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Food and Drug Administration
5630 Fishers Lane, rm 1061,
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USA

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Draft Guidance for Industry on Nonclinical Safety Evaluation of Pediatric Drug Products

Dear Sirs,

The following comments are made on behalf of the Reproductive Toxicologys Group of Covance Laboratories, UK. Covance 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 Covance has completed GLP-compliant juvenile toxicity studies in the rat and dog; facilities are also available to conduct juvenile toxicity studies in non-human primates.

We welcome the Draft Guidance document. It is well written and will provide a firm basis for discussions concerning the design and conduct of juvenile animal studies.

The following comments/suggestions are offered.

Utility of studies in juvenile animals

In section IIB there are strong directives towards conducting juvenile animal studies - "Standard toxicology studies using adult animals, or safety information from adult humans, cannot adequately predict effects in immature systems" and "There is evidence that studies in juvenile animals can be useful in the prediction of age related toxicity in children". This point is supported in Section IIIB.1, concerning long term exposure in pediatric subjects, with "Where pediatric clinical studies involve long-term exposure, juvenile animal studies should be conducted before initiation of the long-term clinical studies". These directives are very welcome and provide a clear basis for proceeding to clinical trials. It is therefore rather disappointing in Section IIIB.2, with reference to shorter-term studies, to see "Where pediatric studies do not involve long-term exposure, it is not necessary to complete juvenile animal studies before initiation of pediatric clinical trials". We feel that some juvenile studies, as a minimum an evaluation of exposure, should be conducted before

initiation of the clinical trials. This view seems to be supported in the final sentence of section IIB.2 with "it may be more efficient to complete juvenile animal studies early so that clinical studies can be designed to evaluate potential long-term hazards".

Issues to Consider Regarding Juvenile Animal Studies

In Section IIID.2 there is an indication to evaluate studies from the package normally used to support adult human clinical trials to judge the necessity for conducting juvenile animal studies. In the standard package of reproduction studies the only postnatal exposure of pre-weaning rat offspring occurs in the pre- and postnatal study (ICH-S5A, design 4.1.2). In this study offspring are only exposed via the mothers milk and in many cases the test article has undergone metabolism or other changes before reaching the offspring. Furthermore, there is no assessment of local effects (e.g. respiratory tract) with exposure by this route. Currently few pre- and postnatal studies are routinely conducted where there is a quantitative evaluation of offspring exposure. Accordingly the information from the standard package of toxicology studies will generally be limited when assessing the design of pediatric clinical studies.

Sex and sample size

In section IIB.3 we feel it would be useful to address the influence of the litter as well as the individual offspring in judging the number of animals to be routinely used in each group. For studies in which a composite litter design is used (ie all animals from the same litter receiving the same dose) there is a requirement to have larger overall group sizes (usually 20 in these laboratories) to provide a sufficient litter contribution (normally 4 per sex from 5 litters in each dose group). Where a split litter design is used (ie different dose levels within each litter) fewer animals in each group could be used (eg 1 per sex from 10 litters in each dose group). To use this distribution with a composite litter design would waste many offspring and would be a welfare issue in the UK.

Frequency and duration of exposure

Although the guidelines states that the "timing of the intended use of the drug be considered as it relates to periods of rapid postnatal growth and development", dosing strategy in the UK is often to cover as much of the development of the animal as possible, i.e. dosing is from as early postnatally as possible, to sexual maturity. This strategy then allows the drug to be prescribed for any period of pediatric development.

For studies in dogs the guideline recommends that these studies are started "earlier than is the usual practice", UK practice is often to start treatment in animals that are as young as is practically possible to allow the maximum flexibility in prescribing.

The guidance document provides a clear position in treating throughout significant periods of relevant postnatal development for the selected species. Where there is evidence of potential effects on the development of the brain or reproductive system this can readily be accommodated in rodent

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studies with treatment to adulthood (probably a 13 week study). However, this is less easy to conduct in studies with dogs and non-human primates where there is a long period from birth to adulthood. This consideration needs to be borne in mind when selecting the test species.

Regarding the frequency of administration, issues may arise in relation to multiple dosing due to large volumes of gavage dose decreasing the ability of the rodent pup to feed, so twice daily dosing would be maximum preferred in young rodents.

Dose selection

In section IVC .3, Dose selection, there is reference to "frank toxicity". In the UK we are governed by the Animals Scientific Procedures Act 1986 and we normally conduct juvenile animal studies under a "mild" category on the project licence. This allows only minimal overt toxicity in terms of changes in body weight and clinical signs. Assuming "frank" toxicity to be moderate or severe, to conduct studies with this expectation would present ethical and welfare issues in the UK.

We feel that with good exposure data, dose levels for juvenile animal studies can be selected without the need for overt toxicity thereby allowing comparison with adult no adverse effect dose levels and a judgement of relative potency. By selecting dose levels that are expected to produce moderate or marked toxicity the risk of high mortality by direct effects or by maternal intervention of a compromised offspring is significantly increased.

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

Yours sincerely

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