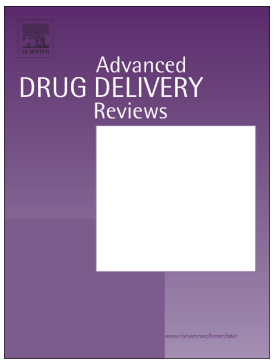

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Pharmacokinetics of Nanotechnology-Based Formulations in Pediatric Populations

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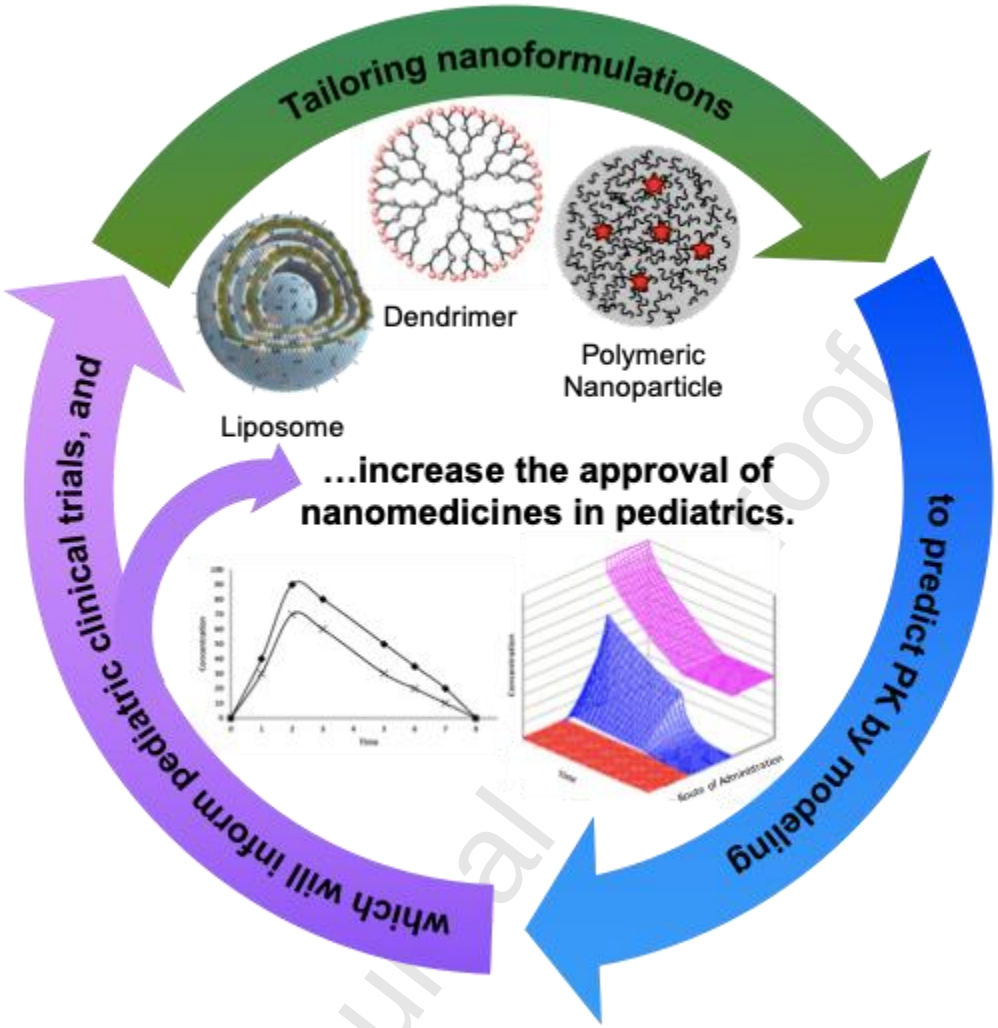
Abstract

The development of therapeutics for pediatric use has advanced in the last few decades. However, off-label use of adult medications in pediatrics remains a significant clinical problem. Furthermore, the development of therapeutics for pediatrics is challenged by the lack of pharmacokinetic (PK) data in the pediatric population. To promote the development of therapeutics for pediatrics, the United States Pediatric Formulation Initiative recommended the investigation of nanotechnology-based delivery systems. Therefore, in this review, we provided comprehensive information on the PK of nanotechnology-based formulations from preclinical and clinical studies in pediatrics. Specifically, we discuss the relationship between formulation parameters of nanoformulations and PK of the encapsulated drug in the context of pediatrics. We review nanoformulations that include dendrimers, liposomes, polymeric long-acting injectables (LAIs), nanocrystals, inorganic nanoparticles, polymeric micelles, and protein nanoparticles. In addition, we describe the importance and need of PK modeling and simulation approaches used in predicting PK of nanoformulations for pediatric applications.

Keywords: Pediatrics, Pharmacokinetics, Nanotechnology, Ontogeny, Half-life, Maturation, Modeling and simulation

Graphical Abstract



1. Introduction

Development of therapeutics for pediatrics has advanced over the past few decades as a direct result of incentives offered by the United States Food and Drug Administration (USFDA) and European Medicines Agency (EMEA) [1-3]. These incentives encouraged drug companies to evaluate their medicines for use in pediatric populations in return for extended patent protection and other financial benefits [4, 5]. In addition, the US Pediatric Formulation Initiative (PFI) recommended investigating adult studies of nanotechnology-based delivery systems for pediatrics [6]. Potential advantages of nanotechnology for pediatric formulations are similar to adult formulations and include improved drug targeting to specific tissues of interest, controlled and sustained release medications to reduce dosing frequency, increased solubility of lipophilic or otherwise insoluble therapeutic agents, and enhanced bioavailability [6]. Nanotechnology-based drug delivery platforms beneficially alter the pharmockinetics (PK) of drugs and result in a different dose-response relationship when compared with the drug itself.

Despite the developments in nanotechnology for improved drug delivery, the lack of high-quality PK data in pediatrics remains a significant problem [7]. Nanoparticle formulation development for the pediatric population is challenging because of the patient group's heterogeneity and dissimilarity to adults. Within the population, there exist subgroups (neonates, infants, toddlers, and children) which are differentiated by age [8, 9]. Pediatric patients have different preferred routes of administration and medicine-related toxicity compared to adults [10, 11], and often both active drug and formulation excipients have different bioactivity in children [12]. Dosing challenges are exacerbated by rapid growth and development during childhood, with doses of certain formulations varying 100-fold during this period [13-15]. The lack of PK data in pediatrics compounds the problem of a lack of age-appropriate formulations, leading to off-label use of drugs by clinicians and resulting in increased risk of toxicity or sub-therapeutic dosing [16].

Understanding the differences in PK of drug formulated in nanoparticles from a drug's normal PK is critical for developing dosing recommendations and evaluating the toxicity of nanoparticle-based pediatric formulations. This review summarizes the existing data on clinical PK of nanotechnology-based formulations used in pediatrics. We first provide a brief summary of the development and maturational aspects in the pediatric population that will affect the PK of nanoformulations, and the goal of regulatory initiatives to further pediatric nanoformulation development. Next, we delve into the relationship between nanoparticle properties and drug PK, and the PK of various nanoparticle-based pediatric formulations. Lastly, in looking forward for

the field of nanotechnology use in children, we discuss the importance of and need for modeling and simulation (M&S) in predicting PK of pediatric nanoparticle formulations.

2. Developmental and maturational aspects affecting nanoformulation PK in pediatrics

Upon administration into the body, nanotherapeutic formulations undergo absorption, distribution, metabolism, and elimination (ADME). The most dramatic physiological changes affecting ADME of nanotherapeutics occur in the infant and toddler ages – these are briefly outlined here and are summarized in Figure 1. During the neonatal period, absorption of nanotherapeutics is affected by relatively high gastric pH, with a pH of 4.6 in the first week of life compared to an adult range of 1.5-3.5. There is also an increased gastric emptying rate at 75 min in neonates compared to 45 min in adult males and 60 min in adult females for calorie-containing liquids [17]. In the intestinal lumen, permeability is generally increased due to the immaturity of the mucosa, but transport systems are also immature, so some transporter-mediated interactions can limit therapeutic absorption [18]. The gut microbiome is highly variable, ranging from completely sterile at birth, to some colonization within 4-8 hours, to adult levels in adolescence [18]. However, factors like whether the infant drinks maternal or artificial milk can influence the microbial composition, increasing observed variability of intestinal permeability at young ages [19]. The relationship between the gut microbiome and intestinal permeability has been covered extensively [20-22]. Developmental changes also affect adsorption after alternative routes of nanotherapeutic administration, such as transdermal [23], oral transmucosal [24], rectal [25], and intrapulmonary [26].

Nanotherapeutic distribution is specifically affected in infants due to proportionally higher body water, with 80-90% body weight (BW) compared to 55-60% BW in adults, and lower body fat, at 10-15% BW compared to 11-20% in adult men and 16-30% in adult women [18]. One consequence of this is relatively high volumes of distribution of water-soluble drugs. For example, gentamicin has a volume of distribution of 0.5-1.2 L/kg in infants compared to 0.2-0.3 L/kg in adults [18]. Metabolism is typically dissimilar between children and adults, and importantly, the cytochrome enzymes responsible for metabolism are immature from birth to approximately 2 years of age [27]. In general, children have higher rates of hepatic clearance than adults, resulting in higher dosages by weight. However, since the maturation of metabolic enzymes is not linear, doses must be carefully determined based on a drug's metabolic pathway and the developmental age of the patient [19, 28, 29]. Broad physiological differences including increased ventilation rate, increased cardiac output, and increased body surface area to weight compared to adults, can further impact the distribution and elimination of pediatric formulations [18]. The largest deviation from adult PK is observed as these organ structures and functions

are developing during the first 12 to 18 months [14, 15, 30]. In older children and adolescents, physiological parameters become more similar to adults, making PK values easier to predict [12, 19, 27, 31].

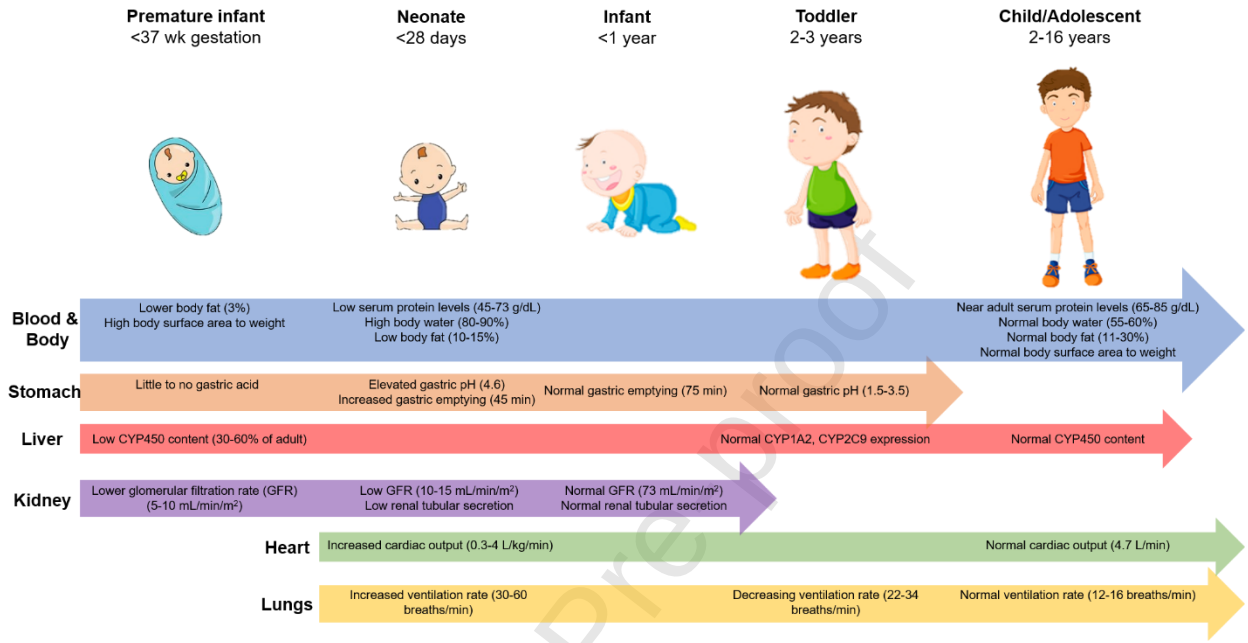


Figure 1. Developmental changes across the pediatric age range from premature infant (<37 weeks gestation) to child/adolescent (2-16 years of age). Changes in blood and body composition, and stomach, liver, kidney, heart, and lung physiology are summarized.

3. Initiatives by the US and EU for pediatric nanoformulation development

As a distinct population with unique physiologies outlined in section 2, pediatric patients require novel formulations rather than an adjusted dose or application of adult medicines. In addition to the US PFI [6], the European Pediatric Formulation Initiative (EuPFI), founded in 2007 by the European Medicines Agency (EMA), [32] recognized that pediatric biopharmaceutics is an under-researched area and highlighted the limitations of the use of biopharmaceutical classification systems in the development of pediatric medicines [30, 33]. EuPFI suggested that there is a need to establish an age-specific biopharmaceutics classification system for children to ensure that development work is relevant in producing age-appropriate medicines for children [30, 33]. Additionally, one of the priorities of the age-appropriateness of formulations workstream of EuPFI is to develop modified release formulations suitable for pediatrics [34]. For both applications of enhancing pediatric biopharmaceutics and developing pediatric-modified release dosage forms, nanotechnology-based platforms can be beneficial.

These initiatives, along with new regulations and additional funding opportunities, are evidence that the US and Europe are supportive of the application of nanotechnology-based platforms for the development of pediatric formulations. However, there remains a lack of information on how nanotechnology-based formulations proven effective for adults can be utilized for pediatric formulations. Specifically, approaches to tailor the unique properties of nanotechnology-based delivery devices, such as tunable size, shape, surface area, and surface chemistry, to fit the requirements of pediatric formulations have to be delineated using appropriate pediatric preclinical and/or clinical studies.

4. Role of properties of nanotechnology-based platforms in altered PK of drugs in pediatrics

Since nanoformulations are used to alter the biological fate of a drug, the PK profile of the nanoformulation will be different from that of the drug alone. Evaluation of a PK profile involves monitoring drug concentrations in blood and tissue over a period long enough to fully capture ADME processes. Key PK parameters used to describe drug concentration in the blood include C_{max} (maximum concentration), $t_{1/2}$ (half-life, which is the time to reduce plasma concentration by half), CL (clearance), AUC (area under the curve, an indication of the total drug exposure), and MRT (mean residence time, or the average time that a drug molecule stays in the body) [35]. An ideal nanoformulation would result in increased drug C_{max}, $t_{1/2}$, AUC, and MRT, and reduced CL compared to the free drug. However, the study and application of nanoformulations in the pediatric population has been limited [36]. Additionally, most preclinical studies probing nanoparticle physicochemical properties are conducted in adult models after intravenous administration [37], while many pediatric formulations are delivered orally [13]. We have summarized the effect of nanoparticle design parameters on nanoformulation PK in adult models, and provide a prediction of how these design parameters will affect PK in pediatrics (Table 1).

Nanoparticle clearance via the mononuclear phagocyte system (MPS) [38] is the most commonly used guide for the size of an ideal nanoparticle. Particles smaller than 5.5 nm in diameter are filtered through the kidney [39]. Fenestrations in the capillaries in the liver are 50-100 nm, and sub-50 nm interact with hepatocytes [40]. The upper limit of particle size is determined by splenic filtration, which is low for particles in the 100 nm size range and increases with increasing size. No current evidence exists to show that these fenestration sizes vary between adult and pediatric populations. Size-based accumulation also occurs in other

Table 1. Role of various nanoparticle design parameters in determining PK, with predicted adjustments for the pediatric population (Section 4).

Nanoparticle Design Parameter	Adult PK Finding	Relevant Pediatric Physiology and Predicted PK Behavior	Refs
Size	Small particles (<5.5 nm) are filtered by the kidney and large particles (200-500 nm) are filtered by the spleen	Filtration is likely similar to adults (endothelial layer is mature at birth)	[40, 41]
	Protein adsorption is greater on larger particles compared to smaller particles leading to increased MPS clearance by opsonization	Opsonization may be reduced (total plasma protein level is lower in neonates and young infants compared to adults)	[12, 42-44]
	Mid-size particles (100-200 nm) have highest circulation time and AUC	Circulation time, AUC, and distribution are likely altered (increased cardiac output, reduced glomerular filtration rate, increased organ surface area to weight ratio)	[18, 45]
Charge	Negatively charged particles (ZP < -10 mV) larger than 20 nm in diameter exhibit strong phagocytic uptake through the MPS	Phagocytic clearance may be reduced (MPS clearance mechanisms are immature in neonates and young infants)	[12, 46, 47]
	Positively charged particles (ZP > 10 mV) induce serum protein binding	Identity of bound serum proteins are likely altered (protein distribution is age-dependent)	[43, 46]
Surface Modification	PEG coating reduces MPS clearance and increases AUC but can induce immunogenicity and hypersensitivity	PEG is well-tolerated in children	[38, 48, 49]
Shape	High aspect ratio and/or flexible shapes (disks, polymeric worms, dendrimers) demonstrate reduced macrophage uptake and increased circulation time compared to low aspect ratio shapes (spheres)	Shape-dependent macrophage uptake may be altered (MPS is immature until 1 year of age) Ability of high aspect ratio and flexible shapes to align with blood flow may increase circulation time (smaller diameter and more delicate blood vessels)	[47, 50-52]
Composition	Increased lipid dose can reduce macrophage uptake due to lipid saturation	Adults and children (older than 1 year) respond similarly to increased lipid doses through macrophage uptake	[53, 54]
	Polymer degradation and toxicity are dependent on chemistry (i.e. amine and hydroxyl groups)	Degradation and toxicity may be altered in children (immaturity of cytochrome enzymes, increased organ surface area to weight ratio)	[27, 55, 56]

organs such as the liver and the lung, which is particularly important in the pediatric population due to decreased airway caliber and increased ventilation rate of children [57]. Although nanoparticles of all sizes demonstrate increased accumulation in the lungs of children compared to adults, tracheobronchial deposition is highest for nanoparticles under 10 nm in size, and alveolar deposition is highest for nanoparticles between 10-20 nm in size [58]. Presence of disease, relevant for children with asthma or obstructive lung disease, can increase pulmonary retention of nanoparticles [57].

An additional consideration for size effects on PK stems from the correlation between nanoparticle size and protein adsorption, which results in MPS clearance. Upon nanoparticle absorption into the bloodstream, a variety of serum proteins adsorb to a particle surface, which allows for recognition, internalization, and clearance by macrophages [59]. Smaller nanoparticles (80 nm) have lower protein adsorption (6%) compared to larger sized nanoparticles (171 and 243 nm, which had 23 and 34% adsorption respectively) due to the smaller surface area, doubling the circulation time compared to the larger particles [42]. In general, serum protein adsorption occurs to a much lesser extent in the pediatric population as it is well known that total plasma protein level is lower in neonates and young infants (45-73 g/L) compared to adults (65-85 g/L), only approaching adult values around 1 year of age [12, 43, 44].

Nanoparticle PK and protein binding is also influenced by nanoparticle surface charge. As a general rule, negatively charged particles (ZP < -10 mV) larger than 20 nm in diameter exhibit strong phagocytic uptake through the MPS [46] and positively charged particles (ZP > 10 mV) induce serum protein binding. Thus, neutrally charged nanoparticles (ZP +/- 10 mV) demonstrate the lowest MPS clearance and the longest circulation times [35]. In the pediatric population, this effect may be slightly less significant as MPS clearance mechanisms are immature and serum protein levels are low [12, 47]. Importantly, the identity of bound serum proteins has been shown to vary with nanoparticle charge. Cationic nanoparticles bind serum proteins like albumin with an isoelectric point (pI) < 5.5, while negatively charged particles adsorb proteins like IgG with a pI > 5.5 [60, 61]. Additionally, each serum protein has unique age-specific variation. For example, the activity of fibrinogen increases up to 5 years of age while α-2-macroglobulin is overexpressed in children compared to adults [43].

Independent of age, protein binding is associated with increased opsonization and hepatic clearance of both positive (ZP > 10 mV) and negative (ZP < -10 mV) nanoparticles [62, 63]. Many groups have successfully shown surface coating with poly(ethylene glycol) (PEG) to neutralize surface charge and shield from MPS uptake [64-66]. PEG is a relatively inert hydrophilic polymer that provides steric hindrance and charge shielding, preventing protein

interaction and binding and ultimately increasing nanoparticle circulation time [38, 48]. Although PEGylation can provide many benefits, PEG has been shown to induce immunogenicity and hypersensitivity [67-71] and is associated with weakened interaction between nanoparticles and target cells, often causing inefficient intracellular delivery. However, there is some indication that children can tolerate PEG exposure; for example, it is a major excipient in factor VIII and factor IX therapies for pediatric hemophilia. Stidl *et al.* estimated the total PEG exposure of the pediatric population to be substantial (over 26 g/year) over the past several decades with no evidence of adverse consequences [49]. Alternatives to PEG are not widely studied but include polyamino acids, glycopolymers, and polyoxazolines, which have all been shown to have similar MPS-shielding activity to PEG [72, 73]. Zwitterionic polymers have demonstrated enhanced protein stability and PK, compared to PEG coatings, without inducing an immunogenic response, although they have yet to be tested in neonatal or pediatric animals. These surface coating strategies may further reduce concerns of toxicity and tolerability for the pediatric population.

Many investigators have shown that nanoparticle shape can play a critical role in phagocytosis, thus affecting circulation time. Champion and Mitragotri conducted a characterization of macrophage uptake with various nanoparticle shapes, and found high aspect ratio particles were more successful at avoiding phagocytosis due to the increased presentation of low curvature regions (flat sides) over high curvature regions (ends) [50, 74]. These findings in adult models may translate well to the pediatric population once the MPS system reaches maturity after 1 year of age [47]. Discher *et al.* have generated high aspect ratio worm-shaped polymer nanoparticles that exhibit ultra-prolonged circulation time (half-life of 5 days), likely due to unique hydrodynamic properties that allowed the nanoparticle to align with blood flow and evade MPS uptake [51, 75]. Worms also have inherent flexibility, which may play a role in extending circulation time. This might be especially advantageous in pediatric populations, where greater cardiac output results in shorter circulation times on average [12].

Lastly, material composition can have a nontrivial effect on serum protein binding. For example, lipid content can affect clearance and circulation time, where an increased lipid dose leads to prolonged half-life of the nanoformulation [76, 77]. In one dose-exposure study of a liposomal antifungal formulation, adults and children (ages 1-17) responded similarly to increased lipid doses [54]. This suggests that compositional trends are preserved between pediatric and adult populations once the MPS system approaches mature function around 1 year of age [47]. Composition also critically affects polymeric and inorganic nanoformulations. Poly(lactic-*co*-glycolic acid) (PLGA) is a favored polymer for drug delivery applications because

of its long clinical experience, biocompatibility, and possibilities for sustained release of a therapeutic [78]. The ratio of lactic to glycolic acid monomers is known to control nanoformulation half-life and degradation in a U-shaped curve, with 50:50 resulting in fastest degradation and increasing either lactic or glycolic components increases half-life and slows degradation [55, 79]. Lower molecular weight PLGA (3-9kDa) has also been shown to have faster degradation than higher molecular weights (>11kDa) [80]. Dendrimers demonstrate compositional trends such as increased cytotoxicity of amine-terminated polyamidoamine (PAMAM) dendrimers compared to polyester dendrimers, due to either increased toxicity of amine groups or a shielding effect of hydroxyl groups on polyester dendrimers [56]. Understanding toxicity and degradation, especially as an effect of compositional parameters, is critical for pediatric formulation development. It will be important to extend these studies to pediatric age groups, including infants and neonates, in order to better inform development and dosing of novel nano-based therapies.

5. Clinical PK of various nanotechnology-based drugs in pediatrics.

While the preclinical evaluation of nanoformulations in pediatric aged animals requires more investigation, a variety of nanoparticle formulations have been tested clinically in the pediatric population. In this section, we highlight several clinical studies of nanoformulation PK in pediatrics, and provide a comparative analysis to adult PK data, where data is available.

5.1 Liposomes

Currently, there are 15 FDA approved liposomal formulations that are clinically used for various indications [81]. Liposomes are the most widely studied nanotechnology-based formulations in pediatrics. Marina *et al.*, 2002 reported a dose escalation (40 - 70 mg/m^2 i.v. over 60 min) PK study of Doxil® in children with recurrent or refractory solid tumors [82]. Doxil®, approved by the FDA in 1995, is a doxorubicin formulation wherein the drug is encapsulated in PEG-coated liposomes. Doxil® was initially approved for the treatment of multiple cancers, including ovarian cancer, AIDS-related Kaposi's sarcoma, and multiple myeloma [83, 84]. Marina *et al.* measured the total doxorubicin (free doxorubicin + doxorubicin in liposomes) in plasma samples obtained from patients. Similar to adults, Doxil® showed low clearance (mean 0.03 liter/h/m^2) and prolonged half-life (mean of 36.4 h) in children when compared to conventional doxorubicin [82]. In pediatrics, the steady-state volume of distribution (V_d) of Doxil® (1.45 L/m^2) was 436 times smaller than that of conventional doxorubicin (632.5 L/m^2) [85]. The small V_d of Doxil® suggests that it is restricted largely to the plasma-intravascular space. Interestingly, the estimated

elimination half-life of Doxil® in pediatrics (mean 36.4 h) is approximately half the estimate in adults (mean 73.9 h) [86]. The low half-life of Doxil® in the pediatric population may be due to decreased protein binding of doxorubicin (74-76 % plasma protein bound) because of reduced concentrations of plasma proteins in pediatrics [87], as discussed in section 4.

The other liposomal drugs whose PK were evaluated in pediatrics are: Marqibo® (Vincristine sulfate liposomes injection) [88], DaunoXome® (liposomal daunorubicin) [89, 90], DepoCyte® (liposomal cytarabine) [91], AmBisome® (liposomal amphotericin B) [54], and SPI-77 (liposomal cisplatin) [92]. In all these studies, the PKs of liposomal formulations in the pediatric population were different from adults (Table 2).

5.2 Dendrimers

Dendrimers are highly branched polymeric materials with well-defined uniform sizes and shapes. PAMAM dendrimers are a class of dendrimers that are widely used for their drug delivery applications [93, 94]. PAMAM dendrimer-based therapeutic OP-101 [Dendrimer N-Acetyl-Cysteine (DNAC)] is currently under Phase 1 clinical study for evaluation of the safety, tolerability, and PK in a pediatric population [95]. However, there are no prior reports of PK studies of PAMAM dendrimers in human pediatric populations. Lesniak et *al.* reported the biodistribution of cyanine dye (Cy5) conjugated fourth generation hydroxyl-terminated PAMAM dendrimers (G4-OH) in healthy and cerebral palsy neonatal rabbits after intravenous administration [96]. Dendrimer uptake was analyzed 24 hours after intravenous administration in rabbits in all major organs, and in blood serum and urine. At this time point, less than 5% of the ID remained in circulation, with over 90% cleared out of the rabbit kit. G4-OH dendrimers, which are 4 nm in size, are expected to clear out via the kidney, and in this model, dendrimer was not seen in the glomerulus 24 hours after administration. In 2018, Sharma et *al.* reported the biodistribution of mannose-conjugated G4-OH dendrimer in a neonatal rabbit model of cerebral palsy [97]. The study reported that mannose conjugation did not affect the dendrimer uptake and cellular localization in the injured brain. However, in other organs such as liver, plasma, spleen, and heart, mannose-conjugated G4-OH dendrimer accumulated at higher concentrations than when compared to G4-OH only. It was concluded from this study that the conjugation of mannose to the dendrimer increased its uptake through mannose receptor-mediated endocytosis [97].

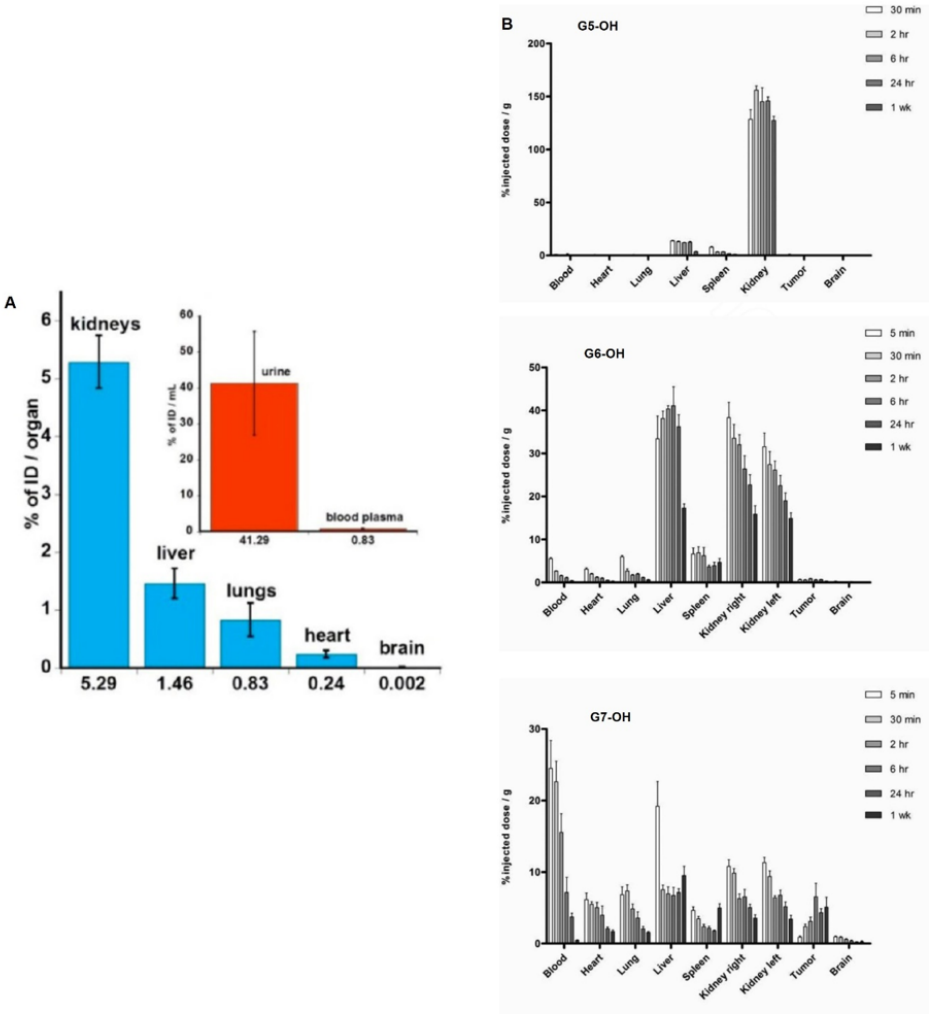
There are no current reports of biodistribution of G4-OH dendrimers in adult rabbits; however, Sadekar *et al.*, 2011 reported the biodistribution of generations-5, 6, and 7 hydroxyl-terminated dendrimers in an adult mouse model [98]. Similar to the neonatal rabbit model, G5-

Table 2. Clinical PK of various liposomal drugs in adult and pediatric populations (Section 5.1).

Name	Lipids Used for Liposomes	Adult PK parameters						Pediatric PK parameters						Ratios of pediatric versus adult PK parameters					
		Dose	$AUC_{0-\infty}$ (ng/ml.hr)	Cmax (ng/ml)	Tmax (hr)	T1/2 (hr)	CL (ml/min)	Dose	$AUC_{0-\infty}$ (ng/ml.hr)	Cmax (ng/ml)	Tmax (hr)	T1/2 (hr)	CL (ml/min)	AUC	Cmax	Tmax	T1/2	CL	Refs
Marqibo® (Vincristine sulfate)	Sphingomyelin and cholesterol	2.25 mg/m^2, i.v	14566	1220	3.7	7.66	5.75	2.25 mg/m^2, i.v	31,043	2150	1.12	10.7	1.2	2.13	1.76	0.3	1.39	0.2	[88, 99, 100]
SPI-77 (Cisplatin)	Soy PC, cholesterol and MPEG-DSPE.	200 mg/m^2, i.v	13,850,680	82,538	N/A	103	0.29	200 mg/m^2, i.v	24,004,000	2414000	N/A	78	0.15	1.73	29.24	N/A	0.75	0.51	[92, 101]
DepoCyt® (Cytarabine)	DOPC, DPPG, cholesterol	25 mg l/T	355,000	25,000	N/A	229	0.09	25 mg l/T	363,700	21,300	N/A	59.3	0.24	1.02	0.85	N/A	0.25	2.66	[102, 103]
DaunoXome® (Daunorubicin)	DSPC, cholesterol	80 mg/m^2, i.v	10330	400	N/A	0.77	233	80 mg/m^2, i.v	108206	900	N/A	12.63	7.6	10.47	2.25	N/A	16.4	0.03	[90, 104]
AmBisome® (Amphotericin B)	Soy PC, DSPG, alpha tocopherol, cholesterol	2 mg/kg i.v	288,000	22,900	N/A	6	0.16	5 mg/kg i.v	442,000	46,200	N/A	12.6	0.75	0.61	0.8	N/A	2.1	4.68	[105]

i.v. - Intravenous, l/T - Intrathecal, PC - Phosphatidylcholine, MPEG - methoxy-polyethylene glycol, DSPE – Distearoylphosphoethanolamine, DOPC – Dioleoylphosphocholine, DPPG – Dipalmitoylphosphoglycerol, DSPC – Distearoylphosphocholine, DSPG – Distearoylphosphoglycerol.

OH dendrimer showed persistent accumulation in the kidney compared to all organs. The clearance of G5-OH dendrimer in the adult mouse model was more rapid than in the neonatal rabbit model. Due to the differences in species and the label (Cy5 for neonatal rabbit studies and ^{125}I for adult mouse studies) it is not possible to draw any conclusions on the differences in PK of dendrimers in both models. Figure 2 shows the comparative PK of dendrimers in pediatric



models.

Figure 2. PK of PAMAM dendrimers in pediatric models. A. Biodistribution of PAMAM dendrimer (G4-OH)-Cy5 conjugates in major organs, plasma, and urine of neonatal rabbits. B. Biodistribution of ^{125}I radiolabeled dendrimers G5-OH, G6-OH, G7-OH in 6-8-week-old mice. Both figures are obtained with permission from references [96] and [98].

5.3 Polymeric long-acting injectables (LAIs)

Polymeric LAI's can be polymer-drug conjugates for increased circulation half-life and bioavailability, or biodegradable polymers for controlled release applications [106, 107]. From a historical perspective, polymeric LAIs were one of the early nanotechnology-based delivery systems that were approved for clinical use [108]. The first polymeric LAI Adagen® (pegademase bovine), a PEGylated adenosine deaminase enzyme, was approved by FDA in 1990 for the treatment of severe combined immunodeficiency disease (SCID) [106, 107]. Polymers used for LAIs can be of natural, synthetic, or pesudosynthetic. PEG is the most well-established polymer for the preparation of LAIs. Other polymers used for LAIs include PLGA, poly(allylamine hydrochloride) (PAA or PAH), and polyglutamic acid (PGA) [106]. Due to their clinical success in adults, many polymeric LAIs were studied for their application in pediatrics.

Adagen® (pegademase bovine) injection is a PEGylated adenosine deaminase (ADA) enzyme indicated for the treatment of SCID [109]. Adagen® PK was investigated in children with SCID-associated ADA deficiency. The 6 children included in this study ranged in age from 6 weeks to 12 years. ADA activity reached peak plasma levels 2 to 3 days after intramuscular administration, with a half-life that ranged from 3 to more than 6 days [110]. Neulasta® (pegfilgrastim) is a PEGylated form of leukocyte growth factor filgrastim indicated for the treatment of febrile neutropenia and myelosuppression due to radiation [111]. The PK of pegfilgrastim was compared to filgrastim in young adults and children with sarcomas [112]. The results showed that the clearance of pegfilgrastim in pediatrics was 11 mL/h/kg, which is similar to clearance in adults at 14 mL/h/kg. Pegfilgrastim has a unique self-regulatory, receptor-mediated clearance, wherein it remains in the body while the patient is neutropenic but is eliminated fast when the neutrophil count is normal. This study also reported that filgrastim was rapidly absorbed and cleared when compared to pegfilgrastim, which is expected as the PEG moiety conjugated to filgrastim increases the circulation half-life by shielding the drug from metabolism [112].

Oncaspar® (pegaspargase) is a PEGylated form of the enzyme asparaginase indicated for the first line treatment of patients with acute lymphoblastic leukemia (ALL) [113]. The PK of intramuscular injection of pegaspargase was evaluated in 34 pediatric patients with standard-risk ALL. The elimination half-life of pegaspargase in pediatric patients was approximately 5.8 days [114]. However, the half-life of pegaspargase varied between 7 days to 12 days in a pharmacokinetic study performed in adults [115]. The reason for this increased half-life in adults is yet to be ascertained.

5.4 Nanocrystals

Nanocrystals are composed of 100% pure drug crystals stabilized by a thin coat of surfactant and with sizes in the nanometer range [106, 107, 116]. Due to the increased surface area, nanocrystals enhance dissolution and saturation solubility of poorly water-soluble drugs and improve their bioavailability [106, 107, 116]. In 2000, the FDA approved the first milled organic nanocrystal drug Rapamune® (sirolimus), an immunosuppressant used in organ transplant patients [106]. Currently, there are 15 FDA approved nanocrystal formulations and many of these are well studied and routinely used in pediatrics [106, 107].

Emend® (aprepitant) is a P/neurokinin 1 (NK_1) receptor antagonist intended for use in pediatric patients 6 months of age and older for the prevention of chemotherapy-induced nausea and vomiting (CINV) [117]. In a multicenter, randomized clinical study, the PK of aprepitant was evaluated in pediatric subjects from birth to 17 years of age followed by oral administration at three doses [118]. The results demonstrated that a clear dose-response relationship across 3 doses of oral aprepitant in all pediatric age cohorts except in the birth to <2-year age cohort. Developmental changes such as organ maturation, body composition, and the ontogeny of drug elimination pathways were thought to contribute to the nonlinearity of the PK findings [118]. However, the bioavailability of aprepitant in <2-year age cohort was either equal or higher than that of 12 to 17 years of age cohort who received adult doses [118].

Rapamune® (Sirolimus) is another nanocrystal formulation whose PK has been extensively studied in pediatrics [119-121]. In a clinical study, sirolimus PK in healthy adult subjects was compared to pediatric patients with renal failure undergoing dialysis [119]. The result indicated that there were no statistically significant differences in PK parameters half-life ($t_{1/2}$), steady-state volume of distribution (Vss/F), or blood to plasma ratio (B/P). However, T_{max} was 20 minutes longer, and clearance was increased by 90% in pediatric patients when compared with healthy adults [119]. Despite these differences in PK, the study reported that absorption of sirolimus was rapid after oral administration over similar doses in pediatric and adult subjects indicating that the nanocrystal formulation does not influence the absorption [119].

In both examples, the purpose of nanocrystal formulation was to improve the oral bioavailability of the drugs. The observed differences in PK between pediatric and adults are mainly due to the drug and due to developmental changes in pediatrics. Table 3 provides a list of nanocrystal formulations that are used in pediatrics with a description of the PK analyses in the pediatric and adult populations.

Table 3. Clinical PK of various nanocrystal drugs in pediatric populations (Section 5.4).

Name	Pediatric indication	Pediatric PK							Adult PK						Refs
		Age Group	Dose (p.o)	$AUC_{0-\infty}$ (ng/ml.hr)	Cmax (ng/ml)	T_{max} (h)	$T_{1/2}$(hr)	Cl (ml/min) or Cl/F (mL/h/kg)†	Dose (p.o)	$AUC_{0-\infty}$ (ng/ml.hr)	Cmax (ng/ml)	T_{max} (h)	$T_{1/2}$(hr)	Cl (ml/min) or Cl/F (mL/h/kg)†	
Ritalin LA® (Methylphenidate hydrochloride extended-release capsules)	Attention Deficit Hyperactivity Disorder (ADHD)	7 to 12 years	20 mg	86.6 ± 64.0	10.2 ± 5.9	N/A	2.4 ± 0.7	N/A	20 mg	45.8 ± 10	6.2 ± 1.6	5.5 ± 0.8	3.3 ± 0.4	N/A	[122]
Zanaflex® (Tizanidine hydrochloride capsules)	Cerebral palsy and mild to moderate spasticity.	2 to 16 years	0.025 mg/kg	AUC_{0-8} – 5.6 ± 1.79	1.87 ± 0.6	N/A	N/A	N/A	8 mg	17.63 ± 15.59	4.6 ± 3.72	3	2.47	N/A	[116], [123]
Emend® (Aprepitant)	Chemotherapy induced nausea and vomiting (CINV)	Birth to <2 years	125 mg	7730±5890	1660±1590	5.17±2.1	N/A	N/A	125 mg	25897.9	1254.7	4	10.3	N/A	[118, 124]
		2 to <6 years		12,900±5650	2390±922	5.43±2.5									
		6 to <12 years		10,900±3530	2060±867	7.03±1.8									
		12 to 17 years		7500±2820	1460±637	5.42±2.4									
Rapamune® (Rapamycin)	Prophylaxis of acute rejection in renal transplantation	5-11 years	15 mg/m^2,	843±454	81.2±21.1	1.34±0.9	52.4±26.7	726 ± 539†	8 mg/m^2	876 ± 234*	83.6 ± 27.13	0.8 ± 0.2	86.4 ± 16.7	256 ± 67†	[119, 125]
		12-18 years		971±62	104±14	0.67±0.0	47.7±12.2	470 ± 12†							

5.5 Inorganic nanoparticles

Metal oxides, metals, or silica are examples of inorganic materials that can be used to create nanoparticles for therapeutic, diagnostic, or theranostic applications [106]. One major advantage of inorganic nanoparticles is their ability to be magnetically controlled, which can be used to guide drug delivery to target sites [126, 127], increase contrast in magnetic resonance imaging (MRI) applications [128], or reinforce cytotoxicity through the production of reactive oxygen species [129]. In particular, iron oxide nanoparticles have been studied in numerous clinical trials investigating their use as MRI contrast enhancement agents [106]. However, most iron oxide nanodrugs that are FDA-approved are used as iron replacement therapies. The most common indications are for the treatment of anemia and associated diseases. These include drugs like Venofer, an iron sucrose injection, Ferrlecit, a sodium ferric gluconate complex in sucrose injection, Infed, an iron dextran injection, and Dexferrum, an iron dextran injection, all of which are used in adults [106]. Venofer® and Ferrlecit® have also been studied for application in pediatrics.

Venofer® is an iron oxide nanoparticle coated with sucrose for slow dissolution of the iron following intravenous injection, preventing a rapid and toxic increase of free iron in the blood. In a clinical study, the PK of iron sucrose was evaluated in pediatric patients ages 12 to 16 [130]. Half-life was increased from 6 hours in healthy adult subjects to 8 hours in pediatric patients with chronic kidney disease. C_{max} and AUC values were increased 1.42- and 1.67-fold, respectively, in pediatric patients compared to adults [130].

Ferrlecit® is a stable macromolecular complex of sodium ferric gluconate in sucrose that has been used in a randomized safety and efficacy study [131]. PK analysis in 66 iron-deficient pediatric hemodialysis patients aged 6 to 15 showed the C_{max} and half-life (22.8 mg/L and 2.5 hours, respectively) were slightly increased compared to adults (19.0 mg/L and 1.45 h), and the AUC was almost 5-fold higher in children (170.9 mg-hr/L compared to 35.6 mg-h/L). Despite these differences in PK, the iron nanoparticles had a significant effect in increasing hemoglobin concentrations for sustained times (4 weeks after the final administration) in both populations [131].

One concern limiting the application of inorganic nanoparticles is that of their toxicity and elimination. While safety must be evaluated in many diverse groups, it is especially important for pediatric populations as they are more vulnerable to illness and have immature defense systems compared to adults [47, 132]. Many studies have shown cytotoxic behavior with silver and iron oxide nanoparticles, likely due to reactive oxygen species production [133-136]. Inorganic nanoparticle cores have varying biodegradability, where some materials like iron

oxide, zinc oxide, and silver may break down into metal ions, but other materials like gold are thought to be inert and thus stable from degradation [137]. It is critical to understand the complete life cycle of an inorganic nanoparticle within the body, especially if the metal is not naturally utilized in cellular activity.

5.6 Polymeric micelles

Polymeric micelles are self-assembling nanoparticles in which the hydrophobic core is loaded with a drug, and a hydrophobic exterior allows for improved aqueous solubility [106, 138]. Micelles can leverage both passive and active targeting mechanisms [139, 140]. Pre-clinical studies have shown increased efficacy with the use of micellar nanoparticles to enhance chemotherapeutic and gene delivery [141-144]. To date, the only FDA-approved micellar formulation is Estrasorb™, a treatment for moderate to severe vasomotor symptoms of menopause. Paclitaxel-loaded polymeric micelles have been evaluated for the treatment of breast cancer and non-small cell lung cancer and are in clinical trials for the treatment of locally advanced or metastatic pancreatic cancer in adults [145]. The only micelle formulation being investigated for pediatric use is the encapsulation of luteolin, a flavonoid associated with chemoprevention, in poly(lactic acid) (PLA)-PEG nanoparticles [146]. In preclinical studies with adult animal models, this formulation successfully inhibited the growth of lung cancer and squamous cell carcinoma of the head and neck cell lines [147]. PK testing reported a half-life of 152 minutes, AUC of 2989 mg/L/minute, and C_{max} of 92.7 mg/L in adult rats [148]. No PK data on this nanoformulation has been reported in pediatric trials.

5.7 Protein based nanoparticles

Protein-based nanoparticles describe a variety of compounds including drug-protein conjugates, formulations where the protein is the active therapeutic, and combined platforms where proteins are used to confer targeting properties [106]. Proteins in a nanoformulation are used to increase solubility, reduce toxicity, and facilitate the transport of the drug [106]. Albumin, the main serum protein, has gained significant attention as a drug carrier and is currently being investigated in several clinical trials [149]. Albumin-bound paclitaxel is clinically approved for the treatment of several adult cancers and is now being investigated through the Pediatric Preclinical Testing Program for the treatment of several pediatric solid tumors [150]. The addition of albumin in the formulation has been shown to increase drug accumulation in solid tumors as well as initiate specific cellular uptake mechanisms mediated by albumin receptors [149].

Mircera® (methoxy polyethylene glycol-epoetin beta) is an erythropoietin (Epo) receptor activator with greater bioactivity and half-life compared to Epo [151]. Production of endogenous Epo is impaired in patients with chronic kidney disease (CKD), and Epo deficiency is the primary cause of their anemia. PK of Mircera® was evaluated in pediatric patients' ages 5 to 17 diagnosed with CKD. The results showed no significant difference in PK parameters including half-life (119 hours in adults compared to 121 hours in children) and total systemic clearance (0.47 mL/h/kg in adults compared to 0.51 mL/h/kg in children) [151].

Pegasys® and PegIntron® (PEGylated interferon alpha-2a and 2b, respectively) induce an innate antiviral immune response against Hepatitis B and C [152, 153]. Since a diversity of cell types respond to interferon alpha-2a and 2b, both therapeutics have pleiotropic effects in the body. With Pegasys®, a PK study was conducted with children 2 to 8 years of age with chronic Hepatitis C (CHC). Results showed 4-fold lower clearance, longer time to steady-state (12 weeks compared to 5-8 weeks), and 25-70% higher AUC in children compared to adults [152]. A study of children with chronic Hepatitis B (CHB) showed similar PK parameter values compared to adults [152]. PegIntron® was evaluated in pediatric patients between 3 and 17 years old and showed approximately 50% increased AUC than in equivalently dosed adults. In both nanoformulations, total bioavailability was increased, and clearance was reduced compared to non-PEGylated counterparts [153].

Adynovate (PEGylated factor VIII) is indicated in children and adults with hemophilia A (congenital factor VIII deficiency) [154]. Conjugation of the PEG polymer extends the half-life of the parent molecule, Advate, by reducing binding to the physiological factor VIII clearance receptor LRP1. A PK study of Adynovate was conducted with children (2-6 years old), older children (6-12 years old), adolescents (12-18 years old), and adults (>18 years old). Results showed that children <12 years of age had higher mean clearance times (3.1-3.5 mL/kg/h compared to 2.27 mL/kg/h) and lower half-lives (11.8-12.4 hours compared to 14.7 hours) than adults [154].

6. PK modeling and simulation (M&S) for the development of nanotechnology-based formulations in pediatrics

The high trial failure rate of pediatric trials (~42%) is one of the challenges of pediatric drug development [155]. The important factors contributing to trial failures in children were incorrect dose selection and suboptimal trial design [35, 156]. Model-based drug development has been proven to overcome these challenges and accelerate advances in pediatric research. In pediatric immunology and infectious disease, the use of models has quantified dose-

concentration-effect relationships to provide clinicians with guidance on appropriate dosing [157]. The use of M&S for improving efficiency, substantiating trial design, and optimizing dose selection in pediatric drug development has been recognized by both the US FDA and EMEA [158, 159]. Both the US FDA and EMEA provided regulatory provisions to support the role of M&S as a rational approach for describing dose-exposure and exposure relationships to support extrapolation of efficacy from adults to pediatric population [158, 159].

The population PK (PopPK) modeling of liposomal amphotericin B (L-AmB) was performed in pediatric patients with malignant diseases [160]. The model estimated the PK parameters, inter-and intraindividual variability, and between-occasion variability. The model was evaluated and can be used in the design on rational dosing strategies for L-AmB based antifungal therapy in pediatrics [160]. A physiologically-based pharmacokinetic (PBPK) modeling approach was applied to predict the developmental pathway of Rapamune® clearance in pediatric patients. [161]. The PBPK model of Rapamune® provided new insights into ontogeny mechanisms in pediatric patients and therefore can be used in the design of prospective clinical studies [161].

Even though M&S approaches have been successfully utilized for pediatric drug approvals, their application in pediatric nanotechnology-based formulations is still in infancy. The applicability of M&S approaches for pediatric development nanotechnology-based formulations can be enhanced by developing specific models that can incorporate the unique characteristics of nanotechnology-based formulations such as size, shape, surface chemistry, etc. Such a robust model would be highly valuable in accelerating the pediatric approval process for nanotechnology-based formulations that are successful in adults.

7. Conclusions and future directions

It is evident that the US PFI and EuPFI recommends application of nanotechnology-based platforms for development of pediatric formulations. Yet, there is a lack of information on how nanotechnology-based formulations proven effective for adults can be utilized for pediatric formulations. In this closing section, we focus on several important considerations that researchers will need to incorporate into future exploration of nanotechnology for more widespread application in the pediatric population.

As highlighted in section 2 and 4, physiological differences in adults and children necessitate greater investigation of how to tailor the unique properties of nanotechnology-based delivery platforms to fit the PK requirements for treatment of pediatric disease. This will require the use of animal models in the necessary range of ages. However, anatomical and

physiological development is species-dependent, and factors like cost, available imaging and molecular techniques, ease of genetic manipulation, and replication of the complexity and heterogeneity of human disease remain ongoing challenges [162]. The rise of transgenic animals expressing human genes has opened new doors to study immunology, autoimmunity, and infectious disease, and could readily be applied to many childhood disorders [163]. Additionally, continued development of "humanized" rodents containing human organs, such as the liver [164], can be invaluable to the study of drug metabolism in the newborn to adolescent population. Naturally occurring species models continue to increase in prevalence, yet are largely restricted to aging-related diseases and cancer. Since this concept promotes the sharing of resources and emphasizes the well-being of all species [165], and as it becomes more mainstream as an adjunct to traditional laboratory animal models, there could eventually be expansion of naturally occurring species models into the pediatric space.

Nanotechnology researchers must also navigate the ongoing challenge of limited resources - the pediatric population has often been defined as a "niche" population with a small population size and limited market, particularly in comparison to adult diseases. Roughly 27% of the world's population is children, but pediatric trials make up only 17% of the total number of trials registered via the World Health Organization, with only 7% of trials taking place in neonates. Industry-based funding is largely weighted towards adult disease indications, leaving primarily non-profit organizations to fund pediatric trials. The combination of this perspective with previous limitations in regulatory paths for nanotechnology development [166] and a tendency to extrapolate from the adult literature has resulted in a paucity of novel therapeutic interventions for almost all complex diseases affecting pediatric patients. In particular, relying on adult safety and efficacy data has resulted in unpredictable and tragic outcomes in children [167]. However, there is an increasing push from pediatric patients, parents, and practitioners to expand and accelerate the path to translation for drug formulation testing in children.

Several ongoing efforts are underway to address the challenges of pediatric therapeutic development and implementation. The Institute for Advanced Clinical Trials (I-ACT) for children is a 501c3 non-profit organization focused on ensuring that innovative medical technologies, including nanotechnologies, are given the same level of urgency and commitment as technology development for adults. This organization works to use child-centered clinical trial networks incorporating trial sponsors, regulators, investigators, hospitals, and patients to optimize and accelerate therapeutic development. I-ACT focuses on generating best practices and data that can be utilized to improve the safety and effective use of therapies, and shorten the time it takes to bring new therapies to clinical use in children. This involves streamlining operations by

building a network of pre-qualified pediatric clinical trial ready sites. The number of children eligible for clinical trials is much lower than that of adults, so in many cases, there is a need for up to 50 trial sites to enroll enough children to complete a single pediatric clinical trial [166].

Creating a network can build an infrastructure with centralized Institutional Review Board (IRB) protocols, educational and research-based tools, and best practices, shared administrative documentation, and shared regulatory administration, all of which reduces the burden and the time to clinical implementation. However, infrastructure cannot be isolated from policy, and therefore setting standards for pediatric clinical research is also necessary, particularly for novel platforms like nanotechnology-based therapeutics. International groups like StaR Child Health are continually working to gather and promote evidence-based standards for clinical trial studies in children. The standards and guidance are disseminated and implemented at all stages of the trial process, from the design to execution to reporting of the trial outcomes. These efforts will further drive the future of existing and novel technology development, including the use of nanotechnology, for the pediatric population.

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9. Competing interests

The authors have no competing interests to declare.

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