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GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS OF PHARMACEUTICALS FOR PAEDIATRIC INDICATIONS

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GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS OF PHARMACEUTICALS FOR PAEDIATRIC INDICATIONS

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EXECUTIVE SUMMARY

The main aim of non-clinical studies to support the development of medicinal products to be used in paediatric patients is to obtain information on the potentially different safety profiles from those seen in adults. Juvenile animal studies can be used to investigate findings that cannot be adequately, ethically, and safely assessed in paediatric clinical trials. Serious adverse reactions that may be irreversible are of particular concern. The design of non-clinical studies in juvenile animals will vary depending on the findings observed in adult human studies and previous animal studies. Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted if there is a need to further address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors. The guideline also makes recommendations on the timing and utility of juvenile animal studies in relation to phases of clinical development.

1. INTRODUCTION

Most medicinal products currently used in paediatric patients have not been formally developed for use in this age group. In most cases, an extrapolation from the clinical experience in adults was used to support the paediatric use.

Approval of medicinal products intended for paediatric patients requires a special risk/benefit assessment, where the possible effects of the product on the ongoing developmental processes in the age group(s) to be treated are also taken into consideration. This risk/benefit assessment should be based on safety and pharmacokinetic data from non-clinical and clinical studies. In some instances, additional studies in juvenile animals will be required to allow such an assessment. There are several examples of medicinal products that have different safety profiles in adult compared with paediatric patients. Such differences might be qualitative and/or quantitative, immediate and/or delayed. They might be caused by pharmacokinetic/dynamic differences, developmental differences in growth and function of target organs or expression of receptor systems, immune system maturation, body weight etc.

Standard non-clinical studies using adult animals, or safety information from adult humans, cannot always adequately predict these differences in safety profiles for all paediatric age groups, especially effects on immature systems such as the developing brain, the pulmonary system, the kidneys, the reproductive system, the immune system, the skeletal system and the organs or tissues which play a role in the pharmacokinetics of a medicinal product.

2. SCOPE

This document provides guidance on the need for, role and timing of studies in juvenile animals in the non-clinical safety evaluation of medicinal products for paediatric use. This guideline is applicable to initial medicinal products applications and also to authorised medicinal products being further developed to include paediatric indications.

This guideline outlines potential safety concerns that cannot be adequately assessed in the adult population, in standard non-clinical studies, or in clinical trials.

3. LEGAL BASIS

This document should be read in conjunction with Directive 2001/83/EC (as amended), Regulation (EC) No 1901/2006 on medicinal products for paediatric use, and all relevant CHMP and ICH Guidelines.

4. MAIN GUIDELINE TEXT

4.1. General Consideration

In general, a medicinal product can be studied in the paediatric population when adequate pharmacokinetic, pharmacodynamic, and clinical efficacy and safety data are available in adults. This also implies, in most cases, the availability of a standard non-clinical data package. At a minimum, results from the core safety pharmacology package, appropriate repeat dose toxicity studies, the standard battery of genotoxicity tests and relevant parts of the reproductive toxicity test programme should be available prior to the commencement of studies in a paediatric population. The data package should be justified, based on the characteristics of the clinical study and the intended paediatric population including age group(s). The need for juvenile animal studies should be taken into consideration.

The conduct of studies in juvenile animals should be considered when human safety data and previous animal studies are considered insufficient for a safety evaluation in the intended paediatric age group. Situations which would justify toxicity studies in juvenile animals include, but are not limited to, findings in non-clinical studies that indicate target organ or systemic toxicity relevant for developing systems, possible effects on growth and/or development in the intended age group or if a pharmacological effect of the test compound will affect developing organ(s). If substantial differences between the adult and young populations with respect to pharmacokinetic characteristics of the active substance are indicated, studies in juvenile animals might in certain cases be warranted. It will depend on the overall dataset including target organs and margins of exposure between animal and human, as well as the magnitude of exposure difference between the adult and the paediatric population at clinically relevant doses. Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted if there is a need to further address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors.

In addition, potential differences between the mature and immature systems for the potential target organs identified should be taken into account, including whether the end-points investigated are similar and/or relevant for the intended paediatric population. Furthermore, effects related to delayed or altered development, which may be evident even after treatment termination, should be taken into consideration.

The predictability of the nonclinical and clinical study results in adults for the paediatric population will be the key issue for the decision on whether studies in juvenile animals are needed prior to the inclusion of paediatric participants into clinical trials. The level of the predictability of data from adults for the paediatric population is age dependent. Predictability is generally low for preterm babies, newborns and infants, and increases with increasing age, being highest for adolescents.

Consideration should be given to any novel aspects of the intended paediatric formulation and whether additional safety data are required to support the specific formulation.

In conclusion, studies in juvenile animals should be performed on a case-by-case basis and only after a careful consideration of the available data and the age and duration of treatment of the intended paediatric population. The Applicant should justify its decision for non-clinical studies to support use in paediatric populations, taking these aspects into account.

4.2. Key Elements for the Need for Juvenile Animal Studies

Major functional differences exist between human neonates/infants and adults. These differences may have an impact on the pharmacodynamic effect induced by the active substance. The potential for exaggerated pharmacological effects as well as toxicity not primarily driven by such effects should be

taken into account. It should also be noted that the development of certain functions related to the pharmacokinetic handling of an active substance may take up to several years.
The development of the major systems is age dependent, *e.g.*:

- Nervous system: Development up to adulthood
- Reproductive system: Development up to adulthood
- Pulmonary system: Development up to two years old
- Immune system: Development up to 12 years old
- Renal system: Development up to one year of age
- Skeletal system: Development up to adulthood
- Organs and / or systems involved in absorption and metabolism of drugs. Development of biotransformation enzymes up to adolescence

It should be noted that the age ranges given above only apply to general development and not applicable to all endpoints related to that organ system. This should be taken into account in the design of the program and the individual studies.

If any of the major functional systems are shown to be potential targets, either from human or from nonclinical studies, studies in juvenile animals should be considered, on a case by case basis.

The following points should be considered when assessing the need for and design of juvenile animal studies. It should be noted that this is not an exhaustive list and the points are not ranked in order of importance.

Clinical Aspects

- Medicinal product for diseases predominantly or exclusively affecting paediatric patients
- Duration of paediatric treatment
- Age of paediatric population
- Primary pharmacodynamics in target organs/tissues with significant postnatal development
- Extent of safety data in adults and/or the paediatric population in relevant age groups
- Results from paediatric treatment with a medicinal product of similar chemical structure and/or of the same pharmacological class
- Medicinal product intended to treat serious or life-threatening diseases
- Relevant pharmacokinetic (ADME) data

Nonclinical Aspects

- Extent of relevant data from existing animal studies
- Adverse and/or irreversible reaction observed
- Target organs/tissues identified
- Mechanism of action
- Ratio between exposure resulting in the non-clinical effect and the human adult exposure, low or high
- Pharmacokinetic data show exposure of organs with significant postnatal development, relevant for the intended age group.
- Data from pre- and postnatal toxicity studies, in light of the extent of pup exposure relative to the expected therapeutic concentrations.
- Juvenile animal data from a medicinal product of similar chemical structure and/or of the same pharmacological class

Pre- and Postnatal Reproduction Studies

Before performing a juvenile animal toxicity study, it should be considered whether a developmental toxicity issue could be addressed in a modified pre- and postnatal development study in rats. Key factors that need to be examined include, but are not restricted to, the amount of the active substance and/or relevant metabolites excreted *via* the milk and the resulting plasma exposure of the pups, which organs under development that will be exposed during the pre-weaning period, physical development and histopathological investigations.

When a pre- and postnatal study is also being used to address a specific aspect of juvenile toxicity, such a study should be extended to include appropriate developmental endpoints. The number of animals should be sufficient to draw scientifically sound conclusions, but a higher number of animals than necessary should be avoided.

If specific developmental endpoints cannot be assessed within the context of pre- and postnatal studies, additional juvenile animal studies will be required.

4.3. Study design

4.3.1. Age and Duration

The age of the animals at the initiation of the dosing period and the duration of dosing will depend on the developing organ system(s) that are likely to be affected by the medicinal product, taking the age and the duration of exposure of the intended paediatric population into consideration.

When adverse reactions are expected on systems with a long development period, *e.g.* brain development, bone growth, immune function *etc*, animals should be treated up to reaching adulthood (approximately up to 13 weeks in rats and 9 months in Beagle dogs). The decision on study duration should be scientifically justified.

When adverse reactions are expected only in an organ system with a relatively short critical period of development (*e.g.* kidneys, lungs), then the dosing period might be confined to that particular period of development.

If warranted, certain maturation endpoints may be necessary to investigate when the animal reaches adulthood, even when the treatment duration is limited to a younger age range.

4.3.2. Route of Administration

Ideally, the intended human route of administration should be used, unless studies in adult animals have indicated that an alternative route is more relevant to the human situation. It is recognised that practical difficulties may occur for certain routes of administration when using juvenile animals. The selected route of administration should be justified, based on the intended objectives of the study as well as feasibility. Potential differences in exposure and distribution due to the chosen route should be acknowledged.

4.3.3. Selection of Species

The juvenile animal species should be appropriate for evaluating toxicity in endpoints relevant for the intended paediatric population. With respect to repeat dose toxicity studies, rats and dogs are traditionally the species of first choice. However, other species might be more appropriate in some instances. Factors that need to be considered when choosing the appropriate species include the pharmacodynamic, pharmacokinetic and toxicological properties of the medicinal product, comparative developmental status of organs of concern, species sensitivity and the feasibility of conducting the study.

Testing of juvenile toxicity in one appropriate species using both sexes will normally be sufficient.

4.3.4. Pharmacokinetics and Toxicokinetics

Pharmacokinetic data (including in vitro data, if relevant) contributes to the evaluation of the relevance of the animal model for human risk assessment. It is recognised that the collection of blood samples to obtain a full kinetic profile of a test compound under study in juvenile animals might sometimes be difficult. However, sampling at a few time points, using pooled samples if necessary, should be performed to obtain an estimate of basic kinetic characteristics, e.g. Cmax and AUC. Inclusion of satellite groups of dosed animals, e.g. excess offspring from a pre-postnatal study, for blood sampling may be considered. The use of methodology allowing population pharmacokinetic/toxicokinetic determinations may also be considered.

Toxicokinetics should also be considered to confirm appropriate exposure levels in different treatment groups.

Under special circumstances, data on absorption, distribution, metabolism and/or excretion in juvenile animals may be valuable to further investigate and e.g. understand a specific safety concern.

4.3.5. Dose selection

The primary purpose of juvenile animal studies is to assess whether juvenile animals have a different sensitivity to a medicinal product compared with adult animals, and to identify effects on developing organs.

It is recommended that doses in the lower part of the dose response curve established in adult animals are selected. To bridge to the existing adult animal data, a common dose, preferably resulting to similar systemic exposure, and preferably in the low dose range (NOAEL or NOEL), should generally be included in the juvenile animal studies.

The high dose should achieve some identifiable toxicity, but not result in marked toxicity which may complicate the assessment. The low dose should preferably result in exposure levels similar to the anticipated clinical exposure in the intended population. An intermediate dose level might not be necessary in juvenile animal studies if the differences between the low and high doses are relatively small.

In the absence of a NOAEL in the general toxicology studies, a dose range finding study in juvenile animals is advocated together with toxicokinetic evaluations to support dose selection.

4.3.6. Endpoints

The selection of endpoints to be monitored in a juvenile animal study is critical for assessing the reactions of a medicinal product on development and growth. Studies may be designed to determine the medicinal product's effects on growth and development overall, or on selected organ systems (e.g., skeletal, renal, lung, neurological, immunologic and reproductive systems). When addressing overall effects on growth and development, studies should include, at a minimum, measurement of growth, external indices of sexual maturation, body weight, physical signs, organ weights, and gross and microscopic examinations. In selected cases, endpoints of pharmacological activity in juvenile animals may be justified.

Clinical laboratory investigations (e.g. clinical chemistry, haematology etc.) can also be useful, but they may be limited by the technical feasibility of obtaining adequate samples for analysis, particularly in the case of juvenile rodents.

Should histopathological effects occur in male and/or female reproductive organs, then the functional consequence of this finding should be investigated.

Juvenile animal studies often include dosing over the greater proportion of the species' postnatal development, and when effects are identified, additional studies may be useful to test the possibility whether the toxicity occurs with more acute, shorter, treatment, when clinically relevant.

The use of in vitro models using juvenile animal tissue or specific disease models in juvenile animals could also be considered to study target organ toxicity.

The inclusion of satellite groups of animals to study the reversibility or long-term consequences of potential adverse reactions should be considered.

Neurotoxicity Assessment

Neurotoxicity studies are only required if the chemical/pharmacological class of compounds or previous studies in humans or animals gives cause for concern for the developing nervous system or influences for neuroendocrine system balance.

For developmental neurotoxicity assessments, where possible validated methods should be used to monitor key functional domains of the central nervous system, including, but not restricted to, assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, social behaviour and learning and memory.

Immunotoxicity Assessment

Immunotoxicity studies are only required if the chemical/pharmacological class of compounds or previous studies in humans or animals gives cause for concern for the developing immune system.

A study should be based on immune assays as described in the Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals (ICH Topic S8).

Nephrotoxicity Assessment

Nephrotoxicity studies are only required if the chemical/pharmacological class of compounds or previous studies in humans or animals gives cause for concern for the developing renal system. For developmental nephrotoxicity assessments, where possible, validated methods should be used to monitor key functional parameters in the urine of a relevant species.

4.4. Timing of Toxicological Studies in Relation to Clinical Development

As stated in the Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (CPMP/ICH/286/95, ICH M3), when paediatric patients are included in clinical trials, safety data from previous adult human exposure would usually represent the most relevant information and should generally be available before paediatric clinical trials. However, on a case-by-case basis, the extent of adult human data to support paediatric indications may be less extensive.

The need for and timing of juvenile animal in support of undertaking clinical studies should be justified. If such studies are considered necessary, they should preferably be available before the initiation of clinical studies in paediatric populations. Pharmacokinetic data from humans and animals (including juvenile animals if available) should also be evaluated before the proposed paediatric clinical trial(s).

Medicinal products under development for specific paediatric indications or in life-threatening or serious diseases without current effective therapies warrant a case-by-case approach. In some cases, some studies may then be adapted, deferred or omitted.

5. REFERENCES

- Note for Guidance on Non-clinical Safety Studies for the Conduct of Human Clinical Trials for pharmaceuticals. (CPMP/ICH/286/95, ICH Topic M3)

- Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population. (CPMP/ICH/2711/99, ICH Topic E11)

- Notes for Guidance on Reproductive Toxicology: Detection of toxicity to reproduction for medicinal products. (e.g. CPMP/SWP/389/95, ICH Topic S5A and CPMP/ICH/136/95, ICH Topic S5B)

- Note for Guidance on Immunotoxicity Studies for Human Pharmaceuticals (CHMP/167235/2004, ICH Topic S8).

- Guideline on the Investigation of Medicinal Products in the term and preterm neonate (EMEA/267484/2007 - released for public consultation until the 15 May 2008).