Guidance for Industry

Nonclinical Safety Evaluation of Pediatric Drug Products

DRAFT GUIDANCE

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Guidance for Industry[1]

Nonclinical Safety Evaluation of Pediatric Drugs

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I.   INTRODUCTION

This document provides guidance on the nonclinical safety evaluation of therapeutics intended for pediatric patients. Some conditions under which juvenile (young) animals are considered meaningful predictors of toxicity in pediatric patients are discussed, and recommendations on nonclinical testing are provided.

A.   Objective

The purpose of this document is to provide guidance on the role and timing of animal studies in the safety evaluation of therapeutics[2] intended for the treatment of pediatric patients. It is intended to serve as a resource for general considerations in testing and to provide recommendations based on the available science and pragmatic considerations. The scope of this document is limited to safety effects that cannot be adequately, ethically, and safely assessed in pediatric clinical trials. Serious adverse effects that are irreversible are of particular concern. The guidance also makes recommendations on the timing and utility of juvenile animal studies in relation to phases of clinical development.

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[1] This draft document was prepared by the Pediatric Subcommittee to the Pharmacology and Toxicology Coordinating Committee within the Center for Drug Evaluation and Research (CDER).

[2] This guidance has been prepared by the Office of New Drugs (OND) in CDER at the FDA. It does not apply to pediatric biological products regulated by the Center for Biologics Evaluation and Research (CBER). For information on products regulated by CBER, consult the International Conference on Harmonisation (ICH) Guidance S6 *Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals* or contact the appropriate CBER office. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

B. Background

Many therapeutics marketed in the United States and used in pediatric patients lack adequate information in the labeling for use in that population. Surveys conducted by the American Academy of Pediatrics showed that the majority of the drugs listed in the *Physicians' Desk Reference* lack information on safety and/or efficacy for pediatric use (Committee on Drugs, American Academy of Pediatrics, 1995).

In most cases to date, safety data from clinical studies in adults, supported by nonclinical studies in adult animals, have been used to support the use of a drug in pediatric patients. However, it is clear that these studies may not always assess possible drug effects on developmental processes specific to pediatric age groups. Some effects also may be difficult to detect in clinical trials or during routine postmarketing surveillance.

II. GENERAL CONSIDERATIONS REGARDING THE IMPORTANCE OF STUDIES IN JUVENILE ANIMALS

This section discusses considerations such as postnatal development and the utility of studies conducted using juvenile animals.

A. Differences in Drug Safety Profiles Between Mature and Immature Systems

Some therapeutics used in pediatric patients have shown different safety profiles when used in adult patients. Inherent differences between mature and immature systems introduce the possibility of drug toxicity or resistance to toxicity in immature systems that are not observed in mature systems. Several factors can contribute to these potential differences. For example, postnatal growth and development can affect drug disposition and action. This effect could cause developmental changes in processes such as metabolism (including the maturation rate of Phase I and II enzyme activities), body composition (i.e., water and lipid partitions), receptor expression and function, growth rate, and organ functional capacity. Conversely, developmental processes are susceptible to modification or disruption by drugs.

There have been several examples of drugs that exhibit differences in toxicity between adult and pediatric patients. These include, but are not limited to, acetaminophen, valproic acid, chloramphenicol, inhaled corticosteroids, aspirin, and lamotrigine. Acute acetaminophen toxicity is a classic example of how maturation can affect the toxicity profile of a drug. Young children are far less susceptible to acute acetaminophen toxicity than adults because children possess a higher rate of glutathione turnover and more active sulfation. Thus, children have a greater capacity to metabolize and detoxify an overdose of acetaminophen when compared to adults (Insel 1996). In contrast, young children treated with valproic acid appear disproportionately vulnerable to fatal hepatotoxicity (Dreifuss et al., 1987). Chloramphenicol is associated with mortality in newborns because of their increased exposure due to a longer half-life ($t_{1/2}$ = 26 h) compared to adults ($t_{1/2}$ = 4 h) (Kapusnik-Uner, et. al., 1996). Inhaled corticosteroids have been found to decrease growth velocity in children, an irrelevant end point in adults (FDA 1998). Aspirin should not be used to treat children with influenza or varicella infections because of their increased risk of developing Reye's syndrome, a complication not

seen in adults (Belay et al., 1999). Children are at greater risk for developing hypersensitivity-type reactions, including Stevens-Johnson syndrome, when treated with lamotrigine (Guberman et al., 1999). While some age-dependent effects can be largely predicted by knowledge of the changes in drug metabolic pathways during development, others cannot be predicted.

B. The Utility of Studies in Juvenile Animals

Given that differences exist between adults and children that might affect drug safety, the Agency recognizes the importance of animal data that can be used to assess potential drug toxicity in the children. Standard toxicology studies using adult animals, or safety information from adult humans, cannot adequately predict drug effects in immature systems. However, these data can provide useful information regarding study design and dose selection for further study in children or juvenile animals. The structural and functional characteristics of many organ systems differ significantly between children and adults as a result of the growth and development that take place during maturation. Examples of these organ systems include (1) the brain, where neural development continues through adolescence (Rice and Barone 2000); (2) the kidneys, where adult levels of function are first reached at approximately 1 year of age (Radde 1985); (3) the lungs, where most alveolar maturation occurs in the first 2 years of life (Burri 1997); (4) the immune system, where adult levels of immunoglobulin G (IgG) and immunoglobulin A (IgA) antibody responses are not achieved until about 5 and 12 years of age, respectively (Miyawaki et al., 1981); and (5) the reproductive system, where maturation is not completed until adolescence. It is thought that pediatric organ systems at highest risk for drug toxicity are those that undergo significant postnatal development.   Thus, postnatal developmental toxicity is a primary concern. However, nonclinical developmental toxicity studies have traditionally focused on prenatal development, with only limited assessment of postnatal effects. Because some juvenile animals (e.g., rodents, rabbits, dogs, nonhuman primates) in general exhibit developmental characteristics similar to those of pediatric patients, these animals are considered appropriate models for assessing drug effects in the pediatric population.

There is evidence that studies in juvenile animals can be useful in the prediction of age-related toxicity in children. Following are examples of such studies: (1) the effects of phenobarbital on cognitive performance in children were predicted by experimental studies that examined the effects of this drug on the developing rodent nervous system (Farwell et al., 1990; Fonseca et al., 1976; Diaz et al., 1977); (2) the vulnerability of human neonates to hexachlorophene neurotoxicity was modeled in developing rats and monkeys (Towfighi 1980); (3) the increased susceptibility of infants to verapamil-induced cardiovascular complications would be expected based on animal studies that demonstrated a greater sensitivity of the immature heart to calcium channel blockade (Skovranek et al., 1986; Boucek et al., 1984); and (4) an increased risk of convulsions in young children treated with theophylline would be predicted by studies of the proconvulsant effects of this agent in developing rodents (Mares et al., 1994; Yokoyama et al., 1997).

Other examples of drug-induced, postnatal developmental toxicity in animals include (1) neurobehavioral impairment in adult rats following early postnatal exposure to methamphetamine (Vorhees et al., 1994), (2) the effects of methylphenidate on growth and

endocrine function in young rats (Greeley and Kizer, 1980; Pizzi et al., 1987), (3) apoptotic neurodegeneration in neonatal rats treated with N-methyl-D-aspartate (NMDA) receptor antagonists (Ikonomidou et al., 1999), (4) decreased myelination and axonal damage induced in preweanling rats by vigabatrin (Sidhu et al., 1997), (5) long-term changes in serotonergic innervation in rats exposed to fluoxetine during early juvenile life (Wegerer et al., 1999), and (6) chondrotoxicity in immature animals treated with fluoroquinolones (Stahlmann et al., 1997). Although the significance of these findings for humans is uncertain, there is evidence that some of these effects can be relevant to growing children, notably those of methylphenidate (Mattes and Gittelman, 1983; Croche et al., 1979) and fluoroquinolones (Chang et al., 1996; Le Loet et al., 1991).

III. GENERAL CONSIDERATIONS FOR EVALUATION OF PHARMACEUTICALS IN JUVENILE ANIMALS

A. Scope of Nonclinical Safety Evaluation

The nonclinical safety evaluation of pediatric therapeutics in juvenile animals should primarily address the potential effects on growth and development that have not been studied or identified in previous nonclinical and clinical studies. The safety evaluation of new pediatric drug products should focus on the toxicological assessment of the active moiety. In limited circumstances, it can be important to include the pediatric clinical formulation's inactive ingredients in testing, particularly in cases where the drug's pharmacodynamics or distribution is altered by the inactive ingredients. The scope of this document does not encompass testing of excipients for use in pediatric populations. Issues related to formulation should be discussed with the Agency. Toxicological assessment should include analysis of effects on postnatal growth and development for systemic and local toxicity in relation to issues of concern to the expected pediatric population in consideration of their developmental status. We recommend addressing toxicities of special concern in juvenile animal studies or by other methods, based on the known pharmacological and toxicological properties of the drug and the patient population. Juvenile animal studies are of special interest when an identified target organ toxicity in adults is also an organ with significant postnatal development.

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

Recommendations regarding the timing of nonclinical studies are available in the ICH guidance for industry *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceutical*s (ICH-M3 safety studies guidance).

1. *Long-term Exposure in Pediatric Subjects*

Juvenile animal studies are primarily conducted to address safety issues associated with long-term exposure during critical developmental periods. Where pediatric clinical studies involve long-term exposure, juvenile animal studies should be conducted before initiation of the long-term clinical studies. Where the indication is for long-term use, but the clinical trials are short-term, the juvenile animal studies should be available before submission of the marketing application.

2.   Shorter Exposure in Pediatric Subjects

The bulk of clinical trials in pediatric subjects do not involve long-term exposure (especially where the studies are intended to determine pharmacokinetics rather than efficacy). Where pediatric clinical studies do not involve long-term exposure, it is not necessary to complete juvenile animal studies before initiation of pediatric clinical studies. Such studies can be conducted in conjunction with the clinical trials. However, because juvenile animal studies may identify potential hazards, and it may be important to clinically evaluate the relevance of identified potential hazards to determine the extent of human risk, it may be more efficient to complete juvenile animal studies early so that clinical studies can be designed to evaluate potential long-term hazards.

3.   Insufficient Clinical Data to Support Initiation of Pediatric Studies

Typically, pediatric subjects are included in clinical trials after there has been considerable experience in the adult population. Where there is not sufficient clinical data or experience because of minimal prior adult and pediatric experience, juvenile animal studies should be completed before initiation of pediatric clinical trials, regardless of whether the clinical trials involve long-term exposures. Similarly, where there have been reports of adverse effects with off-label use in pediatric patients, and there are not adequate data to evaluate the relationship between the drug and the adverse effects, juvenile animal studies should be completed before initiation of pediatric clinical studies.

C.   General Design Considerations for Juvenile Animal Toxicology Studies

The appropriateness and design of juvenile animal studies should consider (1) the intended or likely use of the drug in children, (2) the timing of dosing in relation to phases of growth and development in pediatric populations and juvenile animals, and (3) the potential differences in pharmacological and toxicological profiles between mature and immature systems. Juveniles generally have a more dynamic developmental condition compared to the relatively stable condition of the adult. However, it is recognized that underlying pathology may alter this presumption. While the greatest concern is with chronic, long-term therapy, the duration of anticipated treatment of the pediatric population should be evaluated in relation to the duration of developmentally sensitive phases. For instance, the treatment duration for neonates that would be considered *long term* in relation to development can be substantially shorter than for older, prepubescent children where development changes occur over a long time frame. Juvenile animal toxicology studies should be designed efficiently, using the least number of animals to identify potential pediatric safety concerns. Taking this into consideration, whenever feasible, an initial study designed to address end points of concern for multiple potential pediatric populations should be considered. In all cases, studies using juvenile animals should be considered when adequate information could not be generated using standard nonclinical studies or from conducting clinical trials. These considerations are elaborated further in subsection III.D. of this document. Recommendations regarding the timing of nonclinical studies are available in the ICH-M3 safety studies guidance.

D.   Issues to Consider Regarding Juvenile Animal Studies

This section lists issues specific to studies in juvenile animals for assessing toxicity.

1.   Intended Population

Juvenile animal studies may be important for agents that are expected or likely to be used in pediatric patients. Consideration should be given to the age of the intended population and the stage of postnatal development. The condition to be treated may influence the type, extent, and timing of testing considered appropriate. The end points to be assessed in the nonclinical studies should be tailored to address concerns for a particular pediatric population.

2.   Use of Available Data

Available data should be carefully evaluated when considering the importance of studies in juvenile animals. Toxicity studies in juvenile animals may be important when available nonclinical or clinical data are not sufficient to support reasonable safety of a therapeutic for pediatric patients.

Many drugs that are intended for use in pediatric patients have established efficacy and safety profiles in adult humans. Limited data may also be available from pediatric patients aged 12 years or older. For some drugs a preponderance of clinical data will be obtained from children, as in the case of inhaled corticosteroids (FDA, 1998). For approved drugs that have already undergone extensive clinical testing, nonclinical pharmacology and toxicology data will be available. Toxicology assessment can include studies of general toxicity, reproductive toxicity, genetic toxicity, carcinogenicity, and other special toxicities. Studies in juvenile animals are occasionally available. Target organs of toxicity of the drug both in humans and animals should have been identified in these studies. A thorough evaluation of these data should enable scientists to (1) judge the adequacy of the nonclinical information, (2) identify potential safety concerns for the intended population, and (3) identify any gaps in the data that might be addressed by testing in juvenile animals. Based on this evaluation, in some circumstances it can be concluded that studies in juvenile animals would not be informative and are not necessary.

3.   Duration of Clinical Use

The toxic effects of drugs on postnatal development are believed most likely to occur in those organs and tissues that undergo significant postnatal development. Organ systems identified to undergo considerable postnatal growth and development include the nervous, reproductive, pulmonary, renal, skeletal, and immune systems. As commonly practiced in studying effects on prenatal growth and development, a reasonable approach is to assure that exposure to the drug takes place during periods of rapid growth and

development. Given the variable rate of postnatal development during different periods of childhood, the definition of *long-term* treatment can vary by pediatric population. For example, intended treatment of several weeks may not be considered long term in early adolescence, but it might be considered long term for the neonate, given the duration of some developmental windows.

4. Timing of Exposure

We recommend that the timing of the intended use of the drug be considered as it relates to periods of rapid postnatal growth and development. If the drug is intended for use in children undergoing phases of rapid overall growth and development, efforts should be made to use an animal model undergoing a corresponding growth phase. Different organ systems mature at specific times in specific species. Human to animal comparisons of developmental periods for the nervous, reproductive, skeletal, pulmonary, immune, renal, and metabolic systems are presented in the tables in section VI at the end of this document. These comparisons can be used as a guide in determining appropriate periods of treatment to assess the development of organ systems in different animal models.

5. Selection of Study Models

In addition to consideration of models and end point assessments based on intended pediatric treatment periods, it is important to give special consideration to target organs for toxicological and pharmacological activity identified in adults. Organ systems should be studied in juvenile animals for such activity when those organ systems are identified as targets of drug toxicity in adults and they undergo significant postnatal development. We suggest that toxicological and pharmacological effects be studied even when the primary postnatal developmental period in humans does not coincide with the intended treatment phase. This suggestion is based on the observation that development is generally a continuous event.

IV. GENERAL CONSIDERATIONS IN DESIGNING TOXICITY STUDIES IN JUVENILE ANIMALS

A. Types of Studies

Studies conducted in juvenile animals to support the safety of therapeutics intended for use in pediatric patients can be protocols specifically designed for juvenile animals or modified protocols of traditional toxicity testing. Dedicated juvenile animal protocols can be most aptly designed to address concerns based on known properties of the drug, product class, or other information. Modified repeat-dose toxicity studies can provide a more general screen for potential hazards. However, these studies usually will warrant modification of animal age at study initiation, duration of treatment, and end points assessed. For example, modification of standard ICH studies designed to address developmental stages C to F[3] would include ensuring adequate exposure of pups during the postnatal period and assessing developmental end points

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[3] See the ICH-S5A guidance for industry *Detection of Toxicity to Reproduction for Medicinal Products*.

appropriate for the intended pediatric population. In this case, in addition to assuring adequate exposure to drug, it would be important to perform histopathologic examinations and to study effects on particular parameters (e.g., pulmonary development) in pups. In nonrodents, we recommend that studies be started with younger animals than is the usual practice and extended until the developmental period for the intended pediatric population has been completed in the animal species. Assessment of developmental end points not usually included in standard repeat-dose toxicity studies may also be important. Information from such studies can be compared to the findings from treated adults of the same species to evaluate whether the effects are specific to juvenile animals.

B.   Animals

1.   Species

The species of juvenile animal tested should be appropriate for evaluating toxicity end points important for the intended pediatric population. Traditionally, rats and dogs have been the rodent and nonrodent species of choice. However, other species may be more appropriate in some circumstances (e.g., where there might be a concern for an inappropriate drug metabolic profile compared to humans).   Certain factors should be considered in determining an appropriate species. Examples of these factors are (1) pharmacology, pharmacokinetics, and toxicology of the therapeutic agent; and (2) comparative developmental status of the major organs of concern between juvenile animals and pediatric patients.

A study in juveniles from one animal species can be sufficient to evaluate toxicity end points for therapeutics that are well characterized in both adult humans and animals. It is anticipated that often this evaluation can be accomplished in the rodent using modified perinatal and postnatal developmental studies, although other approaches can be used.

2.   Age

The age of the animals at initiation of dosing should be determined by the postnatal development parameters of interest. The stage of development in animals should be comparable to that in the intended pediatric population.

3.   Sex and Sample Size

Both male and female animals should be used in these studies. An adequate number of animals should be used to clearly demonstrate the presence or absence of effects of the test substance. The magnitude of the biologic effect that is of concern should be considered when determining the sample size.

C.   **Exposure**

1.   *Route of Administration*

The expected clinical route of administration and formulation[4] should be used when feasible, unless it has been demonstrated in nonclinical studies that an alternate route is more relevant to human clinical use. Assessment of toxic effects by more than one route can be appropriate if the drug is intended for clinical use by more than one route of administration. It may be helpful to test by multiple routes where different routes are anticipated to result in different systemic and local exposure of such magnitude that it could be expected to have an impact on the occurrence of postnatal toxicity. Because the primary purpose of these studies is to identify potential hazards, small changes in exposure and distribution by route generally are not considered important.

Under most circumstances, determination of drug metabolism in juvenile animals would not be needed. However, if adverse effects that could be related to metabolic differences between adult and juvenile animals are observed, toxicokinetic studies can provide useful information for assisting in study interpretation.

2.   *Frequency and Duration of Exposure*

The frequency of administration should be relevant to the intended clinical use of the drug, but deviations can be important when variables such as metabolic and kinetic differences are considered. In some cases the use of dosing frequencies similar to those anticipated for clinical administration are not feasible because of technical considerations for the animal models used.

The duration of treatment should include, at a minimum, the significant periods of relevant postnatal development for the selected species. Treatment-free periods designed to assess reversibility of possible adverse effects should also be considered. Inclusion of recovery periods in studies can be valuable in discriminating acute to intermediate pharmacodynamic effects from frank developmental toxicity. Such information could influence the evaluation of potential human risk.

3.   *Dose Selection*

Dose selection should provide a clear dose-response relationship for adverse effects in juvenile animals, where possible. The high dose should produce frank toxicity, developmental or general. The intermediate dose should produce some toxicity so that a dose-response relationship can be demonstrated if one exists. The low dose should produce little or no toxicity and a *No Observed Adverse Effect Level* should be identified if possible. Intermediate and low doses should be considered and potentially modified in relation to those that produce the desired pharmacodynamic effect in the test species.

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[4] Safety evaluations of inactive formulation components should be conducted to determine potential adverse effects in pediatric subjects. The type of testing is dependent on the extent to which this information is already well understood.

D. Toxicological End Points and Timing of Monitoring

The selection of toxicological end points to be monitored in a juvenile animal study is critical for assessing the effects of a drug on development and growth. Studies should be designed to determine drug effects on overall growth of organ systems that develop postnatally (e.g., skeletal, renal, lung, neurological, immunologic, and reproductive systems). Studies should include, at a minimum, measurements of growth (e.g., serial measurements of crown-rump length, tibia length, growth velocity per unit time, or other appropriate parameters), body weight, clinical observations, organ weights, and gross and microscopic examinations. Clinical pathology determinations can also be useful, but they can be limited by the technical feasibility of obtaining adequate samples for analysis, particularly in the case of rodents. For developmental neurotoxicity assessments, well-established methods should be used to monitor key functional domains of the central nervous system, including assessments of reflex ontogeny, sensorimotor function, locomotor activity, reactivity, and learning and memory.

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). To differentiate long-term effects on development from acute effects, it may be appropriate to measure certain end points immediately before daily administration of the drug. Adding another experimental group to the study and allowing these animals to recover for a period of time before toxicologic evaluation also can be helpful in determining whether the drug-induced effects are reversible.

V. APPLICATION OF JUVENILE ANIMAL DATA IN RISK MANAGEMENT CONSIDERATIONS

A. Use in Clinical Trials

Nonclinical toxicology studies designed to support the safety of clinical trials in pediatric subjects should identify hazards specific to this population. These studies also should provide information on methods useful in limiting the risk of and/or monitoring for the identified adverse effect or effects. Where adverse effects are observed in nonclinical toxicology studies, there are a number of possible uses of these findings. For example, biomarkers of adverse effects could be identified in nonclinical studies that can be useful in monitoring subjects in clinical trials. In cases where biomarkers cannot be identified and/or safely used in clinical studies, nonclinical pharmacokinetic data could be useful (i.e., a given adverse effect could be found to be associated with a particular level of systemic exposure). Blood level monitoring could then be used in clinical trials to minimize the probability that such an adverse effect would occur. Where useful pharmacokinetic parameters or biomarkers are not identified in juvenile animal models, doses and lengths of exposure associated with adverse effects in these nonclinical toxicology studies might prove useful in the design and conduct of clinical trials. In some cases where toxicities of significant concern are observed, studies in juvenile animals might indicate that pediatric trials could not be conducted that would provide for an adequate margin of safety compared to

apparent efficacious doses. It may not be possible to safely conduct pediatric clinical trials if toxicities identified in juvenile animal studies (1) are likely to occur in pediatric patients, (2) cannot be monitored clinically, and (3) would not be considered acceptable potential consequences of treatment. Demonstration of irreversible adverse effects in juvenile animal studies could preclude clinical studies in pediatric subjects.

B. Use in Product Approval

Nonclinical toxicology studies in juvenile animal models could demonstrate adverse effects that the sponsor should consider (1) in seeking postmarketing commitments, (2) in labeling a product for pediatric use, or (3) in determining the approvability of a drug for pediatric use. For example, delayed or irreversible adverse effects might be identified in animal studies but not in clinical trials. The clinical trials conducted in pediatric patients might not have been of sufficient duration to demonstrate the adverse effects observed in juvenile animal studies. It may be important for the sponsor to conduct long-term, follow-up human safety studies as a postmarketing commitment, depending on the nature and severity of these adverse effects and the benefit/risk relationship of the intended use. Long-term, follow-up studies may be called for after acute drug exposure if these effects were found to be delayed or irreversible. Use of the drug could be restricted to serious indications based on nonclinical findings, even if the adverse effects were not demonstrated in clinical trials. In this case, the product label should include information on the relevant adverse effects observed in nonclinical studies. Adverse effects associated with chronic drug exposure in nonclinical studies might not have been observed in clinical trials of comparable length; therefore, the label might be written to reflect these findings. It is possible that biomarkers of adverse effects could be identified in nonclinical studies that were not seen in clinical trials, but they might nevertheless be important to include in the product label. Juvenile animal studies might also be useful in identifying specific age groups in which the drug should not be used or in determining unsafe parameters of exposure. Finally, it is possible that nonclinical findings could result in a product label that specifically warns against use in pediatric patients.

VI. TABLES: COMPARISONS OF HUMAN TO ANIMAL DEVELOPMENTAL STAGES BY ORGAN SYSTEMS

The following information on comparative developmental timing was current at the time this guidance was developed. This information should be considered, along with new information as it becomes available, in deciding the best way to design appropriate juvenile animal studies to address risks to the pediatric population. Neither the human nor the animal data represent a precise determination of the timelines of development because of the inherent variability and different end points examined. These tables should serve only as a general starting point.

A. Nervous System

Developmental Event	Critical Postnatal Developmental Period	
	Human (Year)	Rat (Day)
Glutamate receptors[1] (maximal binding)	1 to 2 cortex Decline to adult 2 to 16	28 Decline to adult >28
Monoamine system[2]	2 to 4 maximum receptor density	21 to 30 adult levels
Ocular dominance[3]	0 to 3	21 to 35
Cerebellum persistent external germinal layer[3]	0.6 to 2	0 to 21
Rapid phase of myelination ends[4]	2	25 to 30

B. Reproductive System

Developmental Event	Critical Postnatal Developmental Period				
	Human	Rhesus monkey	Mouse	Dog	Rat
	(Year)	(Year)	(Day)	(Day)	(Day)
Onset of sexual maturity[5]	12	5	45	315	100

C. Skeletal System

Developmental Event	Critical Postnatal Developmental Period (Year)			
	Human	Dog	Rat	Cynomolgus monkey
Epiphysial plate closure[6]	12 to 25	0.6 to 0.9	Fusion through life	5.5 to 6.5

D. Pulmonary System

Developmental Event	Critical Postnatal Developmental Period (Day)		
Alveoli formation[7,8,9]	Human	Rat	Mouse
Onset	Prenatal	1 to 4	1 to 2
Completion	730	28	28

E.   Immune System

Developmental Event	Critical Postnatal Developmental Period (Day)	
	Human	Mice
B-cell development[10]	Prenatal	Prenatal
T-cell development[10]	Prenatal	Prenatal
NK-cell development[10]	Prenatal	21
T-dependent antibody response[10]	0	14 41 to 56 adult level
T-independent antibody response[10]	45 to 90	0 14 to 21 adult level
Adult level IgG[10]	1,825	42 to 56

F.   Renal

Developmental Event	Critical Postnatal Developmental Period (Day)	
	Human	Rat
Glomerulo-/nephrogenesis[11,12]	Prenatal	8 to 14
Adult GFR and tubular secretion[11,12]	45 to 180	15 to 21

G.   Metabolism

Developmental Modulation of Phase I and II Metabolism			
	Maturation of Enzyme Activity		
Enzyme	Human (Year)	Rat (Day)	Rabbit (Day)
CYP1A2 [13,14,15,16]	0.5 1(> adult)	7 to 100 low levels	21 to 60
CYP2C8 [15,17]	<1	NA	NA
CYP2C9 [15,17]	<0.5 0.5 (> adult)	NA	NA
CYP2D6 [15,17]	0 to 3	NA[1]	NA
CYP2E1 [17,18,19]	0 to 1	4 to 17 ↓ Post weaning male>female	14 to 35 2X adult @ 35
CYP3A4 [17]	0 to 2	NA	NA

Developmental Modulation of Phase I and II Metabolism			
Acetylation [15,17]	1 (35% adult)	NA	NA
Methylation [15,17]	<1 (50% adult)	NA	NA
Glucuronidation [15, 17]	0 (>adult) 12		NA
Sulfation [15,17]	0	NA	NA

NA= not available

[1] Ikonomidou et al. (1999)
[2] Rice and Barone (2000)
[3] Sidhu et al. (1997)
[4] Radde (1985)
[5] DeSesso and Harris (1995)
[6] Tassinari (1999)
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