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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061,
Rockville, MD 20852
USA

24 April 2003

[Docket No. 03D-0001]

Draft Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products

Dear Sirs,

The following comments are made on behalf of the Reproductive Studies Group of Huntingdon Life Sciences (HLS), UK. HLS is a Contract Research Organisation performing a wide range of toxicity studies intended for submission to regulatory agencies throughout the world. Reproductive tests are performed for all sectors of the market and recently HLS has completed five GLP-compliant juvenile toxicity studies in the rat.

In general we consider the Draft Guidance to be well written and a valuable document which will provide a firm basis for discussion with our Clients and be of great assistance in the development of appropriate study designs.

The following comments/suggestions are offered.

III. GENERAL CONSIDERATIONS FOR EVALUATION OF PHARMACEUTICALS IN JUVENILE ANIMALS

B. Timing of Juvenile Animal Studies in Relation to Clinical Testing

C. General Design Conditions for Juvenile Animal Toxicology Studies

The Guidance make reference to ICH-M3 relating to Timing of Pre-clinical Studies in Relation to Clinical Trials (Amended Guideline M3 (M) issued in the EU as CPMP/ICH/286/95, modification). ICH-M3 (M) includes a statement that a pre- and postnatal development study (i.e. ICH-S5A, design 4.1.2) should be submitted for market approval, or earlier if there is cause for concern. Separately, it notes that all reproduction toxicity studies should be available prior to the initiation of trials in pediatric populations.

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The conventional pre- and postnatal study does not include direct treatment of the offspring, although these may have been subjected to indirect exposure to the test material and/or its metabolite(s) via the mother from implantation through to weaning (ICH stages C – E). Latent effects or long-term significance of earlier disturbance of development are tracked through ICH stage F. Later in the Guidance document (Section IVA (Types of Studies), there is a comment suggesting that if a standard ICH study pre- and postnatal development study were to be modified in a way that would ensure adequate exposure of the pups, this might preclude the need for a separate juvenile toxicity study. Is this a correct interpretation?

Currently, stand-alone juvenile toxicity studies effectively fill the data gap between ICH-S5 studies and repeat-dose toxicity studies in the adult population. In view of the potential saving of animals that could be made by combining a pre- and postnatal and juvenile toxicity designs, it would be useful if the proposed Guidance could include a more specific comment on the use and relevance of the pre- and postnatal development study in relation to timing, conduct and design of juvenile toxicity studies.

IV. GENERAL CONSIDERATIONS IN DESIGNING TOXICITY STUDIES IN JUVENILE ANIMALS

B. Animals

3. Sex and Sample Size

The document currently states that 'An adequate number of animals should be used to clearly demonstrate the presence or absence of effects of the test substance.'

Juvenile toxicity studies are widely regarded as being akin to repeat-dose toxicity studies that are frame-shifted to a younger population. Parallel guidance notes within the EU on Repeated Dose Toxicity studies (CPMP/SWP/1042/99) are phrased in the same way (i.e. 'The size of the treatment groups should be sufficient to allow meaningful scientific interpretation of the data generated ... '). With this in mind, general toxicity studies of up to 90 days duration are commonly conducted with a basic group size of 10 males and 10 females.

Guidelines for reproductive studies (ICH-S5A) are a little more specific, suggesting evaluation of between 16 to 20 litters for rodents. In our laboratory, the target group size for evaluation of postnatal development and function is 20.

In situations where the pharmacological activity of the drug is directed at the central nervous system, there would be primary concerns for possible effects on the developing nervous system with probable inclusion of a number of neurobehavioural tests such as auditory startle, motor activity, neuromuscular co-ordination and complex learning and memory investigations. The results of such behavioural tests can show

more inter-animal variability than more traditional endpoints of toxicity and, ideally, the group size needs to take this into account in order to discriminate between true effects of treatment and false positive data.

Because of significant differences in the objectives and number of endpoints being assessed in juvenile toxicity studies compared with more 'conventional' repeat-dose toxicity studies it would be very useful if the agency could indicate a ball-park figure for target group size. This would avoid:

- Inadequate numbers being allocated that could compromise assessments, particularly where the significance of relatively small differences need to be evaluated.
- Design of over-elaborate studies that could be criticised for excessive use of animals.

Typically, we have been designing juvenile toxicity studies in the rat around 20 litter-units, where each litter contributes a male and a female pup to each group; we feel this allows a robust group size with offspring of known parentage and optimum use of animals.

C. Exposure

2. Frequency and Duration of Exposure

Paragraph 2 mentions that treatment-free periods to assess reversibility of possible adverse effects should also be considered. 'Reversibility' and 'recovery' phases are frequently included in repeat-dose toxicity studies. In these studies the animals (particularly rodents) are usually considered to be adults at the start of the treatment so it is possible to assess change from a stable baseline and return to this baseline. With juveniles undergoing continuing development and maturation it may be more appropriate to refer to a treatment-free period as giving an opportunity to assess any long term consequence of changes noted during the treatment phase.

3. Dose selection

From considerations of animal welfare, the term 'frank toxicity' should be avoided. This phrase is open to misinterpretation and could imply marked debilitation and even death as an acceptable level of effect. A more qualified comment such as 'should be chosen to with the aim to induce some systemic/target organ toxicity but not death or severe suffering'

D. Toxicological End Points and Timing of Monitoring

Paragraph 1. Measurement of growth : although not impossible, reliable (reproducible) measurement of crown-rump length and particularly of tibia length is difficult when dealing with large numbers of animals and serial recording. In-life, accurate, measurement of crown-rump length becomes increasingly difficult as the pups mature and become more mobile. Measurement of tibia length is not routinely recorded in any toxicity studies that we are aware of and we would be interested to know how other laboratories react to this proposal.

Paragraph 2. 'It can be helpful to determine the relationship between toxicologic end points and drug exposure (e.g., predosing, immediate postdosing, time of peak plasma concentration).'

It is not clear which toxicological end points this comment refers to. Would it be correct to assume that this relates to the previous examples of developmental neurotoxicity assessments rather than to measurement of parameters such as haematology and clinical chemistry? Determination of peak plasma concentration would certainly imply that the main investigation is preceded by collection of toxicokinetic (TK) data in the young animal since it is acknowledged that the TK profile may not be the same as the adult and, therefore, reliable extrapolation from adult data may be misleading.

If we have correctly interpreted the intention of paragraph 2, there are implications for behaviour tests that are focused on assessment of learning and memory. Sophisticated test methods, such as the Morris maze, are best used in a single situation for assessment of short-term memory. Longer-term recall can be investigated if the same animals are re-tested several weeks later. Developmental neurotoxicity guidelines, such as those of the EPA OPPTS 870.6300, recommend that tests of learning and memory are not repeated in the same animals at different timepoints (e.g. at around weaning and 60 of age). Applying the same criteria to testing regimes related to different times pre- and post dosing would generally require group sizes large enough to subset and still allow reliable interpretation of the data without undue influence of inter-animal variability. It would be useful if this point could be clarified.

Additional comments

The Guidance document makes no specific reference to the potential for monitoring the treated (or previously treated) animals for attainment of sexual maturation (vaginal opening, balano-preputial separation) or confirmation of establishment of normal estrous regularity (where appropriate).

The notes quite correctly make the point that the toxic effects of drugs on postnatal development are believed quite likely to occur in those organs and tissues that undergo significant postnatal development. The reproductive system is included in the list of

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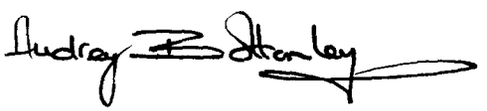
Life Sciences

candidate organs but no reference is made to consideration of extending the study design to assess reproductive function and fertility by inclusion of a mating trial.

We hope these comments are of use in the finalisation process of this document.

Yours sincerely



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