Submission of comments: Adoption of International Scientific Guidelines in Australia R01-2023: Guideline S11 Nonclinical Safety Testing in Support of Development of Paediatric Medicines; International Council for Harmonisation

Submission by Animal-Free Science Advocacy

General Comments:

Animal Free Science Advocacy (AFSA) acknowledges the significant difficulties with development of medicines for paediatrics: on top of the nine years for adult drug development, an additional seven to eight years are required to have that same product approved for use in children (Bi et al, 2019). Therefore, AFSA appreciates the intent behind the S11 guideline, which aims to provide internationally harmonised guidance on the nonclinical studies recommended to support the development of paediatric medicines. However, AFSA also acknowledges the significant international regulatory milestones that have been achieved since the adoption of this guideline by the ICH in April 2020; most notably, the FDA Modernization Act 2.0. AFSA would therefore like to propose several amendments to the current S11 guideline for consideration prior to its adoption.

Particularly of note, is the redefining of the term 'nonclinical test' in the FDA Modernization Act as: *"the term 'nonclinical test' means a test conducted in vitro, in silico, or in chemico, or a nonhuman in vivo test, that occurs before or during the clinical trial phase of the investigation of the safety and effectiveness of a drug. Such tests may include the following:(1) Cell-based assays.(2) Organ chips and microphysiological systems.(3) Computer modeling.(4) Other nonhuman or human biology-based test methods, such as bioprinting.(5) Animal tests."*

Considering that one of the stated key objectives of the guideline is to promote a reduction in the use of animals in accordance with the 3Rs principles, **AFSA have some serious concerns regarding; 1) the lack of examples and limited guidance provided on nonclinical testing methods other than juvenile animal studies (JAS), and 2) the unsubstantiated support for JAS as a standard approach, rather than as a last resort option.** Aligning with the FDA in this regard would also be supportive of the recommendations made in a recently published CSIRO non-animal model report (CSIRO, 2023).

AFSA's below commentary aligns largely with the International Council on Animal Protection in Pharmaceutical Programs (ICAPPP) and the following submission has been adapted from ICAPPs original submission (dated 02 April 2019) to the FDA titled: "Submission of comments on 'S11 Nonclinical Safety Testing in Support of Development of Pediatric Medicines; International Council for Harmonisation; Docket No. FDA-2018-D-4524'".

Key Points:

- There is unsubstantiated support for juvenile animal studies (JAS) as a standard approach – There is little evidence to support the use of juvenile animals as a reliable or practical solution to addressing safety concerns in paediatric drug development. ICAPPP summarized a significant amount of literature to support this statement. AFSA urge against JAS studies being performed as a 'tick-box' exercise or default option for addressing safety concerns. Considering that the data generated may be of little relevance, the use of the JAS method (especially routinely) could be considered unethical as it may provide false reassurance regarding safety but will certainly cause significant suffering of animals.
- There is limited guidance on other nonclinical testing methods – ICAPP suggested that greater guidance be provided on the use of in silico, in vitro and ex vivo methods to support the development of paediatric methods. ICAPPP also requested that, in accordance with the 3Rs principles, these methods be prioritized before considering JAS as a last resort. As outlined in the FutureTox IV workshop several opportunities exist for use of non-animal models in paediatric drug development: Lifestage-specific in vitro approaches and in silico models—including PK and pharmacodynamics (PD)—can increase confidence in making predictions that are based on nonpaediatric models, and should be utilized wherever possible as part of a model informed drug development (MIDD) approach (Bi et al., 2019, Knudsen et al., 2021).

The below points 1 and 2 are taken unchanged from the ICAPPP submission:

1. Limited guidance on other nonclinical testing methods

The title of the guideline is "nonclinical safety testing in support of development of pediatric medicines" and not 'juvenile animal testing in support of pediatric medicines'. Therefore, we would expect to see more guidance on other nonclinical testing methods that should be considered before recommending JAS. Examples of non-animal alternative methods to JAS, which still permit safe and effective drug development and use, should be included in the guideline.

Section 2 of the guideline describes the importance of conducting a weight-of-evidence (WoE) analysis as a first step to determine the need for additional nonclinical studies. We support this approach and appreciate the emphasis on the use of existing information from both human and animal studies, pharmacological properties, and data from pharmacokinetic (PK) modelling and computer simulations. If the WoE analysis suggests that additional nonclinical studies are warranted, the guideline states that further in vitro or ex vivo investigations or tests in juvenile animals will be needed. However, the guideline then jumps to a section on the 'design of nonclinical juvenile animal studies' without any further discussion, examples or guidance on the use of the aforementioned in vitro/ex vivo methods.

With the goals of minimising animal testing in mind, a section should be added in between Section 2 and Section 3 to provide guidance on the use of in vitro and ex vivo methods to support the development of pediatric medicines. It should also be made clear that, in accordance with the 3R principles, these methods must be prioritized before considering JAS, which have yet to prove their value (see comments below) and should be viewed as a last resort option under very rare circumstances.

2. Unsubstantiated support for JAS as a standard approach, rather than as a last resort

According to the 'background' section, the guideline reflects current thinking based on collations of examples from regulatory agencies, industry surveys and literature. None of these references are provided in the text and we feel that it would be useful to include some of these key sources so that readers can better understand the rationale behind the guideline's recommendations.

For decades, the use of medicinal products in children has mostly been determined based on clinical experience with the drug in adults, factoring the dose by a child's body weight (Anderson et al., 2009). However, due to recent changes in regulatory thinking, concerns with off-label drug use and unpredicted toxicities in the pediatric population, and a rise in the number of drug development programs focusing on pediatric-only indications, the number of JAS being requested by regulators and/or conducted by drug developers has increased exponentially over the past 10 years (Downes, 2012).

While we appreciate the need to improve the way drugs are regulated and used in the vulnerable pediatric population, there is little evidence to support the use of juvenile animals as a reliable or practical solution. If data from human adults is not enough to predict safety in human children, it is difficult to see how extrapolation of data from young animals to young humans can be meaningful, especially considering the vast species differences (e.g. shorter lifespan, varying developmental schedules etc.) that must be accounted for. "Juvenile animal models are not only inflicted with the common difficulties of species-to-species translation but also with additional ambiguities to translate postnatal development across species" (Schmitt, 2015). The difficulty in predicting safety in human children based on data from human adults calls into question extrapolation even between similar groups within the same species; the extrapolation between different species in the JAS method is likely to be even less relevant.

We are concerned that JAS are becoming an accepted part of the safety assessment package for new drugs even though their true utility has not yet been fully characterized (Baldrick, 2018). According to the literature, there are not enough clear-cut examples to determine whether JAS are useful or necessary to support pediatric drug development (Baldrick, 2010). Where reviews into the utility of JAS have been conducted, the results are far from satisfactory:

Data from 39 JAS, conducted by ten pharmaceutical companies in a variety of species, were compiled and analyzed (Bailey & Marien, 2009). Novel toxicity was only observed in four out of the 39 studies compiled, one of which could have been predicted from the pharmacology data. The review found that only in 20% of the studies was it felt that JAS contributed to the pediatric clinical trials and that the JAS were considered to have contributed to the product label in only 30% of cases. “The general perception was that despite these studies, we were not generating anything new; there was no clear indication of novel toxicity or sensitivity; and the findings that were observed were predictable from the known pharmacology, toxicology and the stage of development”. The authors concluded that it “could be considered disappointing, in view of the time, number of animals, complexity and cost of the studies, that only between one in three and one in five studies generate data that makes a difference” and that “it would be a terrible waste of time, animals and money, if we perform these studies for no benefit”.

Another study looked at data from 241 JAS, conducted by 24 pharmaceutical companies, predominantly covering small molecules in a variety of species to support registration of drugs (Bailey & Marien, 2011). The authors found that the JAS contributed to the pediatric clinical trials in 12% and 14%, respectively for the rat and dog and the JAS contributed to the product label in 16% and 19% of cases. In 75% of the rat JAS, all the results were predictable from either the pharmacology (56.9%) or the adult toxicity data (68.1%) and in the dog JAS this was 85.7% (pharmacology – 76.2%, adult toxicity data – 76.2%), which suggests that the studies only contributed new data in less than 25% of cases. “Although this may imply that these studies were therefore justified and had an impact on the safety assessment this should be viewed with caution as the simple collection of new data does not necessarily correspond to a better safety assessment unless the data have a clinical relevance”. The authors concluded that “in view of the huge cost in animals, the financial and time implications, the ethical view (3R) and the complex nature of these studies one could ask if we are doing smart science?”.

One article stated that “it is currently not clear if there are many (or genuinely any?) clear examples when juvenile animal toxicology studies predicted novel human toxicities that would have an impact in pediatric medicine” and that “animal use (especially in puppies or young monkeys) with no clear goal for risk assessment is totally unacceptable” (Baldrick, 2010). The article also highlighted the need for “push-back” to occur to regulators for requesting JAS if not felt fully justified.

Another paper has suggested that the contribution of JAS for “the detection of novel toxicities remains questionable” (Soellner & Olejniczak, 2013). The authors point out that the usefulness of the results from these studies for pediatric development remains unclear and that interpretation of the data and extrapolation to the pediatric population remains difficult.

One recent study specifically considered the potential value of JAS in dose selection and safety monitoring of 21 molecularly targeted agents for which human adult data were available (Visalli et

al., 2018). Their analysis showed that "JAS are not needed in order to safely conduct Phase 1 trials in pediatric subjects, either for selecting the starting dose or informing on potential toxicities that may be unique to a pediatric population". Importantly, this study concludes that "in the absence of case examples showing that findings of JAS allowed clinical catastrophes to be avoided, we do not believe that JAS provide any value in this setting" and that "abandoning the practice of routinely conducting JAS for most molecularly-targeted oncology drugs would expedite testing in pediatric oncology patients and allow precious drug development resources utilized for JAS to be applied to other promising agents". This makes the vital point that time and money are being wasted on ineffective JAS that could be better used in more effective testing methods which could accelerate drug development.

According to a review of EU Pediatric Investigation Plan (PIP) decisions covering the period of 2007 to 2013, it was not clear how many JAS are "actually needed or indeed how useful they are as a means of allowing safe administration of the drug in a pediatric population" (Baldrick, 2018). The author also pointed out that despite increasingly being included in drug product labels, "it is unclear how a health care professional would use the presented study findings (often in technical jargon) when considering prescribing the drug to a child" and "what the differences actually mean when compared with adult animal results". The review concluded that JAS should be strictly avoided as a default, for box-ticking reasons or even to give "comfort factors" for safe use.

US Food and Drug Administration (FDA) approvals of New Drug Applications (NDAs) covering the period from 2015 to 2018 are currently under review by the Physicians Committee for Responsible Medicine. A total of 64 JAS were found to have been submitted in 33 NDAs out of a total of 125 NDAs approved during this time period. In six of the NDAs, FDA reviewers note that the submitted JAS were not required. This indicates a need for clear guidance to industry on the circumstances under which JAS are required by FDA for drug approval and when JAS may be avoided.

There are also those that believe that the traditional approach is sufficient; "from decades of clinical pharmacology research of the use of marketed drugs in children we know about the differences of absorption, distribution, metabolism and excretion in the maturing body of the child" (Rose, 2011) and that "despite the lack of pediatric studies, there are many drugs that have been used safely in children" (Anderson et al., 2009).

As well as the many scientific issues outlined in numerous review studies such as these, JAS pose a significant animal welfare burden due to the use of vulnerable young animals and the length of time for which the animals are in the laboratory environment. While the severity of these studies is somewhat acknowledged in the 'notes' section of the guideline (e.g. "the propensity for mortality to occur is generally higher in juvenile animals compared to adult animals"), we feel it should be emphasized within the main text of the guideline and that the use of JAS, especially multiple studies in one or more species, should be discouraged (see specific comments on text below).

Based on the available evidence, it is difficult to understand why regulators seem to be encouraging the use of JAS and why this draft guideline places so much emphasis on the design of a study that runs counter to the 3Rs. Instead of promoting unreliable and inhumane science, this guideline should be used as an opportunity to steer regulators and drug developers in the right direction and deter unnecessary requests for additional experiments in young animals which, as evidence has shown, are difficult to justify from a cost-benefit point of view.

Additionally, recent innovations in personalized medicine for the identification of effective drug regimes (Berkers et al., 2019), use of adult clinical data for evaluating safe starting doses for children (Visalli et al., 2018) and refinement of in silico methods for pharmacokinetics (Smits et al., 2018) are all relevant and important methods with more direct applicability to drug development in neonates and children than the use of non-human animal models in JAS. This guideline could promote the use of advanced tools such as these within an integrated package, ensuring that JAS are considered as an absolute last resort. For example, Smits et al conclude that "PBPK [physiologically-based pharmacokinetic modelling is one of the tools to overcome the current limitations in neonatal drug development, with a proven track record in adults, and promising results in children".

A recent article suggested that "publication of the rationale with details of why juvenile animal work is being proposed by a drug company or requested by the regulators" would be useful for a fully transparent debate on the case for JAS. (Baldrick, 2013). We agree that this information should be made available to the public and we request that serious consideration is made to the conduct of a multi-national review on the true value of JAS to inform pediatric risk assessment. In the meantime, the use of JAS, especially multiple JAS studies in one or more species or those with multiple complex endpoints, should be discouraged.

Some of the literature described above should be included in the guideline, even as recommended reading, to guide and better inform industry and regulators.

The below specific comments are taken in part from ICAPPP original submission:

2. Specific Comments on text

1.4. General principles, lines 68-73 "The conduct of additional nonclinical investigations should be undertaken only when previous animal and human data are judged to be insufficient to support pediatric studies. JAS are designed to address identified safety concerns that cannot adequately be addressed in other nonclinical studies or pediatric clinical trials, including potential long-term safety effects. This guideline recommends a customized JAS that comprises core design elements and potential additional elements driven by specific concerns".

Proposed change:

The conduct of additional nonclinical investigations should be undertaken only when previous animal and human data, pharmacological data and data from pharmacokinetic modelling/simulation systems are judged to be insufficient to support pediatric studies. JAS are designed to address If identified safety concerns that cannot adequately be addressed in other nonclinical studies such as in vitro and ex vivo investigations, or in adult or pediatric clinical trials, including potential long-term safety effects then a JAS may be considered as a last resort if scientifically justified. However, it should be noted that the value of JAS has not been fully elucidated and should therefore only be considered under rare circumstances and not as a default approach. Furthermore, the propensity for mortality to occur is generally higher in juvenile animals compared to adult animals and, in accordance with the 3Rs principles, their use should be avoided as much as possible. This guideline recommends describes a customized JAS that comprises core design elements and potential additional elements driven by specific concerns.

2.4. Application and outcome of weight of evidence evaluation, lines 210-213 “When a study is warranted, the specifics of the identified safety concerns will define the objectives of the nonclinical investigation; this could be a JAS or another study (e.g., in vitro or ex vivo investigations)”.

Proposed change:

“When a study is warranted, the specifics of the identified safety concerns will define the objectives of the nonclinical investigation; this could be an in vitro or ex vivo investigation or, under rare circumstances, a JAS. or another study (e.g., in vitro or ex vivo investigations).

This should then lead into a new section that covers the design of in vitro and ex vivo studies, as suggested in our general comments above. For example, more information on the use and design of biosimulation studies should be provided e.g. physiologically-based PK models from in vitro-in silico data, which have proven to be a consistent and reliable evidence-based approach to optimise clinical trial design and inform the drug label for paediatric medicines (Marier et al. 2016, Zhao et al 2014). This section should also provide guidance on the use of other in vitro models (e.g. in vitro gastrointestinal tract models to study drug bioavailability in children) and ex vivo models (e.g. use of tumour cells and biopsies) to support paediatric drug development.

3.1. General considerations/study objectives, lines 218-221“This section contains recommendations on study design considerations, core endpoints to be included in all studies, and additional endpoints that can be included to address specific concerns. A JAS design including all potential endpoints is not recommended without rationale”.

Comment:

A recent review (described in the general comments section above) found that, of the small proportion of JAS that revealed novel toxicities, “the elucidation of the toxicities was accomplished using routine toxicological assessments and not as a consequence of performing a large complex

study with every possible endpoint monitored, as seems to be the current trend" (Bailey & Marien, 2009). The authors express their concern that "investigators are continually being requested to perform bigger and more complex studies" without any proven benefit or evidence that these more sophisticated and complex study designs actually generate any meaningful results. Other authors have also warned against "inappropriate or unnecessary studies being performed or the inclusion of parameters, which generate little or no useful information" (De Schaepdrijver et al., 2008). We therefore suggest that more effort is made to stress that the use of the described 'additional endpoints' should be limited to very rare situations only.

Proposed change:

This section contains recommendations on study design considerations, core endpoints to be included in all studies, and additional endpoints that can may, under rare circumstances, be included to address specific concerns. A JAS design including all potential endpoints by default is not recommended without rationale.

3.3. Animal test system selection, lines 263-274 Comment:

The main "factors for consideration when selecting an appropriate species" for JAS are listed here. Ethical and animal welfare considerations are missing from this list and should be added to further promote the importance of the 3Rs.

Proposed change:

Add the following bullet point to the list: 'Ethical and animal welfare considerations of conducting the study in the selected species'.

3.3. Animal test system selection, Lines 277-281 "While for biopharmaceuticals NHPs are pharmacological responders in many cases, the conduct of JAS in NHPs is challenging for both scientific and practical reasons. There is limited added value of performing JAS in younger NHP as compared to the 2-4 year old NHP used in general toxicity studies and, therefore, alternative approaches to obtaining the necessary data are encouraged. Only in rare cases is the value of JAS conducted in NHP justifiable".

Comment:

We appreciate that the use of NHPs in JAS is not recommended by the guideline. However, based on the available literature, the use of dogs and rodents in JAS is also of questionable value and should therefore be discouraged. As described above, a review study found that 85.7% of the results generated from JAS in puppies, and 75% of the results from JAS in rat pups, could have been predicted by pharmacology or adult toxicity data (Bailey & Marien, 2011). As well as being predictable, results in JAS using dogs have also been shown to be unreliable. For example, "quinolones affect the cartilage of young dogs. This resulted in broad warnings against the use of

quinolones in children. Were these warnings justified? For pediatric clinicians quinolones are important reserve antibiotics" (Rose, 2011). Due to insurmountable species differences between the development of puppies and human children, one article concluded that "the dog is unsuitable in so many ways that it is difficult to many any case for its use in juvenile studies" (Downes, 2012).

Proposed change:

While for biopharmaceuticals NHPs are pharmacological responders in many cases, the conduct of JAS in NHPs is challenging for both scientific, and practical and ethical reasons. There is limited added value of performing JAS in younger NHP as compared to the 2-4 year old NHP used in general toxicity studies and, therefore, alternative approaches to obtaining the necessary data are encouraged. Only in rare cases is the value of JAS conducted in NHP justifiable. Similarly, while dogs are often used as the second non-rodent species in general toxicology studies, there are substantial developmental differences between dogs and humans, which limits the added value of performing JAS in puppies.

3.8. Endpoints, lines 400-402 "Each JAS should include the core endpoints defined in Section 3.8.1 below, unless justified otherwise. Each additional endpoint (see Section 3.8.2) should be considered and justified to address an identified safety concern (Note 2)".

Proposed change:

Each JAS should include the core endpoints defined in Section 3.8.1 below, unless justified otherwise. In rare circumstances, Each additional endpoints (see Section 3.8.2) should may be considered and justified to address an identified safety concern. However, the inclusion of each additional endpoint must be scientifically justified, and a rationale provided for how the results are expected to add value to the risk assessment (Note 2).

4. Considerations for pediatric-first/only development, lines 616-620

In these cases, the FIH trial will be in pediatric patients and the nonclinical program, would generally include one JAS in a rodent and one JAS in a non-rodent species, if feasible. Safety pharmacology and genotoxicity testing would be conducted as appropriate for adults use; in vivo studies need not be conducted in juvenile animals.

Comment:

We do not support the current recommendation that the default approach for testing pediatric-first drug is to conduct two JAS in a rodent and a non-rodent species. According to a recent industry review on nonclinical safety considerations for the development of pediatric-first drugs, "consideration should given to conducting toxicity studies in adult rodent and nonrodent, followed by a juvenile study in the rodent only, provided this covers all concerns" and that only in certain occasions "where studies in adult animals are inappropriate for the clinical plan (e.g. in some rare disease indications)" would JAS in two species be warranted (Schmitt et al., 2016). In accordance

with the 3Rs, it would be more appropriate to recommend, conditionally, the conduct of a single JAS and limit the conduct of additional JAS to rare cases only.

Proposed change:

In these cases, the FIH trial will be in pediatric patients and the nonclinical program, may would generally include one JAS in a rodent and one JAS in a non-rodent species, if the weight of evidence raises safety concerns that cannot adequately be addressed in other nonclinical studies feasible. Only in rare circumstances, (e.g. in some rare disease indications) might a second JAS also be considered. Safety pharmacology and genotoxicity testing would be conducted as appropriate for adult use; in vivo studies need not be conducted in juvenile animals.

Table A1. Principle advantages and disadvantages of various mammalian species for use in juvenile animal studies Comment/proposed change:

"Ethical reservations" are listed as one of the disadvantages to using NHPs in JAS in this table. According to a review on the need for juvenile animal studies, "in general, the use of animals for toxicity testing and in particular of young animals is a very emotional and controversial issue in our society and testing in monkeys and dogs is even less accepted than testing in rodents" (Soellner & Oleniczak, 2013). Another review stated that "animal use (especially in puppies or young monkeys) with no clear goal for risk assessment is totally unacceptable" (Baldrick, 2010). We therefore feel that it would be appropriate to also include "ethical reservations" as a disadvantage to using all species listed in JAS.

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