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DRAFT

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

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GUIDELINE ON THE NEED FOR NON-CLINICAL TESTING IN JUVENILE ANIMALS ON HUMAN 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 potential 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 in order to address a specific concern or to study reversibility or possible aggravation of the expected findings, as well as to establish safety factors. The guidance 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 properly developed for the 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 developmental processes ongoing 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 have been several examples of medicinal products that have different safety profiles in adults compared with paediatric patients. Such differences might be qualitative and/or quantitative, immediate and/or delayed. They might be caused by pharmacokinetic/dynamic differences as well as developmental differences in growth and function of target organs and 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 reaction on immature systems such as the developing brain, the pulmonary system, the kidneys, the reproductive and the immune systems.

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) and all relevant CHMP 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, available results from appropriate repeat dose toxicity studies, the standard battery of genotoxicity

tests and a full reproductive toxicity test programme should be available prior to the commencement of trials in a paediatric population.

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). Even if adverse reactions on developing organ(s) can be predicted from adult human or animal data, studies in juvenile animals might be warranted in order to 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 the consideration whether the end-points investigated are similar and/or relevant for the intended paediatric population.

Studies in juvenile animals will usually not be needed for compounds with a well-known use, especially one that has been used for other indications in the paediatric population.

The predictability for the paediatric population, based on clinical and nonclinical study results in adults, will be the key issue for the decision on whether studies in juvenile animals are needed prior to the inclusion of paediatric participants onto clinical trials. This predictability could be high, *e.g.* in children 2 to 11 years, or low, *e.g.* in preterm newborns and infants up to 2 years old.

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.

4.2 Key Elements for the Need for Juvenile Animal Studies

Major functional differences exist between human neonates/infants and adults. 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

It should be appreciated 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.

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
- Medicinal product intended to treat serious or life-threatening diseases
- Duration of paediatric treatment
- Age of paediatric population

- Results from paediatric treatment with a medicinal product of similar chemical structure and/or of the same pharmacological class
- Primary pharmacodynamic target organs/tissues
- Adult human data
- Adverse reactions data
- Relevant pharmacokinetic (ADME) data

Nonclinical Aspects

- Relevant data from existing animal studies
- Adverse and/or irreversible reaction observed
- Target organs/tissues identified
- Mechanism of action
- Pharmacokinetic data show exposure of organs with significant postnatal development
- Pre- and postnatal toxicity studies show sufficient exposure of the pre-weaning animals
- Pre- and postnatal toxicity studies show severe reactions in offspring
- Safety margins of nonclinical effect in relation to human adult exposure, low or high
- Juvenile animal data from a medicinal product of similar chemical structure and/or of the same pharmacological class

4.3 Study design

4.3.1 Duration

The duration of the dosing period in juvenile animal studies, and the age of the animals at the initiation of dosing, will depend on the developing organ system(s) that are likely to be affected by the medicinal product, taking the age 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 investigated up to reaching adulthood (approximately up to 13 weeks in rats and 9 months in Beagle dogs).

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

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 human use. It is recognised that practical difficulties may occur for certain routes of administration when using juvenile animals. However, the primary purpose of these studies is to identify potential safety concerns relevant to paediatric use and as such, small differences in exposure and distribution due to route may be of little significance.

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 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

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 impractical. 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.* C_{max} and AUC. The use of methodology allowing population pharmacokinetic 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 for studying a specific safety concern. Such detailed data will only be necessary if (based on *in vitro* data, scientific rationale *etc*) it is anticipated that the pharmacokinetic and toxicokinetic characteristics of the juvenile animal model (s) are comparable to the human situation at the stage of development so that the data can be used in efficacy and/or safety evaluation.

4.3.5 Dose selection

The primary purpose of juvenile animal studies is to assess whether young animals are more sensitive to a reaction of a medicinal product than adult animals, and to identify reactions on developing organs. Therefore, the high dose should be selected such that frank toxicity does not occur and it is recommended that doses in the lower part of the dose response curve established in adult animals are selected. 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.

Moreover, in order to bridge the juvenile animal data to the existing adult animal data, a common dose, preferably in the low dose range (NOAEL or NOEL), should generally be included in the juvenile animal studies.

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 should be designed to determine medicinal product reactions on the overall growth of the organ systems that develop postnatally (*e.g.*, skeletal, renal, lung, neurological, immunologic and reproductive systems). Studies should include, at a minimum, measurement of growth (*e.g.*, serial measurements of crown-rump length, tibia length, growth velocity per unit time, or other appropriate indices), external indices of sexual maturation, body weight, physical signs, organ weights, and gross and microscopic examinations.

Clinical pathology determinations 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.

To differentiate long-term effects on developmental organs from acute effects, it might be appropriate to measure certain endpoints immediately before the first administration of the medicinal product.

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.

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 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.

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

Neurotoxicity Assessment

Neurotoxicity studies are only required if the chemical/pharmacological class of compound 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, and learning and memory.

Immunotoxicity Assessment

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

Pre- and postnatal exposure can potentially result in all types of immunotoxicity in the offspring, *e.g.* immune suppression, hypersensitivity, allergy and autoimmune disease.

A study should be based on immune assays already validated, but the experimental design should be flexible. Histopathology should be included as well as functional assays such as T-cell dependent antibody response, host resistance assay and cell-mediated immune assay.

Nephrotoxicity Assessment

Nephrotoxicity studies are only required if the chemical/pharmacological class of compound 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.

Studies in juvenile animal, if considered necessary, should be available before the initiation of trials in paediatric populations. Pharmacokinetic data 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, Topic M3);

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

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