very slow to recruit and timelines may be missed through no fault of company. | 1.6 PART E: APPLICATIONS FOR DEFERRALS<br>The paediatric regulation allows for deferral of the initiation or completion of the measures included in a paediatric investigation plan. Any request for deferrals of the start or the completion of measures should be justified by indication, route of administration and pharmaceutical form. **Where deferrals are requested because studies are slow to recruit through no fault of company, e.g. for orphan indications, evidence should be provided of recruitment strategy and serious efforts made.** |
| 1.7<br>Last bullet<br>Page 16 | Did you need to expand last bullet? | • Latest approved product information (SPC, PL, Labelling) for a product already authorised; **in all MS and/or elsewhere** |
| 3.2 | Do you mean individual country authorities or EMEA – some | To qualify for the rewards of Articles 36, 37 and 38 |

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| Para 2<br>Page 18 | companies are confused about the role that each may play here. | significant studies need to be completed after the entry into force of the paediatric regulation. A study will be considered as completed<br>when the last visit of the last patient has occurred, as foreseen in the latest version of the protocol (as submitted and **approved by** competent authorities **and ethics committees**) and falls after the date of entry into force of the paediatric regulation. Open extensions of studies consisting of treatment maintenance for patients included, will not be considered as continuing after the entry into force if this was not part of the protocol submitted to the relevant competent authorities. |
| 3.2<br>Final par<br>Page 19 | | However, exceptionally, studies conducted in a single subset of the paediatric population will be considered as significant if carried out a subset considered particularly difficult to study, for example neonates **or rare disease**. |
| 3.2<br>Final par<br>Page 19 | It would be helpful to describe what studies are <u>not</u> significant, so that companies don't waste valuable time and resources preparing a PIP. See possible examples: | **3.4 Studies not considered significant/allowable:**<br>**1. "Me too" medicines where safe, effective medication is already available in all MS and all paediatric subsets.**<br>**2. Studies that have already been performed and replicated elsewhere. Further studies would therefore be unethical.**<br>**3. Studies that would not clinically benefit any subset of the paediatric population but are being done for reward alone.** |

Thank you for your time reading this.