10 February 2017
EMA/72007/2017

Overview of comments received by EMA on 'Questions and answers - ICH S9 guideline on nonclinical evaluation for anticancer pharmaceuticals - Step 2b' (EMA/CHMP/ICH/453684/2016)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	Paediatric Committee (PDCO) EMA
2	ICAPPP International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP), submitted by Japanese Anti Vivisection Association (JAVA)

Please note that comments will be sent to the **ICH S9 IWG** for consideration in the context of Step 3 of the ICH process.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment (if any)
2	ICAPPP welcomes the creation of this Q&A document, which aims to provide clarity on certain areas of the existing guideline that have been open to broad interpretation. This level of ambiguity could have had a significant impact on animals as well as time and cost to market in cases where additional animal tests were being conducted when they are not actually needed. We therefore appreciate the effort made throughout this Q&A to provide clarity on cases where animal tests are not needed and where in vitro tests can be used. Where tests in animals are considered necessary, we appreciate the effort made to provide opportunities where shorter study durations or fewer species can be used, which is in keeping with the council's aim to continue progress in the 3Rs.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes
Answer to question 3.9, page 35 (no line number available)	1	**Comments**: 1. Context in scope of ICH S9 and need for case-by-case decision In the draft answer to question 1.3 it is stated that "*The S9 Guideline does not make a reference to years of life expectancy and the application of the guideline should not be based on an expectation of survival as measured in years*", and in 1.1 that "*Most initial development programs are performed in patients (adult and paediatric) whose disease is resistant and refractory to available therapy, the nonclinical program described in ICH S9 is applicable.*" Furthermore, the draft answer to question 3.9 includes, "*When clinical development is pursued in children with longer life expectancy, the need for juvenile toxicity testing should be a case by case decision […].*" This may indicate that S9 provides guidance on the non-clinical studies needed to treat cancer in patients with limited life expectancy following several previous treatments, mainly chemotherapies, which failed to be curative and for whom no effective treatments are known. However, paediatric oncology is changing as regards testing and using anti-cancer medicines. Some children with previously incurable diseases are long(er)-term survivors (for years) after receiving treatments that were originally intended as only palliative treatments or in last-line trials, such as an expanding repertoire of individually-selected, targeted and biologic experimental treatments as well as prolonged chemotherapy regimens of moderate toxicity. The experience over the last years is that such treatments may change rapidly fatal diseases into more chronic diseases with prolonged survival even after multiple previous relapses. Achieving long-term disease control has become an intention in some initial trials with children on anti-cancer medicines. The long(er)-term survivors are still treated and followed with palliative intentions; the aim is to maintain normal activities of daily live and to permit staying at home and in school, with minimized hospitalisations and follow-up schedules avoiding clinically unnecessary investigations. In this context and given the fact that these patients have already been submitted to a high treatment burden due to aggressive treatments, they represent a vulnerable population, and attempts should be made to minimize and or prevent severe toxicities including when investigating further therapies. 2. Importance of adult data in view of differences between adult and paediatric patients

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		The answer to question 3.9 states that: *"Clinical data from adults is typically available prior to initiation of these paediatric trials; this data is used to set a starting dose and inform monitoring plans."* This statement duplicates to some extent and in general terms recommendations in other guidances (ICH E11, ICH E4) and as such does not seem needed. In addition, it indicates that safety may be extrapolated from adult non-clinical and clinical data to paediatric cancer patients. This is particularly applicable for adolescents, and there is a willingness to include them in adult cancer studies whenever possible (Chuck et al. 2017). However, this approach is usually not appropriate for the youngest patient populations, for whom pharmacodynamics (e.g. sensitivity and responsiveness due to different biological features [such as infant leukaemia, brain tumours] as well as different tumour load in paediatric cancers), pharmacokinetics and toxicity (e.g. possible interference with organs/systems undergoing maturation) are not necessarily predictable from adult data. As a consequence, the need for additional non-clinical data concerns mainly the youngest populations, below about 2-4 years of age (see also section 3 below). Currently, paediatric oncology phase I/II studies are aimed at evaluation of pharmacokinetics and safety of new drugs under development together with the intention to provide a potential anti-tumour treatment option, at a likely active dose. In fact, some of the novel and targeted medicines can be expected to have such a favourable anti-tumour activity that large and sustained treatment effects may occur in an initial (first) trial. A recent striking example is the first paediatric crizotinib trial, with complete and durable responses in 7 out of 9 paediatric patients with an anaplastic large-cell lymphoma, previously refractory to therapy and for whom there was no known curative treatment at the time of trial recruitment (Mossé et al. 2013). For such patients who may benefit from innovative treatments, secondary/long-term toxicities should be known and kept as low as possible. Based on the willingness to apply personalized medicines concepts in order to maximize therapeutic chances of success, many investigations are ongoing addressing the need to increase the knowledge of markers indicative of tumour progression or efficacy. For youngest patients and in view of longer-term survival in initial (first) trials, the risks have to be minimized as much as possible to preserve the safety and quality of life of these patients. Whenever these trials are initiated, they should be conducted in an informed way, knowing as much as possible about the safety profile that is to be expected - and to be managed - in the target patient population. This view is generally supported by academicians, who were driving novel concepts for desirable early drug development for children with cancer of targeted therapies (Pearson et al. 2016): *"Selection of the right drug(s) for clinical evaluation is needed, for which factors such as safety and posology are important considerations."*

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		In addition, if the non-clinical studies to support the treatment of youngest children were planned at the time non-clinical studies are planned in development for adults, there would not be any delay of access to new therapies for younger paediatric populations. 3. Youngest patients in initial trials and in targeted indication The draft answer to question 3.9 also states*: "To support the clinical development in a paediatric-only indication, the age of animals in the repeat-dose toxicity studies should be chosen to cover the age of the patient population in the initial clinical trials."* The adult indication rarely correlates with the paediatric indication, because in children embryonal tumours, undifferentiated tumours with high growth rate are observed, while in adults rather different tumour types occur (more differentiated, mostly epithelial and with a slower growth rate). This implies different PK/PD relationships and potentially different toxicity profiles between paediatric and adult patients (see also section 2 above). Therefore, whether for a paediatric-only development or not, it is relevant to consider juvenile animal studies and to systematically assess the need for such studies for paediatric oncology developments. The draft answer to question 3.9 also states that: *"In addition, these trials are usually done in a controlled setting with substantial safety monitoring"*. It is unrealistic that much safety data can be generated in youngest children in these initial paediatric trials and if safety monitoring can be relied upon to minimise adverse outcomes in this subset, considering that the major risks are in younger children but these are scarcely included in initial trials. Initial trials are mostly late-line trials and this means that patients after a number of failed treatments are no longer in the youngest age. However, the indication targeted in paediatric patients is often curative (e.g. first or second line) and the treatment of youngest patients is clearly part of the indication targeted by the paediatric development. References Chuk MK, Mulugeta Y, Roth-Cline M, Mehrotra N, Reaman GH: Enrolling Adolescents in Disease/Target-Appropriate Adult Oncology Clinical Trials of Investigational Agents. Clinical Cancer Research 2017, 23: 9-12 Mosse YP, Balis FM, Lim MS et al: Efficacy of crizotinib in children with relapsed/refractory ALK driven tumors including anaplastic large cell lymphoma and neuroblastoma: A Children's Oncology Group phase I consortium study. J

Line no.	Stakeholder no.	Comment and rationale; proposed changes
		Clin Oncol 2013, 14: 472-480 Pearson A, Herold R, Rousseau R et al.: Implementation of Mechanism of Action Biology-Driven Early Drug Development for Children with Cancer. Europ J Canc 2016, 62: 124-131 Voss D, Glade-Bender J, Spunt S et al.: Growth Plate Abnormalities in Pediatric Cancer Patients Undergoing Phase 1 Anti-Angiogenic Therapy: A Report From the Children's Oncology Group Phase I Consortium. Pediatr Blood Canc 2014, 62: 45-51 **Proposed change**: "The need for juvenile toxicity testing should be a case by case decision based on the available knowledge about pharmacology, pharmacokinetics, non-clinical and clinical safety, the relevance of these data for the targeted population and disease, the expected safety concerns and the remaining uncertainties. Juvenile toxicity studies should be performed as appropriate when available animal models are deemed believed to generate data relevant for paediatric safety, and there is a clear value anticipated for such data for supporting clinical paediatric development. Such juvenile studies should be planned early on so as not to delay the initiation or progress of the paediatric clinical program. A juvenile toxicity study could add important information for minimizing safety risks and protecting particularly youngest patients. When studies are needed, ICH S11 should be consulted to address the design of the juvenile animal study. A dialogue with the regulatory agency is encouraged. To support the clinical development in a paediatric-only indication, the age of animals in the repeat-dose toxicity studies should be chosen to cover the age of the patient population in the development."