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Review

SPECIFICITY OF PHARMACOLOGICAL AND TOXICOLOGICAL STUDIES ON JUVENILE ANIMALS

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Abstract. With levels of medicine and pharmacology individualization constantly increasing, the scientific community is becoming seriously concerned about the safety of existing and developing drugs for the pediatric population insufficient assessment. The aim of this review is to analyze the main problems arising in the development and preclinical evaluation of drugs for children and adolescents, taking into account their age-related physiological and biochemical characteristics, as well as the selection of adequate juvenile experimental models among various animal species.

Juvenile animal studies planning should be based on the specific age group of the pediatric population for which a specific drug is being developed. They cannot be conducted using standardized research protocols and require an individual approach in each specific case. Their design should include the study of drug effects at all ontogenesis stages, without exception, that correspond to the growth and development of the relevant pediatric population. Also fundamental are the correct choice of animal species, based on its sensitivity to the effects of the drug, the availability of relevant data from preclinical studies on adult animals and the planned procedures and types of studies, some of which can only be carried out on certain animal species. Pathologists should be able to compare tissue structures in parallel in an experiment, both normal and drug-treated, at all stages of ontogenesis, and have access to as many reference and image databases as possible. All of the above requirements are the minimum to ensure adequate support for clinical trials in the pediatric population.

Keywords: juvenile animals' studies; ontogenesis stages; choice of animal species; safety; drug effects; pediatric population

Introduction

The individualization of modern medicine and pharmacology requires maximum consideration of the age, physiological, and biochemical characteristics of each individual patient. New treatment regimens, new drug combinations, and new dosage forms are constantly being developed. However, all of this primarily applies to the adult patient population [1–3]. Other specific groups remain under the spotlight, especially for new drug developers. This applies to both the geriatric population and children and adolescents. The issue is particularly pressing when it comes to developing medications for young, growing and developing individuals.

This situation is largely due to the fact that for a long time, insufficient attention was paid to the specific therapeutic and toxic effects of drugs in growing and developing organisms. There was no active search for adequate experimental models, and even when studies were conducted on juvenile animals, there was insufficient scientific evidence to demonstrate that this juvenile experimental model accurately corresponds to the age characteristics of the intended pediatric patient population [4].

In recent decades, however, awareness of the scale of this problem has gradually begun to emerge. The scientific community is seriously concerned about the safety of existing and developing pediatric medications due to insufficient assessment of their effects in relation to age-related physiological and biochemical characteristics.

This, in turn, has fueled growing interest in conducting pharmacological and toxicological studies on young animals at an appropriate scientific level. One step in this direction is the development and implementation of specific pediatric legislation in the United States of America (US) and the European Union (EU) [5–7], which imposes specific requirements on the development of pediatric medications and the evaluation of their efficacy and safety.

Despite these measures, the scientific community has not yet reached a consensus on the specifics of such studies, their significance and scientific value, or

the situations requiring their mandatory implementation, and the debate is still active. Data accumulated over recent decades allows us to identify several key areas in this debate.

The aim of this review is to analyze the main problems arising in the development and preclinical evaluation of drugs for children and adolescents, taking into account their age-related physiological and biochemical characteristics, as well as the selection of adequate juvenile experimental models among various animal species.

Approaches to medicines' doses determination for pediatric use

The understanding that children are not miniature adults and require fundamentally different approaches to treatment, drug dosing regimens and dosage forms choices came to clinicians and pharmacologists more than 100 years ago [8]. As our knowledge of human growth and development continues to expand, so does our understanding of how the body responds to medications at different stages of its development. Accordingly, there is a need for age-appropriate adjustments to drug dosages.

Gradually, a new direction in pharmacological sciences has emerged – developmental pharmacology. Before its approaches were incorporated into the decision–making processes of clinicians and therapists, there were many ways to medicines doses determination for pediatric use (Young's rule, Clark's rule, etc.), which were based on either discrete age points or on assuming the presence of linear relationships between mass and body surface area in infants, children, adolescents and adults [9–11].

However, the increase in human body size during its development from a newborn to an adult is not a linear process. Changes in the structure and functions of the entire body and its individual organs caused by growth and development are very dynamic and not always mutually coordinated during the first ten years of life. This circumstance determines the inadmissibility of using simplified (without individualization) approaches to medicines' dose determination throughout the entire period of childhood [12].

The use of formulas for drug dose calculation for a certain body weight or body surface area is acceptable only for the therapy initiation, but is completely insufficient for long–term treatment since maintenance therapy must be individualized taking into account pharmacokinetic or pharmacodynamic data, or both. Thus, only taking into account the role of ontogenesis stages in the implementation of drug action allows us to develop the basis for its safe and effective therapy for children.

During the process of absorption, a medicinal product passes through chemical, physical, mechanical and biological barriers of absorbent surfaces (gastrointestinal tract, skin, lungs and bronchi). Ontogenetic changes in their structure can significantly change a drug's degree of bioavailability and the rate of adsorption.

For example, in newborns, the intragastric pH is increased [13, 14]. Therefore, when taking orally such acid–labile drugs, as penicillin G, their bioavailability in newborns will be significantly higher than in older children [15].

Insufficient production and transport of bile acids and their salts into the intestinal lumen in children reduces their ability to dissolve and then absorb lipophilic drugs [16, 17].

A systematic study of the ontogenetic changes development effects on drug absorption and bioavailability in infants and children has been conducted by several groups of scientists, who studied the absorption of phenobarbital, sulfonamides, digoxin, arabinose and xylose [18]. It was shown that compounds passive and active transport processes begin to function fully in infants at about four months [18]. Most drugs are absorbed in newborns and young infants much more slowly than in older children. Accordingly, the time to reach maximum drug levels in the blood plasma is much longer in newborns and younger children.

From birth, the intestinal surface area and average intestinal length (as a percentage of adult values) decrease [19]. In addition, changes in blood flow in the child's organs during the first weeks of life can affect the rate of transport along the concentration gradient across the intestinal mucosa [20–22]. In infants and children, the activity of the drug-metabolizing enzymes epoxide hydrolase and glutathione peroxidase depends slightly on age [23], the activity of cytochrome P-450 1A1 (CYP1A1) increases during ontogenesis [24], and the activity of glutathione–S–transferase decreases [25]. Intestinal microflora also changes depending on age [26].

The thinner *stratum corneum*, the more intense cutaneous perfusion and the greater hydration of the epidermis in infants (compared to adults) increase transcutaneous absorption of drugs (corticosteroids, antihistamines and antiseptics) [27–29]. The use of insufficiently individualized doses in this case can cause toxic effects [10, 30, 31].

The distribution of drugs is influenced by the relatively large extracellular and water spaces of the infant body (compared to adults), the higher water–to–lipid ratio, the composition and amount of circulating plasma (albumin, alpha-1-acid glycoprotein, fetal albumin) and transport proteins (P-glycoprotein), variability in regional blood flow, organ perfusion, cell membrane permeability, changes in acid-base balance and cardiac output [32–37].

The activity of drugs-metabolizing enzymes i

the processes of xenobiotics biotransformation at phase I (oxidation) and phase II (conjugation) reaches optimal values much later than birth [38, 39]. Insufficiently intensive biotransformation of chloramphenicol in newborns leads to the development of toxic phenomena (cardiovascular collapse) [40, 41]. Taking into account age–related features of infants' metabolism is vitally important when determining dosage regimens for morphine, captopril, methylxanthines, nafcillin, and third–generation cephalosporins.

Full renal function development in children is a long process. After birth, child's glomerular filtration rate and tubular secretion constantly increase until reaching adult values (approximately by the age of 1 year) [42, 43]. Any delays or deviations in the development of renal function in infants seriously impair the plasma clearance of drugs excreted from the body through these organs (for example, ceftazidime, tobramycin and famotidine) [43–45].

Pharmacokinetic data indicate a clear correlation between the plasma clearance of such drugs and changes in renal function during ontogenesis. Failure to adjust the dosage regimens of aminoglycosides taking into account the ontogenesis of renal function leads to the development of these preparations' toxic effects [7, 10, 11, 46]. And more over, the use of a combination of indomethacin with betamethasone in newborns generally disrupts the processes of normal renal maturation [47].

Ontogenesis significantly affects the medicines' pharmacodynamics, in particular interaction processes between drug molecules and the corresponding receptors, changing both the action of the preparation itself and the body's response to it. Examples of such an effect include warfarin [48], cyclosporine [49], midazolam [50, 51].

A number of diseases can aggravate age differences in drugs effects [52, 53]. For example, valproic acid hepatotoxicity increases sharply in toddlers with convulsive syndrome [54]. Prematurity, accompanied by motilin receptors impaired expression and peristalsis violations, leads to a pronounced prokinetic effect of erythromycin in such children [55].

Thus, developmental physiological changes are accompanied by multiple age–dependent changes in the processes of drug absorption, distribution, metabolism and excretion [7, 10, 11]. Altered pharmacokinetics determines the need for dosages individualization depending on age. The insufficiency of our current data on age–related features of the drugs metabolizing hepatic and extrahepatic enzymes functioning, on drug transporting proteins expression, on other factors affecting the drug's bioavailability, does not allow us to develop any general formulas for dosage and allometric scaling [56].

Advances in pediatric clinical pharmacology over the past decades, driven by a deeper understanding of the ontogenesis influence on the drug's pharmacokinetics and pharmacodynamics, put forward new requirements for preclinical studies of preparations intended for the pediatric population.

Juvenile preclinical studies

Preclinical data on juvenile animals are necessary to obtan information on the possibility of a particular drug use in pediatric populations [7, 10, 11]. At the same time, an important circumstance is that, unlike adult animals, in juvenile and, in particular, newborn animals, the main parameters of pharmacokinetics and pharmacodynamics may differ significantly in immature and developing organs.

Conducting such studies of drug efficacy, safety, and toxicity in juvenile animals' experimental models presents a number of conceptual and logistical challenges. The development of a young animal is continuous, but different organs mature and begin to normally function at different rates and over different time periods. These differences in structural and functional maturation alter the pharmacokinetic and pharmacodynamic profiles of drugs.

This is especially important to consider when conducting preclinical toxicity studies on juvenile animals, since toxic effects are more likely to manifest in tissues just in the postnatal period. In particular, the degree of structural and functional maturity of the liver and kidneys (excretory organs) has a decisive effect on drug pharmacokinetics, in particular on the processes of their distribution in tissues and organs. The most significant changes are recorded during the first days or months of a newborn animal's life.

At present, there is insufficient data on the relationship between ontogenesis and drugs' pharmacodynamics in juvenile animals, especially regarding the sensitivity of maturing tissues/organs to the medicines' actions, and all of them are fragmentary. It is also important to note that various pathological conditions of a juvenile organism can change the pharmacokinetic and pharmacodynamic profiles of the drug differently than in adult animals, which creates additional potential for the toxic effects development.

The design of a preclinical study of the drug efficacy, safety, and toxicity in juvenile animals is primarily influenced by the available preliminary data on this compound's mechanism of action, its metabolic profile, receptor–ligand interactions, available experimental animal species sensitivity to it, the intended pediatric population, routes and timing of administration.

It is important to select the correct juvenile species and experimental group size, as there may be great variation between litters due to juveniles' physical and behavioral variability. These parameters are critical to ensure the experimental design adequacy

and the obtained results validity.

The nature of the drugs being studied also has a significant impact on the design of the study. In particular, the study of biotechnological drugs (monoclonal antibodies, vaccines, hormones, allergens, antitoxins, blood–derived preparations, etc.) involves particular difficulties in their testing due to the variability of their structure and biological properties, strict species specificity and immunogenicity. In this case, juvenile animals of a species for which the pharmacological relevance and cross–reactivity of a given biological molecule have been previously established are selected as an experimental model. In them, this drug should act on the same targets as in humans, causing similar pharmacological effects *in vitro or in vivo*, and its effects should be comparable between the experimental species and humans. In practice, this means that biologics preclinical testing on juvenile animals is often limited to the experimental model of infant non–human primates (NHPs).

The choice of the most suitable juvenile animal species is determined by preliminary pharmacology data, PK/ADME profile, species used in preclinical studies on adult animals, information on target organs in adult animals, and the level of financial costs.

Therefore, it is not surprising, that rodents are the most often used species in juvenile animal studies (more than 70% of the total number of juvenile animals' studies), which are distinguished by their well–studied ontogenesis and high fertility [7, 10, 11, 57, 58]. Among rodents, the most common model is the rat, whose offspring, due to their size, are more convenient for work compared to the offspring of a mouse [7, 10, 11, 57, 58].

Six times less often, preclinical studies on juvenile animals are conducted using dog puppies – 9% – 12% of the total number of studies on juvenile animals [7, 10, 11, 57, 58]. Dogs belong to well–characterized nonrodent species with longer (in comparison with rodents) gestation length (ca. 63 days) [54, 55]. The advantage of conducting studies on puppies is that very often preliminary data on adults already exists.

Non-human primates are used in only 2% – 4% of the total number of studies on juvenile animals. These are mainly, as noted above, cases of studying drugs of biological origin [7, 10, 11, 57, 58].

Experiments on mini-piglets account for only 1% – 2% of all studies on juvenile animals [7, 10, 11, 57, 58]. These piglets are more developed at birth than juvenile animals of other commonly used species. Significant similarities between humans and mini–pigs have been demonstrated in terms of skin and nasal cavity structure, gastrointestinal tract structure and functioning, cardiovascular and genitor–urinary systems, reproductive sensitivity, metabolic processes in general and xenobiotic metabolism in particular. In addition, their use is more cost–effective than sheep or monkeys.

As for other types of experimental animals, such as rabbits and sheep, they are used the least often – in about 0.5% of cases [7, 10, 11, 57, 58].

The rates of various organ systems development in growing animals of different species vary significantly [10], but the general age range at the developmental and growth stages is used by scientists to construct a relative scale of comparison with humans. An example of one of these scales is presented in Table 1[59].

The juvenile animals of various rodent species mature very quickly – within days or weeks, which is not always convenient when studying the action of drugs with cumulative effect, which develops over time as the dose accumulates [10].

At the same time, the juvenile animals of non–rodent species mature much more slowly – within months or years, which also affects the design and time scale of the studies.

Table 1. Interspecies comparison of age (development phase) [59]

Species	Preterm	Newborn	Infant	Child	Adolescent
Mouse	0–4 days	0–10 days	1.5–3 weeks	3–5 weeks	5–7 weeks
Rat	0–4 days	0–10 days	1.5–3 weeks	3–6 weeks	7–11 weeks
Rabbit	0–4 days	0–10 days	1.5–5 weeks	5–12 weeks	3–6 months
Pig	–	0–15 days	2–4 weeks	4–14 weeks	4–6 months
Dog	–	0–21 days	3–6 weeks	6–20 weeks	5–7 months
Monkey	–	0–15 days	0.5–6 months	0.5–3 years	3–4 years
Human	–	0–28 days	1–23 months	2–12 years	12–16 years

However, it should be noted that these figures are not something definitively established and can vary greatly among different groups of researchers depending on the criteria they choose for assessing the degree of organism's maturity and the genetic characteristics of the specific lines or breeds of experimental animals they use [60–63].

For example, if a drug affecting the nervous system is to be studied, then the key parameter in determining the comparative ages of experimental animals will be the parameters of the development of the central nervous system (CNS) [10, 62, 63].

Approximately the same time periods were obtained by scientists when using indicators of reproductive system development as key parameters in determining the comparative ages of experimental animals [10, 62].

In general, except for primates and humans, juvenile animals of all other species reach sexual maturity over a period that is approximately 10% of their total lifespan. Thus, reaching sexual maturity in a rat takes 5% of its total lifespan, in a mouse this parameter is 4.5%, in humans – 14%, in a cow – 9%, in primates – 13%, in sheep – 3%, in rabbits – 7%, in horses – 6%, in cats – 5, in dogs – 6.5% [64].

The formation of the skeletal–muscular system of the body lasts much longer. Thus, the closure of the epiphysis growth plates in a rat occurs after about 28% of the lifespan, in a mouse this parameter is 22%, in a human – 21%, in a cow – 16%, in primates – 15%, in sheep – 9%, in a rabbit – 7.5%, in a horse – 6.2%, in cats – 6.5%, in dogs – 6% [64].

Systemic exposures are the most relevant for assessing drugs effectiveness, safety and toxicity in juvenile preclinical studies. It must be noted, that there are a number of pharmacokinetic intervals (with different dose levels) corresponding with different ages and maturity of ADME components throughout the entire period of juvenile study. Pharmacokinetic parameters are very useful to make comparisons across ages and between species, as well as for characterizing plasma levels of investigated compound, and all its metabolic derivatives. Obtained results allow to detect any selective functional/developmental changes or to demonstrate levels of internal exposures when changes actually happen in juvenile animals comparing to adults.

The young animals' body sizes impose certain technical limitations when conducting juvenile pharmacology studies. The start of dosing in young animals varies greatly depending on the species and the route of administration [11, 61, 65]. Oral gavage to young rats, dogs, and minipigs could be started on the first postnatal day while to mice it becomes possible on the 4th and to rabbits – even on the 14th postnatal day. Subcutaneous and intramuscular administrations may be started at the first postnatal day in the case of young mice, rats, dogs, and minipigs while for rabbits it becomes possible at the 6th postnatal day. Intravenous infusion, inhalation into the nose, and dermal applications start in young mice and rats on the 21st postnatal day while in rabbits it becomes possible on the 28th postnatal day. Inhalation in special inhalation chambers (whole body) could be started on the second postnatal day to minipigs, to mice and rats – on the 4th, to rabbits – on the 6th, to dogs – on the 10th postnatal day.

The study design is directly dependent on the litter composition since the offspring of the same female (within her 1 litter) show less variation in responses than offspring from different females and different litters [61]. They are not "independent subjects", which should be taken into account when distributing such animals into experimental groups.

There are various ways to overcome this. For example, animals from each litter can be included in all available experimental groups or at least in some of the experimental groups [61]. Sometimes, one animal of a certain sex from each individual litter is included in the experimental group. There are also other approaches, each of which has its disadvantages and advantages [61].

Table 2. Interspecies comparison of age (overall central nervous system) [62]

Species	Preterm	Newborn	Infant	Child	Adolescent
Rat	<9 days	9–10 days	10–21 days	21–45 days	45–90 days
Pig	–	<2 weeks	2–4 weeks	4–14 weeks	14–26 weeks
Dog	<0,5 weeks	0,5–3 weeks	3–6 weeks	6–20 weeks	20–48 weeks
Monkey	–	<0,5 months	0.5–6 months	6–36 months	36–48 months
Human	–	<0,08 years	0,08–2 years	2–12 years	12–16 years

The most optimal approach in terms of obtaining statistically reliable results is the "one offspring per sex per litter" design, which eliminates the "litter effect" [61]. Its serious disadvantage is the need for a large number of potentially required litters. For an extensive preclinical pharmacological and toxicological study, up to 48 litters may be needed. However, a significant number of cubs remain unused – approximately 288 cubs for a standard study, indicating the high cost of this approach [61].

About the number of different species included in preclinical studies in juvenile animals, it is generally considered sufficient to select one (most appropriate for the study) animal species to support the development of pediatric products [7, 66–69]. For example, at the FDA guidance it is directly stated that ‘‘a study in juveniles from one animal species may be sufficient to evaluate toxicity endpoints for therapeutics that are well characterized in both adult humans and animals.’’ [67]

However, this is only true if the most suitable species has been selected optimally and young animals at the most appropriate age have been selected [66]. However, in reality, such situations are very rare. This is due to the need to simultaneously take into account several fundamental factors.

A relative similarity in organs postnatal development in children and the juvenile animals of selected species must be ensured, as well as a similarity in tested drug main pharmacological and pharmacokinetic parameters in the pediatric population and in this species of animals [66]. At the same time, the levels of sensitivity to the effects of this drug in children and the young of the selected species of animals must also be the same [66].

All of the above requires the creation of a unified database of experimental comparative interspecies studies of ontogenesis, especially in postnatal development. Significant efforts in this direction have been made within the framework of the Health and Environmental Sciences Institute (HESI) project [70]. These studies focused on rats as the most common and economically feasible among experimental animal species.

A significant amount of data has been studied in detail and published by several groups of researchers regarding the juvenile rats heart, behavioral aspects of the central nervous system, postnatal growth and morphological development of the brain, the immune system, the male reproductive system, the female reproductive system, the lung, the kidney, the gastrointestinal system, and bone [70–80].

An analysis of all the obtained results allows us to state that in a large number of cases, the rat can be regarded as a completely acceptable species, in which the postnatal maturation of the main organ systems proceeds in approximately the same order as in humans.

However, in several situations, the use of a rat as an experimental animal in juvenile studies is difficult. For example, if preliminary studies on adult animals were conducted on a different experimental model. Or, in the case when the rat itself is not sensitive to the action of a given substance being studied.

Well, and of course estimation of complex neurobehavioral parameters must be carried out using a functional observational battery (FOB) such species as dogs or primates.

The timeline for conducting studies in young animals before initiating clinical trials in pediatric patients can vary greatly depending on the drug’s therapeutic indication, the planned duration of its administration in the clinic, and the age of the pediatric population. Most often, studies in juvenile animals are conducted to support testing of the drug efficacy and safety during long-term repeated administrations to children.

Juvenile animals’ histological studies conducting

Correct interpretation of histopathology data from studies on a juvenile population can be extremely difficult. Recognizing the normal state at each specific stage of ontogenesis, during the development of animal tissues at different ages, identifying the consequences of the development of a particular pathology model against the background of ontogenetic changes, and identifying the negative effects of a drug under these same conditions requires extensive experience and a verified study design.

Pathologists are well aware of the structure and characteristics of adult animal tissues. However, the tissues of a growing and developing young organism are very different from mature tissues of adult animals. Certain populations of proliferating cells in juvenile animals are particularly vulnerable at certain times that are not the case in adults. There are also many differences between the tissues of young animals of different ages. For example, the structure of rat liver or small intestine tissues on the 10th and 42nd days of postnatal development differs significantly [81].

This difference is even more obvious in the case of the kidneys [82]. It should be noted that the processes of kidney development in all mammals proceed approximately the same way. The kidney, like other tissues and organs of mammals, has critical periods in its development – the so-called "sensitive windows of action". Administration of drugs to juvenile animals during such critical periods can change the pharmacological effect of the drug, cause malformations, inhibit

the functional maturation of organs, and cause the appearance of signs of nephrotoxicity.

Since the time frames of "sensitive windows of action" vary greatly depending on the type of animal, it is important to establish them and take them into account when extrapolating experimental data to humans.

An important aspect is the fact that genetically determined congenital anomalies of the kidneys or malformations are much more common in humans than in laboratory animals, which necessitates the use in some cases of special lines of genetically modified animals in juvenile studies.

For example, genetically modified mice are needed to study the role of certain genes in normal and abnormal kidney development.

The seriousness of the effects of drugs on kidney development is demonstrated by the analysis of numerous preclinical studies conducted by Schreuder and colleagues [83]. The researchers noted that "No drug, in their experience, has been proven safe to use during renal development" [83].

Immature rats undergo two critical periods of reproductive tissue formation: the first is a period of rapid cell proliferation, lasting from the 4th to the 13th day of postnatal development, and the second period, associated with the formation of a protective blood–testicular barrier, lasting from the 15th to the 20th day of postnatal development [84].

Microscopic examination of the testicles of young rats showed the presence of a morphologically distinct primary population of gonocytes – up to the 9th day of postnatal development; the presence of Sertoli cell mitoses – up to the 18th day of postnatal development [80].

In young rats, in contrast to adults, accelerated proliferation and differentiation of spermatogonial cells, a gradual increase in the number of Leydig cells, and increased apoptosis of spermatocytes during the phase of formation of the hematotesticular barrier in the period between the 15th and 20th days of postnatal development were also noted. At the same time, more mature types of germ cells constantly appear at certain postnatal periods [84].

The researchers found an increase in the effect of drugs in the periods from the 15th to the 20th day of postnatal development [84].

A common design for preclinical studies in rats involves test drug administration from postnatal day 7 to postnatal day 60 and performing pathological examinations at the end of the experiment. Another approach recommended specifically for the endocrine–disrupting chemicals evaluation [85, 86] involves drug administration from postnatal day 23 to postnatal day 53.

However, histopathological examinations at the end of the experiments (in fact, on animals that have already reached sexual maturity) do not provide any information about the developmental phases that were affected by the test substance but only allow one to state the presence of a particular effect. Such results are also of little use in extrapolating the data obtained to pediatric patients.

Therefore, it is important to evaluate not only the overall effect of a drug on the structure and functions of tissues and organs of a growing and developing organism but also to pay special attention to critical periods of ontogenesis, based on preliminary information about the mechanism of its action in adults and data on critical phases of development in a given type of experimental animal.

To gain insight into the effects of a drug on the structure and functional activity of a given tissue in a young growing organism and to understand the translational significance of these data to a potential pediatric population, targeted studies with administration of the compound during specific critical periods are necessary. Without such studies, histopathological data in young rats may be misinterpreted and may not provide a reliable basis for assessing risks to children [82].

Among this, if a study on juvenile animals lasts long enough, then tissues from control animals of the corresponding age are needed to analyze the tissues of animals that died at certain stages of the experiment, which should be taken into account when developing the design of such studies [81].

The pathologist must be able to familiarize himself with the structure of normal tissues of young animals at all stages of their development during the experiment. At the same time, he must understand that the rate of different tissue development is not the same and know the time scales of development of specific organs and their systems in ontogenesis. This is currently facilitated by the creation of data and images bases on this issue by several laboratories [81].

In an optimal design of a study on young animals, the investigators plan in advance for an additional group of control animals to be used for comparison at necropsy if any early deaths of experimental animals occur well before the end of the experiments.

In addition, laboratories conducting studies on juvenile animals should establish and continuously maintain a database of information on young animals, especially a historical control database (body weight, clinical pathology, organ weight, histology) for different experimental animal species at different stages of their development, from neonatal to adult.

Conclusions

Juvenile animal studies planning should be based on the specific age group of the pediatric population for which a specific drug is being developed. They

cannot be conducted using standardized research protocols and require an individual approach in each specific case. At ICH M3 guidance it is declared, that "the age of the trial participants in relation to the duration of the clinical study (i.e., the fraction of a developmental period of concern during which clinical study participants are exposed) is among the most important considerations".

Their design should include the study of drug effects at all ontogenesis stages, without exception, that correspond to the growth and development of the relevant pediatric population. Also fundamental are the correct choice of animal species, based on its sensitivity to the effects of the drug, the availability of relevant data from preclinical studies on adult animals and the planned procedures and types of studies, some of which can only be carried out on certain animal species.

Pathologists should be able to compare tissue structures in parallel in an experiment, both normal and drug-treated, at all stages of ontogenesis, and have access to as many reference and image databases as possible.

All of the above requirements are the minimum to ensure adequate support for clinical trials in the pediatric population.

Interests disclosure

The authors have no conflicts of interest to declare.

References

[1] Janczura M, Sip S, & Cielecka–Piontek J. The Development of Innovative Dosage Forms of the Fixed–Dose Combination of Active Pharmaceutical Ingredients. Pharmaceutics, 2022; 14(4): 834. DOI: 10.3390/pharmaceutics14040834

[2] Galkin OYu, Lutsenko TM, Gorshunov YuY, Motronenko VV. Development of the method for microbiological purity testing of recombinant human interleukin–7–based product. The Ukrainian Biochemical Journal, 2014; 89(3):52–59. DOI: 10.15407/ubj89.03.052

[3] Volodina TT, Korotkevich NV, Romaniuk SI, Galkin OYu, Kolybo DV, Komisarenko SV. Implementation of Dietary Supplements with Effect of Dezintoxication and Improvement of Osteogenesis and Metabolism. Science and Innovation, 2017; 13(6): 39–50. DOI: 10.15407/scine13.06.039

[4] Turner MA, Cheng K, de Wildt S, Hildebrand H, Attar S, Rossi P, Bonifazi D, Ceci A, Claverol J, Nafria B, & Giaquinto C. European research networks to facilitate drug research in children. British Journal of Clinical Pharmacology, 2022; 88(10): 4258–4266. DOI: 10.1111/bcp.14545

[5] Department of Health and Human Services (US); Food and Drug Administration (FDA); Center for Drug Evaluation and Research (CDER). *Nonclinical Safety Evaluation of Pediatric Drug Products*; Pharmacology and Toxicology, Office of Training and Communications, Division of Drug Information: Rockville, MD, USA, 2006. https://www.fda.gov/media/119658/download

[6] European Medicines Agency (EMA). *Paediatric Committee (PDCO)—Guideline on Pharmaceutical Development of Medicines for Paediatric Use*; EMEA: London, UK, 2014. https://www.ema.europa.eu/en/pharmaceutical–development–medicines–paediatric–use–scientific–guideline

[7] Tavares D, Chien H–T, Sheean ME, Theunissen P, van Meer P and Van Malderen K. From guideline to practice: three years of ICH S11 insights and recommendations. *Front. Med*. 2025; 12:1537001. DOI: 10.3389/fmed.2025.1537001

[8] Halpern SA. American pediatrics: the social dynamic of professionalism, 1880–1980. Berkeley: University of California Press, 1988:52.

[9] Drug dosage in children. In: Ritschel WA. Handbook of basic pharmacokinetics. 2nd ed. Hamilton, Ill.: Drug Intelligence, 1980:296–310.

[10] Rao D.B. , Hoberman A.M., Brown P.C. , Varela A., Bolon B. Regulatory Perspectives on Juvenile Animal Toxicologic Pathology. *Toxicologic Pathology*. 2021; 49(8):1303–1404 DOI: 10.1177/01926233211046869

[11] Baldrick P. Juvenile animal studies in human drug development. *Expert opinion on pharmacotherapy*.2025; 26, no. 3, 227–229. DOI: 10.1080/14656566.2025.2456589

[12] Kearns GL. Impact of developmental pharmacology on pediatric study design: overcoming the challenges. *J Allergy Clin Immunol.* 2000; 106: Suppl:S128–S138. DOI: 10.1067/mai.2000.109419.

[13] Agunod M, Yamaguchi N, Lopez R, Luhby AL, Glass GB. Correlative study of hydrochloric acid, pepsin, and intrinsic factor secretion in newborns and infants. *Am J Dig Dis*. 1969;14:400–414. DOI: 10.1007/BF02239360

[14] Rodbro P, Krasilnikoff PA, Christiansen PM. Parietal cell secretory function in early childhood. *Scand J Gastroenterol*. 1967;2: 209–213. DOI: 10.3109/00365526709180071

[15] Huang NN, High RH. Comparison of serum levels following the administration of oral and parenteral preparations of penicillin to infants and children of various age groups. *J Pediatr 1953*;42:657–68. DOI: 10.1016/s0022–3476(53)80422–1.

[16] Suchy FJ, Balistreri WF, Heubi JE, Searcy JE, Levin RS. Physiologic cholestasis: elevation of the primary serum bile acid concentrations in normal infants. *Gastroenterology.* 1981;80:1037–1041. DOI: 10.1016/0016-5085(81)90078-0

[17] Poley JR, Dower JC, Owen CA Jr, Stickler GB. Bile acids in infants and children. *J Lab Clin Med* .1964;63:838–846.

[18] Heimann G. Enteral absorption and bioavailability in children in relation to age. *Eur J Clin Pharmacol*. 1980;18:43–50. DOI: 10.1007/BF00561477.

[19] Weaver LT, Austin S, Cole TJ. Small intestinal length: a factor essential for gut adaptation. *Gut*. 1991;32:1321–1323. DOI: 10.1136/gut.32.11.1321.

[20] Yanowitz TD, Yao AC, Pettigrew KD, Werner JC, Oh W, Stonestreet BS. Postnatal hemodynamic changes in very–low–birthweight infants. *J Appl Physiol*. 1999;87:370–380. DOI: 10.1152/jappl.1999.87.1.370.

[21] Martinussen M, Brubakk AM, Vik T, Yao AC. Mesenteric blood flow velocity and its relation to transitional circulatory adaptation in appropriate for gestational age preterm infants. *Pediatr Res*. 1996;39:275–280. DOI: 10.1203/00006450–199602000–00015.

[22] Martinussen M, Brubakk AM, Linker DT, Vik T, Yao AC. Mesenteric blood flow velocity and its relation to circulatory adaptation during the first week of life in healthy term infants. *Pediatr Res*. 1994;36:334–339. DOI: 10.1203/00006450–199409000–00011.

[23] Hall SD, Thummel KE, Watkins PB, et al. Molecular and physical mechanisms of first–pass extraction. *Drug Metab Dispos*. 1999;27:161–166. DOI: 10.1016/S0090-9556(24)15271-3

[24] Stahlberg MR, Hietanen E, Maki M. Mucosal biotransformation rates in the small intestine of children. *Gut*. 1988;29:1058–1063. DOI:10.1136/gut.29.8.1058

[25] Gibbs JP, Liacouras CA, Baldassano RN, Slattery JT. Up–regulation of glutathione S–transferase activity in enterocytes of young children. *Drug Metab Dispos*. 1999;27:1466–1469. DOI: 10.1016/S0090-9556(24)14957-4
[26] Linday L, Dobkin JF, Wang TC, Butler VP Jr, Saha JR, Lindenbaum J. Digoxin inactivation by the gut flora in infancy and childhood. *Pediatrics*. 1987;79:544–548. DOI: 10.1542/peds.79.4.544
[27] Rutter N. Percutaneous drug absorption in the newborn: hazards and uses. *Clin Perinatol*. 1987;14:911–930. DOI: 10.1016/s0095-5108(18)30740-1
[28] Okah FA, Wickett RR, Pickens WL,Hoath SB. Surface electrical capacitance as a noninvasive bedside measure of epidermal barrier maturation in the newborn infant. *Pediatrics*. 1995;96:688–692. DOI: 10.1542/peds.96.4.688
[29] Fluhr JW, Pfisterer S, Gloor M. Direct comparison of skin physiology in children and adults with bioengineering methods. *Pediatr Dermatol*. 2000;17:436–439. DOI: 10.1046/j.1525–1470.2000.01815.x.
[30] Amato M, Huppi P, Isenschmid M, Schneider H. Developmental aspects of percutaneous caffeine absorption in premature infants. *Am J Perinatol*. 1992;9:431–434. DOI: 10.1055/s–2007–999282.
[31] West DP, Worobec S, Solomon LM. Pharmacology and toxicology of infant skin. *J Invest Dermatol*. 1981;76:147–150. DOI: 10.1111/1523–1747.ep12525553.
[32] Friis–Hansen B. Water distribution in the foetus and newborn infant. *Acta Paediatr Scand*. Suppl 1983;305:7–11. DOI: 10.1111/j.1651–2227.1983.tb09852.x.
[33] Siber GR, Echeverria P, Smith AL, Paisley JW, Smith DH. Pharmacokinetics of gentamicin in children and adults. *J Infect Dis*. 1975;132:637–651. DOI: 10.1093/infdis/132.6.637.
[34] Windorfer A, Kuenzer W, Urbanek R. The influence of age on the activity of acetylsalicylic acid–esterase and protein–salicylate binding. *Eur J Clin Pharmacol*. 1974;7:227–231. DOI: 10.1007/BF00560385.
[35] Ehrnebo M, Agurell S, Jalling B, Boreus LO. Age differences in drug binding by plasma proteins: studies on human foetuses, neonates and adults. *Eur J Clin Pharmacol*. 1971;3:189–193. DOI: 10.1007/BF00565004
[36] Fredholm BB, Rane A, Persson B. Diphenylhydantoin binding to proteins in plasma and its dependence on free fatty acid and bilirubin concentration in dogs and newborn infants. *Pediatr Res*. 1975;9:26–30. DOI: 10.1203/00006450-197501000-00005
[37] Lin JH, Yamazaki M. Role of P–glycoprotein in pharmacokinetics: clinical implications. *Clin Pharmacokinet*. 2003;42:59–98. DOI: 10.2165/00003088–200342010–00003.
[38] Hines RN, McCarver DG. The ontogeny of human drug–metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther*. 2002;300:355–360. DOI: 10.1124/jpet.300.2.355
[39] McCarver DG, Hines RN. The ontogeny of human drug metabolizing enzymes: phase II conjugation enzymes and regulatory mechanisms. *J Pharmacol Exp Ther*. 2002; 300:361–366. DOI: 10.1124/jpet.300.2.361
[40] Young WS, Lietman PS. Chloramphenicol glucuronyl transferase: assay, ontogeny and inducibility. *J Pharmacol Exp Ther*. 1978; 204:203–211. DOI: 10.1016/s0022-3565(25)31127-4
[41] Weiss CF, Glazko AJ, Weston JK. Chloramphenicol in the newborn infant: a physiologic explanation of its toxicity when given in excessive doses. *N Engl J Med*. 1960; 262:787–794. DOI: 10.1056/NEJM196004212621601.
[42] Arant BS Jr. Developmental patterns of renal functional maturation compared in the human neonate. *J Pediatr*. 1978;92:705–712. DOI: 10.1016/s0022–3476(78)80133–4.
[43] van den Anker JN, Schoemaker RC, Hop WC, et al. Ceftazidime pharmacokinetics in preterm infants: effects of renal function and gestational age. *Clin Pharmacol Ther*. 1995;58:650–659. DOI: 10.1016/0009–9236(95)90021–7.
[44] James LP, Marotti T, Stowe CD, Farrar HC, Taylor BJ, Kearns GL. Pharmacokinetics and pharmacodynamics of famotidine in infants. *J Clin Pharmacol*. 1998;38:1089–1095. DOI: 10.1177/009127009803801202
[45] Brion LP, Fleischman AR, Schwartz GJ. Gentamicin interval in newborn infants as determined by renal function and postconceptional age. *Pediatr Nephrol*. 1991;5:675–679. DOI: 10.1007/BF00857868.
[46] Szefler SJ, Wynn RJ, Clarke DF, Buckwald S, Shen D, Schentag JJ. Relationship of gentamicin serum concentrations to gestational age in preterm and term neonates. *J Pediatr*. 1980;97:312–315. DOI: 10.1016/s0022–3476(80)80506–3.
[47] van den Anker JN, Hop WC, de Groot R, et al. Effects of prenatal exposure to betamethasone and indomethacin on the glomerular filtration rate in the preterm infant. *Pediatr Res*. 1994;36:578–581. DOI: 10.1203/00006450–199411000–00006.
[48] Takahashi H, Ishikawa S, Nomoto S, et al. Developmental changes in pharmacokineticsand pharmacodynamics of warfarin enantiomers in Japanese children. *Clin Pharmacol Ther*. 2000;68:541–555. DOI: 10.1067/mcp.2000.110977.
[49] Marshall JD, Kearns GL. Developmental pharmacodynamics of cyclosporine. *Clin Pharmacol Ther*. 1999;66:66–75. DOI: 10.1016/S0009–9236(99)70055–X.
[50] Marshall J, Rodarte A, Blumer J, Khoo K–C, Akbari B, Kearns GL. Pediatric pharmacodynamics of midazolam oral syrup. *J Clin Pharmacol*. 2000;40:578–589. DOI: 10.1002/j.1552-4604.2000.tb05983.x
[51] deWildt SN, Kearns GL, Sie SD, Hop WCJ, van den Anker JN. Pharmacodynamics of intravenous and oral midazolam in preterm infants. *Clin Drug Invest*. 2003;23:27–38. DOI: 10.2165/00044011–200323010–00004.
[52] Silverman ES, Liggett SB, Gelfand EW, et al. The pharmacogenetics of asthma: a candidate gene approach. *Pharmacogenomics J*. 2001;1:27–37. DOI: 10.1038/sj.tpj.6500005.
[53] Pui CH, Campana D, Evans WE. Childhood acute lymphoblastic leukaemia — current status and future perspectives. *Lancet Oncol*. 2001;2:597–607. DOI: 10.1016/S1470–2045(01)00516–2
[54] Leeder JS. Ontogeny of drug–metabolizing enzymes and its influence on the pathogenesis of adverse drug reactions in children. *Curr Ther Res*. 2001;62:900–912. DOI: 10.1007/978–1–0716–1554–6_18.
[55] Jadcherla SR, Berseth CL. Effect of erythromycin on gastroduodenal contractile activity in developing neonates. *J Pediatr Gastroenterol Nutr*. 2002;34:16–22. DOI: 10.1097/00005176–200201000–00005.
[56] Alcorn J, McNamara PJ. Ontogeny of hepatic and renal systemic clearance pathways in infants. *Clin Pharmacokinet*. 2002;41:1077–1094. DOI: 10.2165/00003088–200241130–00005.
[57] Hurtt MA, Engel S. An update of juvenile animal studies in the European Union: what do the numbers say? *Reprod Toxicol*. 2015;56:105–108. DOI: 10.1016/j.reprotox.2015.04.011. Epub 2015 Apr 30.
[58] Bailey G, Marien D. The value of juvenile animal studies "What have we learned from preclinical juvenile toxicity studies? II". Birth Defects Res. Part B. *Dev Reprod Toxicol*. 2011;92:273–291. DOI: 10.1002/bdrb.20328
[59] Barrow PC, Barbellion S, Stadler J. Preclinical evaluation of juvenile toxicity. *Methods Mol Biol*. 2011;691:17–35. DOI: 10.1007/978–1–60761–849–2_2.
[60] Kaufman RE. Drug therapeutics in the infant and child. In: Yaffe SJ,Aranda JV, eds. Pediatric Pharmacology: Therapeutic Principles in Practice. Washington, DC: Saunders Company; 1992:212–219.

[61] Parker RM. Juvenile toxicology. In: Derelanko M, Auletta C, eds. Handbook of Toxicology. 3rd Edition. Boca Raton, FL: CRC Press; 2014:399.
[62] Buelke–Sam J. Comparative schedules of development in rats and humans: implications for developmental neurotoxicity testing. *Toxicological Sciences*. 2003; 72(Suppl 1): 169
[63] Löscher W, Kaila K. CNS pharmacology of NKCC1 inhibitors. *Neuropharmacology*. 2022 Mar 1;205:108910. DOI: 10.1016/j.neuropharm.2021.108910. Epub 2021 Dec 6.
[64] Kilborn S, Trudel G, Uhthoff H. Review of growth plate closure compared with age at sexual maturity and lifespan in laboratory animals. *Contemp Top Lab Anim Sci*. 2002;41(5):21–26.
[65] Hoberman AM, Lewis EM, eds. Pediatric Non–Clinical Drug Testing: Principles, Requirements and Practices. Hoboken, New Jersey: John Wiley; 2011:339 p. DOI: 10.1002/9781118168226
[66] Cappon GD, Bailey G P, Buschmann J, et al. Juvenile Animal Toxicity Study Designs to Support Pediatric Drug Development. *Birth Defects Research (Part B)*. 2009; 86:463–469. DOI: 10.1002/bdrb.20220.
[67] EMEA. 2008. European Medicines Agency (EMEA), Committee for Human Medicinal Products (CHMP). Guideline on the need for non-clinical testing in juvenile animals on human pharmaceuticals for paediatric indications. January 2008. https://www.ema.europa.eu/en/human–regulatory–overview/research–development/scientific–guidelines/multidisciplinary–guidelines/scientific–guidelines–paediatrics
[68] FDA. 2006. United States Food and Drug Administration (FDA).Guidance document. Nonclinical safety evaluation of pediatric drug products. Silver Spring, MD: FDA. https://www.fda.gov/regulatory–information/search–fda–guidance–documents/nonclinical–safety–evaluation–pediatric–drug–products
[69] ICH. 2009. ICH M3 guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. Geneva: ICH. https://www.ema.europa.eu/en/documents/scientific–guideline/ich–guideline–m3r2–non–clinical–safety–studies–conduct–human–clinical–trials–and–marketing–authorisation–pharmaceuticals–step–5_en.pdf
[70] Hurtt ME, Sandler JD. Comparative organ system development: introduction. *Birth Defects Res B. Dev Reprod Toxicol*. 2003 Apr;68(2):85. DOI: 10.1002/bdrb.10011.
[71] Beckman DA, Feuston M. Landmarks in the development of the female reproductive system. *Birth Defects Res B. Dev Reprod Toxicol*. 2003;68:137–143. DOI: 10.1002/bdrb.10016.
[72] Hew KW, Keller KA. Postnatal anatomical and functional development of the heart: a species comparison. *Birth Defects Res B Dev Reprod Toxicol*. 2003; 68:309–320. DOI: 10.1002/bdrb.10034.
[73] Holsapple MP, West LJ, Landreth KS. Species comparison of anatomical and functional immune system development. *Birth Defects Res B Dev Reprod Toxicol*. 2003; 68:321–334. DOI: 10.1002/bdrb.10035.
[74] Marty MS, Chapin RE, Parks LG, Thorsrud BA. Development and maturation of the male reproductive system. *Birth Defects Res B Dev Reprod Toxicol*. 2003; 68:125–136. DOI: 10.1002/bdrb.10015
[75] Walthall K, Cappon GD, Hurtt ME, Zoetis T. Postnatal development of the gastrointestinal system: a species comparison. *Birth Defects Res B Dev Reprod Toxicol* 2005; 74:132–156. DOI: 10.1002/bdrb.20040
[76] Watson RE, Desesso JM, Hurtt ME, Cappon GD. Postnatal growth and morphological development of the brain: a species comparison. *Birth Defects Res B Dev Reprod Toxicol.* 2006; 77:471–484. DOI: 10.1002/bdrb.20090
[77] Wood SL, Beyer BK, Cappon GD. Species comparison of postnatal CNS development: functional measures. *Birth Defects Res B Dev Reprod Toxicol.* 2003; 68:391–407. DOI: 10.1002/bdrb.10037
[78] Zoetis T, Hurtt ME. Species comparison of anatomical and functional renal development. *Birth Defects Res B Dev Reprod Toxicol.* 2003; 68:111–120. DOI: 10.1002/bdrb.10013
[79] Zoetis T, Hurtt ME. Species comparison of lung development. *Birth Defects Res B Dev Reprod Toxicol.* 2003; 68:121–124. DOI: 10.1002/bdrb.10014
[80] Zoetis T, Tassinari MS, Bagi C, Walthall K, Hurtt ME. Species comparison of postnatal bone growth and development. *Birth Defects Res B Dev Reprod Toxicol.* 2003; 68:86–110. DOI: 10.1002/bdrb.10012
[81] Kim NN., Parker RM., Weinbauer GF., et al.Points to Consider in Designing and Conducting Juvenile Toxicology Studies. *International Journal of Toxicology*. 2017; 36(4): 325–339 DOI: 10.1177/1091581817699975
[82] Seely JC.A brief review of kidney development, maturation, developmental abnormalities, and drug toxicity: juvenile animal relevancy. *J Toxicol Pathol*. 2017; 30: 125–133. DOI: 10.1293/tox.2017–0006
[83] Schreuder MF, Bueters RR, Huigen MC, Russel FG, Masereeuw R, and van den Heuvel LP. Effect of drugs on renal development. *Clin J Am Soc Nephrol*. 2011; 6: 212–217. DOI: 10.2215/CJN.04740510
[84] Whitney KM. Testicular histopathology in juvenile rat toxicity studies. Systems Biology in *Reproductive Medicine*. 2012; 58: 51–56. DOI: 10.3109/19396368.2011.647380
[85] Stoker, T.E., Parks, L.G., Gray, L.E. and Cooper, R.L. Endocrine–disrupting chemicals: Prepubertal exposures and effects on sexual maturation and thyroid function in the male rat. A focus on the EDSTAC recommendations. *Crit Rev Toxicol*. 2000; 30:197–252. DOI: 10.1080/10408440091159194.
[86] Wang Y, Yang XD, Chen ZQ, Hu C, Wang YB. Recent advances in the application of Injectable hydrogels for myocardial infarction. *Biomed Eng Commun*. 2025;4(4):25. DOI:10.53388/BMEC2025025

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СПЕЦИФІКА ФАРМАКОЛОГІЧНИХ ТА ТОКСИКОЛОГІЧНИХ ДОСЛІДЖЕНЬ НА МОЛОДЯЧИХ ТВАРИНАХ

Анотація. Оскільки рівень індивідуалізації медицини та фармакології постійно зростає, наукове співтовариство стає серйозно занепокоєним недостатньою оцінкою безпеки існуючих і розроблюваних ліків для педіатричної популяції. Метою цього огляду є

аналіз основних проблем, що виникають під час розробки та доклінічної оцінки лікарських засобів для дітей та підлітків, з урахуванням їхніх вікових фізіологічних та біохімічних характеристик, а також при виборі адекватних ювенільних експериментальних моделей серед різних видів тварин. Планування досліджень на молодих тваринах має базуватися на конкретній віковій групі дитячого населення, для якої розробляється конкретний препарат. Вони не можуть проводитися за стандартизованими протоколами досліджень і вимагають індивідуального підходу в кожному конкретному випадку. Їх дизайн повинен включати дослідження дії лікарських засобів на всіх без винятку етапах онтогенезу, які відповідають росту та розвитку відповідної дитячої популяції. Також фундаментальними є правильний вибір виду тварини, заснований на його чутливості до дії препарату, наявності відповідних даних доклінічних досліджень на дорослих тваринах і запланованих процедурах і типах досліджень, деякі з яких можуть бути проведені тільки на певних видах тварин. Патологоанатоми повинні мати можливість паралельно порівнювати тканинні структури в експерименті, як контрольних тварин, так і тварин із введенням лікарського засобу, на всіх етапах онтогенезу, і мати доступ до якомога більшої кількості довідкових баз даних і баз даних зображень. Усі вищезазначені вимоги є мінімальними для забезпечення адекватної підтримки клінічних випробувань у педіатричній популяції.

Ключові слова: дослідження на молодих тваринах; етапи онтогенезу; вибір виду тварин; безпека; дія препаратів; педіатрична популяція.