The Journal of Clinical Pharmacology
2019, 59(8) 1130–1143

DOI: 10.1002/jcph.1406

Monoclonal Antibodies and Fc-Fusion Proteins for Pediatric Use: Dosing, Immunogenicity, and Modeling and Simulation in Data Submitted to the US Food and Drug Administration

Xiaomei I. Liu, PharmD[1,2]*, André Dallmann, PhD[3]*, Yow-Ming Wang, PhD[1], Dionna J. Green, MD[4], Janelle M. Burnham, MD[1], Beatrice Chiang, PharmD[5], Perry Wu, PharmD[5], Mark Sheng, PharmD[5], Kelley Lu, PharmD[6], John N. van den Anker, MD, PhD, FCP[2,3], and Gilbert J. Burckart, PharmD, FCP[1]

Abstract

The experience with the use of monoclonal antibodies and Fc-fusion proteins (mAb/Fc) in the pediatric population is limited. The objective of this study is to review those factors impacting the clinical efficacy and product safety of mAb/Fc products in pediatric patients during drug development. We reviewed the list of biologic products in the US Food and Drug Administration's Purple Book as of March 2018 with a focus on mAb/Fc products that are indicated for use in both adults and pediatric patients. Of 68 mAb/Fc products in the Purple Book (excluding biosimilars), 20 products have approved indications in both adults and children. Thirteen products had concurrent approval for both adult and pediatric populations. The sample size of pediatric studies generally ranged from approximately 2% to 70% of the sample size of adult studies with the same indication. In general, pediatric dosing regimens were found to be more based on body weight and weight tiered than the regimens for adults. Modeling and simulation techniques comprised mainly population pharmacokinetic and pharmacodynamic models. A review of the immunogenicity incidence did not reveal any notable difference in the 5 products having data on both pediatric and adult patients. In conclusion, most of the mAb/Fc products have a different weight-based dosing regimen for pediatric patients versus adults. An understanding of the comparative experience in drug development for mAb/Fc products between adult and pediatric patients coupled with the application of advanced modeling and simulation methods should assist future development of new mAb/Fc products for pediatric patients.

Keywords

dosing, drug development, Fc-fusion proteins, immunogenicity, modeling and simulation, monoclonal antibodies, pediatrics

Antibody-based therapeutic proteins have emerged as an important treatment modality that confers a more targeted therapeutic effect with the potential for better safety profiles than small-molecule drugs. However, the development of monoclonal antibodies and Fc-fusion proteins (mAb/Fc) has different challenges than that of small-molecule drugs because different mechanisms govern the pharmacokinetics (PK) and pharmacodynamics (PD) of these proteins. While knowledge about these mechanisms in adult patients is growing, fewer programs have focused on the development and use of mAb/Fc products in pediatric patients. Moreover, the development of mAb/Fc therapy for pediatric patients has not been fully explored with regard to the disposition, dosing, efficacy, and adverse effects of these products.

Immunogenicity to exogenously administered proteins is a unique side effect of mAb/Fc products that can have consequences for safety, including concerns of anaphylaxis and infusion reactions. Immunogenicity can also have an effect on product efficacy, for example,

[1]Office of Clinical Pharmacology, Center for Drug Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA
[2]Children's National Medical Center, Washington, DC, USA
[3]Pediatric Pharmacology and Pharmacometrics Research Center, University Children's Hospital Basel (UKBB), Switzerland
[4]Office of Pediatric Therapeutics, Commissioner's Office, US Food and Drug Administration, Silver Spring, MD, USA
[5]School of Pharmacy, University of Southern California, Los Angeles, CA, USA
[6]College of Pharmacy, University of Texas, Austin, TX, USA

Submitted for publication 24 October 2018; accepted 23 February 2019.

Corresponding Author:
Gilbert Burckart, PharmD, FCP, Office of Clinical Pharmacology, Bldg 51, Rm 3184, US Food and Drug Administration, 10903 New Hampshire Ave, Silver Spring, MD 20903
E-mail: Gilbert.Burckart@fda.hhs.gov

*Contributed equally to the manuscript.

loss of efficacy due to formation of binding antibodies or neutralizing antibodies.[1] Understanding the immunogenicity of mAb/Fc products in pediatric patients is essential to ensure patient safety and product efficacy. Currently, limited immunogenicity data for mAb/Fc products in pediatric populations and significant technological shortcomings in evaluating antidrug antibodies (ADAs) present challenges in the characterization of an immunogenicity profile in pediatric patients treated with mAb/Fc products. Due to the significance of detecting and analyzing potential immune responses observed during clinical trials, the US Food and Drug Administration (FDA) has recently published a new Guidance for Industry on the immunogenicity testing of therapeutic protein products that includes recommendations for developing and validating assays for ADA detection.[2]

While the experience and confidence in applying modeling and simulation techniques for large molecules in adults has increased during recent years, extension of these techniques to pediatric patients remains limited to date. One of the reasons is the complex PK and PD of therapeutic proteins. Displaying a high affinity to their target, mAb/Fc products typically bind to a substantial extent to their target if the latter is highly abundant and easily accessible. Consequently, the kinetics of the target can directly affect the PK of the drug, a phenomenon termed *target-mediated drug disposition*.[3,4] This mutual interdependence of PK and PD introduces nonlinearity and requires integrated modeling analysis of PK and PD data, rendering a typical empirical modeling approach, where the PK model is initially established and thereafter coupled to a PD component, to be highly unreliable. However, target-mediated drug disposition may be of less concern at therapeutic concentrations when the nonlinear process is saturated. This is particularly true for pediatric trials, where the doses studied are typically within the therapeutic exposure range due to ethical and safety concerns.

In the past, population PK/PD and physiologically based pharmacokinetic (PBPK) models have frequently contributed to guiding drug development and optimizing dosing strategies, as well as pharmacotherapeutic outcome of the small-molecule drugs used in pediatrics.[5–8] In parallel, the number of pediatric PK/PD- and PBPK-related studies has risen substantially in recent years. Accordingly, in industry guidances on pediatric clinical studies, the FDA advocates the use of modeling and simulation (M&S) during the drug development process to support dose selection and/or study design, data analysis, and interpretation for planned pediatric studies.[9] Furthermore, in rare pediatric diseases, the FDA industry guidance explicitly stipulates that a mechanism-based approach, such as PBPK/PD modeling or mechanistic disease PK/PD models, should play a key role for dose characterization and that M&S approaches should be used to optimize pediatric studies (eg, design, sample size, starting doses, timing of sampling, and number of samples) when new studies in children are deemed necessary.[10]

With the approval of a number of mAb/Fc products for use in pediatric patients in the United States, an understanding of the dosing, safety, appropriate inclusion of pediatric patients in drug development studies of mAb/Fc products, and the application of M&S techniques to these studies is critically important. The similarities and dissimilarities in approval date, sample size, dosing, applications of M&S techniques (in particular, population PK/PD and PBPK models), and immunogenicity of mAb/Fc products are all important issues for which a review and comparison between adult and pediatric studies would be informative. The objective of this study is to review those factors impacting the clinical efficacy and product safety of mAb/Fc products in pediatric patients during drug development.

Materials and Methods

The primary source of our product database is the Purple Book, which contains a list of biologic products licensed by the FDA.[11] The FDA-approved biologic products in the Purple Book are generally referred to as therapeutic proteins, which have diverse molecular types.[12] The focus of our review is the antibody-based proteins and Fc-fusion proteins.

For each of the mAb/Fc products indicated for use in both adults and pediatric patients, publicly available medical and clinical pharmacology reviews of pediatric studies[13] and FDA labels were the primary sources of information for the adult and pediatric development programs. Approval dates of the reviewed mAb/Fc products were available on the FDA website.[13] The pivotal clinical trials, described in the FDA labels and reviews, were analyzed for sample size and immunogenicity differences in adult and pediatric studies. Clinical pharmacology reviews for pediatric products were used as the primary basis for identification of M&S techniques (in particular, population PK/PD, exposure-response [ER] and PBPK models) used in the marketing authorization application submitted to the FDA. Published research articles, if available, complemented the clinical pharmacology reviews. Other M&S techniques besides the population PK/PD, ER, and PBPK models in the pediatric reviews, such as disease progression models and noncompartmental modeling analyses, were not considered herein.

Results

As of March 20, 2018, the Center for Drug Evaluation and Research list of biologic products in the Purple Book has 68 mAb/Fc products (excluding biosimilars), which are defined to include antibody-based proteins and Fc-fusion proteins. Twenty of 68 products have approved indications in both adults and children (Table 1). A summary of the pivotal adult and/or pediatric trials with respect to sample size is shown in Table 1. The subsections below describe our findings by topic.

Pediatric Approval

The interval between initial adult approval and the initial pediatric approval ranges from 1 to 12 years for 7 products, and the remaining 13 products had concurrent approval for both patient populations (see Table 1). Etanercept indicated for plaque psoriasis had the longest time to pediatric approval of 12 years whereas etanercept for juvenile idiopathic arthritis was approved 1 year after the approval for rheumatoid arthritis in adults, the shortest lag time. Excluding the 13 mAb/Fc products that received concurrent initial pediatric indications with adult approval, the average length of time to pediatric approval is around 5.8 years.

Study Population Size

Study population sizes between the adult and pediatric mAb/Fc drug development studies were dissimilar. The study population for pediatric studies generally was smaller and ranged from approximately 2% to 70% of the study population for adult studies with the same indication. Whereas the majority of programs have separate dedicated studies in adults and children, studies for canakinumab did not stratify for adult and pediatric populations. Therefore, Table 1 shows the same sample size for the composite number of pediatric and adult patients for canakinumab. Studies on raxibacumab and obiltoxaximab were both nonclinical studies because these products were approved under the FDA Animal Rule, and both products were indicated for the treatment and prevention of inhalation anthrax in the pediatric and adult populations. The pembrolizumab program for 2 adult indications had 1 study for each indication, whereas the single study in the pediatric population was designed for both indications. Therefore, the total study population from the 2 indications for pembrolizumab combined was the basis for the study population comparison.

Dosing

Pediatric dosing regimens for mAb/Fc products are based more on body weight than are the regimens for adults (see Table 2). Ten of the 20 products have a fixed dosage regimen for adults, and 6 of these 10 products used either a body weight–tiered dose or a mg/kg dose in pediatrics. The adult dose regimens for the remaining 10 products were based on body weight, that is, weight-tiered (n = 4), or mg/kg (n = 6). Among these 10 products, 5 had an mg/kg dose that differed by body weight tiers for pediatric use. Table 2 displays the dosing regimen of the 20 mAb/Fc products according to the indication described in the FDA label. Dosing regimens fell under 3 categories: fixed dosing (mg), weight- or surface area–based dosing (mg/kg or mg/m^2), or weight-tiered dosing (in 2-3 tiers). Weight-tiered dosing in adults generally involves an increasing amount or dosing frequency of flat dose for the higher weight tier.

Weight-tiered dosing in children can have an additional variation where a higher weight tier received a smaller mg/kg dose. For example, tocilizumab indicated for juvenile idiopathic arthritis in pediatrics is dosed by 2 weight tiers (body weight <30 kg or ≥ 30 kg), and each has a weight-based dosing regimen: 10 and 8 mg/kg, respectively, for polyarticular juvenile idiopathic arthritis (JIA) and 12 and 8 mg/kg, respectively, for systemic JIA.[14] Canakinumab, indicated for cryopyrin-associated periodic syndrome in adults and children 4 years of age and older, is dosed by 2 weight tiers (body weight ≥ 15 to ≤ 40 kg) as a mixed dosing regimen, with low-body-weight patients receiving weight-based dosing (2 mg/kg for body weight 15-40 kg) and high-body-weight patients receiving flat dosing (150 mg for body weight >40 kg).[15] A more detailed description of the derivation of the canakinumab dosing has been published elsewhere.[16]

Immunogenicity

Overall, a comparison of the immunogenicity incidence for mAb/Fc products in adult and pediatric patients did not reveal any notable difference. A comparison across products is not feasible because of differences in the immunogenicity assays used in the development programs. Figure 1 presents the ADA rates that are currently cited in the FDA-approved labels for the products having both adult and pediatric immunogenicity incidences. Adalimumab, etanercept, infliximab, omalizumab, and toculizumab had immunogenicity data in both adult and pediatric studies. Rilonacept had the highest incidence of ADA (35%) in its adult study.

Use of M&S

Table 3 gives an overview of the M&S techniques that were applied in drug research and development programs and, ultimately, approval for the mAb/Fc products. M&S techniques were applied throughout all phases of clinical drug development of the adult indications, and 2 models were applied to preclinical data to support interpretation of plasma concentration–time data measured in mature animals (obiltoxaximab and

Table 1. Patient Population Size and Lag Time in Pediatric Approval for the 20 mAb/Fc Products Approved in Pediatric Patients

mAb/Fc (Brand Name) Latest Label	Indication (Adult; Pediatric)	Adults		Pediatric Patients		Time Between Adult and Pediatric Approvals (y)	Age Range When First Approved in Children (y)
		Current Dosage; Initial Approval Year	Study Size	Current Dosage; Initial Approval Year	Study Size		
Abatacept[46]	Rheumatoid arthritis;	Weight-tiered;	1457	Weight-tiered;	395		
(Orencia) 6/2017	pJIA	2005		2008		3	≥6
Adalimumab[47]	Rheumatoid arthritis; pJIA	Fixed dose	2869	Weight-tiered;	203	6	≥4
(multiple) 12/2018	Crohn disease	2002, 2007	1478	2008, 2014	192	7	≥6
Avelumab[48]	Merkel cell carcinoma	mg/kg dose;	200	Same as adult;	NA		
(Bravencio) 10/2018		2017		2017		0	≥12
Basiliximab[49]	Acute organ rejection	Fixed dose;	1540	Weight-tiered;	41		
(Simulect) 9/2003		1998		1998		0	2-15
Benralizumab[50]	Severe asthma, eosinophilic phenotype	Fixed dose	2522	Same as adult;	108		
(Fasenra) 11/2017		2017		2017		0	≥12
Blinatumomab[51]	MRD-positive B-cell precursor ALL	Fixed dose;	501	mg/m^2 with max;	70		
(Blincyto) 5/2018		2014		2014		0	0-17
Canakinumab[15]	TRAPS, HIDS/MKD, FMF, CAPS, sJIA	Weight-tiered;	125	mg/kg with weight limits	56		
(Ilaris) 12/2016		2009 (CAPS), 2016 (others)		2009 (CAPS) 2016 (others)		0	≥4
Eculizumab[52]	aHUS	Fixed dose (>40 kg);	89	Weight-tiered (fixed);	41	0	2 mo to 17 y
(Soliris) 7/2018		2007 (PNH); 2011 (aHUS)		2011			
Etanercept[53]	Rheumatoid arthritis; pJIA	Fixed dose;	2031;	mg/kg dose;	69		4-17
(Enbrel) 5/2018	Plaque psoriasis	1998, 2004	1283	1999, 2016	211	1, 12	≥4
Evolocumab[54]	Homozygous familial	Fixed dose;	49	Same as adult;	10		
(Repatha) 10/2018	hypercholesterolemia	2015		2015		0	≥ 13
Infliximab[55]	Crohn disease;	mg/kg dose;	653	Same as adult;	112		≥6
(Remicade) 6/2018)	ulcerative colitis	1998, 2005	364	2006, 2011	60	8,6	
Ipilimumab[56]	Metastatic melanoma;	mg/kg dose;	1627	Same as adult;	57		≥12
(Yervoy) 7/2018	colorectal cancer	2011		2017		6	
Mepolizumab[57]	Asthma with eosinophilic phenotype	Fixed dose	1327	Same as adult	28		
(Nucala) 12/2017		2015		2015		0	≥12
Obiltoxaximab[58]	Inhalational anthrax	mg/kg dose;	64 (b)	Weight-tiered with mg/kg;	64 (a)		0-17
(Anthim) 10/2016		2016		2016		0	
Omalizumab[59]	Asthma;	Weight-tiered and IgE;	1412	Weight-tiered and IgE	962		≥12
(Xolair) 9/2018	chronic idiopathic urticaria	2003	602	2003	39	0	
Pembrolizumab[60]	PMBCL, MSI-H, MCC;	Fixed dose;	210	mg/kg dose;	40 (b)		
(Keytruda) 12/2018	cHL	2017	149	2017		0	2-18
Raxibacumab[61]	Inhalational anthrax	mg/kg dose	48 (b)	Weight-tiered with mg/kg	48 (a)		0-17
(Raxibacumab) 1/2018		2012		2012		0	
Rilonacept[62]	CAPS, FCAS, MWS	Fixed dose;	47	Fixed mg/kg;	8		
(Arcalyst) 9/2016		2008		2008		0	12-17
Tocilizumab[14]	Rheumatoid arthritis; pJIA, sJIA	mg/kg dose (IV); fixed (SC)	601	Weight-tiered with mg/kg (IV) or fixed (SC)	601		≥2
(Actemra) 12/2018	Cytokine release syndrome	2010, 2017		2011, 2017		1, 0	

(*Continued*)

Table 1. Continued

mAb/Fc (Brand Name) Latest Label	Indication (Adult; Pediatric)	Adults: Current Dosage; Initial Approval Year	Adults: Study Size	Pediatric Patients: Current Dosage; Initial Approval Year	Pediatric Patients: Study Size	Time Between Adult and Pediatric Approvals (y)	Age Range When First Approved in Children (y)
Ustekinumab[63]	Plaque psoriasis	Weight-tiered;	1996	Weight-tiered with mg/kg;	110		
(Stelara) 6/2018		2009		2017		8	≥12

aHUS, atypical hemolytic uremic syndrome; ALL, acute lymphoblastic leukemia; CAPS, cryopyrin-associated periodic syndrome; cHL, classical Hodgkin lymphoma; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; pJIA, pediatric juvenile idiopathic arthritis; mAb/Fc, monoclonal antibody and Fc-fusion protein; MCC, Merkel cell carcinoma; MKD, Mevalonate Kinase Deficiency; MRD, minimal residual disease; MSI-H, microsatellite instability-high cancer; MWS, Muckel Wells syndrome; PMBCL, primary mediastinal large B-cell lymphoma; sJIA, systemic juvenile idiopathic arthritis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome.
Note: (a) rabbit (nonclinical study); (b) for all indications.

raxibacumab). The human models were developed on the basis of different populations, with large ranges in age and body weight.

Population PK models were generally built for an adult or mixed pediatric/adult population. The application of M&S techniques to clinical data was consistently observed for most products (19 of 20), with publicly available clinical pharmacology reviews of the data supporting the adult indications. The use of population PK modeling was the most frequently observed M&S approach described in the FDA reviews and labels for the pediatric studies (see Table 3). Frequently, these models were used to analyze the influence of various covariates (eg, body weight and age) on specific PK parameters (eg, area under the plasma concentration–time curve, clearance, and volume of distribution), thereby providing important information on whether flat or weight-based or tiered dosing would be supported.

Support for a specific dose as indicated by a population PK model was complemented in some programs by an ER analysis using regression models, such as generalized additive models or logistic regression models. Predictor variables in these regression models were PK parameters estimated by the population PK model (eg, steady-state area under the plasma concentration–time curve in case of ustekinumab and pembrolizumab and trough concentrations in case of ipilimumab). An ER analysis for pediatric patients was often not possible due to a small number of patients and having different primary outcome measures than in the adult studies.

While population PK/PD models were frequently applied, a PBPK approach was applied to only 1 mAb/Fc product (blinatumomab). The blinatumomab PBPK model was developed exclusively on the basis of adult data and addressed the potential indirect effect of transient interleukin-6 elevation in the first week of blintumomab treatment on several cytochrome P450 (CYP) enzymes, in particular CYP1A2, CYP3A4, and CYP2C9. The model has been described in detail in a separate publication.[17] Yet because the ER relationship between plasma interleukin-6 levels and change in CYP activities in humans has not been established, the clinical pharmacology review concluded that the model cannot adequately address the drug interaction potential of blinatumomab. Other examples of PBPK models were not available in the clinical pharmacology reviews.

Discussion

The Pediatric Research Equity Act, signed into law in 2003, addresses the lack of pediatric information in drug labels. Under the Pediatric Research Equity Act, new drug applications and biologics licensing applications with changes in active ingredient, indication, dosage form, dosing regimen, or route of administration are required to include pediatric assessments for indications for which sponsors were receiving or seeking approval in adults, unless the requirement was waived or deferred.[18] The advent of the Pediatric Research Equity Act paved the way to a large increase in pediatric studies conducted to establish clinical efficacy and safety of drug products in children. In addition, processes to hasten or facilitate pediatric approval are being developed and implemented. Two such examples of facilitating pediatric approvals are extrapolation of efficacy from adult to pediatric patients and the use of M&S techniques in pediatric studies.

Pediatric Approval

Thirteen of the mAb/Fc products had concurrent approval of adult and pediatric indications, partially as a result of encouragement by the FDA to initiate pediatric trials as early as possible in the drug development program. For some mAb/Fc products, the gap between the approval of drug products in adults and pediatric patients is decreasing due to the increased use of efficacy extrapolation from adults to pediatric patients, as pediatric and adult diseases and response

Table 2. Adult and Pediatric Dosing Regimen of 20 mAb/Fc Products Approved for Pediatric Use

		Dosing[a]	
mAb/Fc (Label Date)	Indication[a]	Adult	Pediatric
Abatacept (6/2017)	RA (adults); pJIA (pediatrics) (≥6 yo)	IV: 500 mg (if BW <60 kg), 750 mg (if BW 60-100 kg), or 1000 mg (if BW >100 kg); SC: 125 mg once weekly	IV: 10 mg/kg (BW <75 kg;); for BW ≥75 kg, use adult dose up to 1000 mg SC: weekly dosing: 50 mg (BW 10 to <25 kg); 87.5 mg (BW 25 to <50 kg); 125 mg (BW ≥50 kg)
Adalimumab (12/2018)	RA (adults); pJIA (pediatrics) (≥2 yo)	SC: 40 mg every other week	SC: 10 mg (if BW 10 to <15 kg), 20 mg (if BW 15 to <30 kg), or 40 mg (if BW ≥30 kg) every other week
	Crohn disease (≥6 yo)	SC: 160 mg at week 0; 80 mg at week 2; then 40 mg every other week	SC: BW 17 to <40 kg: 80 mg at week 0; 40 mg at week 2; then 20 mg every other week. If BW >40 kg: adult dosing
Avelumab (10/2018)	Merkel cell carcinoma (≥12 yo)	IV: 10 mg/kg every 2 weeks	IV: same as adult every 2 weeks
Basiliximab (9/2003)	Acute organ rejection	IV: 20 mg on day 0 and day 4	IV: 10 mg (if BW <35 kg), or 20 mg if BW ≥35 kg; administer on day 0 and day 4
Benralizumab (11/2017)	Severe asthma, eosinophilic phenotype	SC: 30 mg every 4 weeks for 3 doses, then every 8 weeks	Same as adult (≥12 yo)
Blinatumomab (5/2018)	MRD-positive B-cell precursor ALL	IV: 28 μg/day for BW ≥45 kg	IV: 15 $\mu g/m^2$/day (not to exceed adult dose) for BW <45 kg
Canakinumab (12/2016)	CAPS	SC: 150 mg (if BW >40 kg) every 8 weeks	SC: 2 mg/kg (BW ≥15 to ≤40 kg) every 8 weeks
	sJIA		SC: 4 mg/kg (BW ≥7.5 kg) every 4 weeks (max 300 mg)
	TRAPS, HIDS/MKD, FMF	SC: 150-300 mg (BW >40 kg) every 4 weeks	SC: 2-4 mg/kg (BW ≤40 kg) every 4 weeks
Eculizumab (7/2018)	aHUS	IV: 900 mg weekly for 4 weeks; then 1200 mg 1 week later; then 1200 mg every 2 weeks	IV: complex schedule fixed dose by body weight tier (BW 5-40 kg); see labeling
Etanercept (5/2018)	RA, pJIA (>2 yo)	SC: 50 mg once weekly	SC: 0.8 mg/kg weekly, with a maximum of 50 mg per week
	PsO (>4 yo)	SC: 50 mg twice weekly for 3 months, followed by 50 mg once weekly	SC: 0.8 mg/kg weekly, with a maximum of 50 mg per week
Evolocumab (10/2018)	HoFH	SC: 420 mg once monthly	Same as adult (≥13 yo)
Infliximab (6/2018)	Crohn's disease, UC	IV: 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks	Same as adult (≥6 yo)
Ipilimumab (7/2018)	Metastatic melanoma colorectal cancer	IV: 3 mg/kg every 3 weeks for 4 doses IV: 1 mg/kg every 3 weeks for 4 doses	Same as adult (≥12 yo) Same as adult (≥12 yo)
Mepolizumab (12/2017)	Asthma with eosinophilic phenotype	SC: 100 mg every 4 weeks	Same as adult (≥12 yo)
Obiltoxaximab (10/2016)	Inhalational anthrax	IV: 16 mg/kg	IV: 32 mg/kg (BW ≤15 kg); 24 mg/kg (BW >15-40 kg); 16 mg/kg (BW >40 kg)
Omalizumab (9/2018)	Asthma (≥6 yo)	SC: dose based on BW and initial serum IgE (see FDA label)	SC: 75-375 mg every 2-4 weeks: dose based on BW and serum IgE (see FDA label)
	Chronic idiopathic urticaria (≥12 yo)	SC: 150-300 mg every 4 weeks	Same as adult
Pembrolizumab (12/2018)	cHL, PMBCL, MSI-H, MCC	IV: 200 mg every 3 weeks	IV: 2 mg/kg (up to 200 mg) every 3 weeks
Raxibacumab (1/2018)	Inhalational anthrax	IV: 40 mg/kg single dose	IV: 80 mg/kg (BW ≤10 kg); 60 mg/kg (BW >10-40 kg); 40 mg/kg (BW >40 kg) single dose
Rilonacept (9/2016)	CAPS, FCAS, MWS (≥12 yo)	SC: 320 mg loading dose, then 160 mg once weekly	SC: 4.4 mg/kg loading dose, then 2.2 mg/kg (up to adult dose) once weekly

(*Continued*)

Table 2. Continued

mAb/Fc (Label Date)	Indication[a]	Dosing[a]	
		Adult	Pediatric
Tocilizumab (12/2018)	pJIA (>2 yo) sJIA (>2 yo) CRS (>2 yo)	IV: 4-8 mg/kg every 4 weeks SC: 162 mg every other week (if BW <100 kg); 162 mg every week (if BW ≥100 kg)	pJIA: 10 mg/kg IV q4weeks or 162 mg SC q3weeks (BW <30 kg); 8 mg/kg IV q4weeks or 162 mg q2weeks (BW ≥30 kg) sJIA: 12 mg/kg IV or 162 mg SC q2 weeks (BW <30 kg); 8 mg/kg IV q2weeks or 162 mg SC q1week (BW ≥30 kg). CRS: IV 12 mg/kg (BW <30 kg) or 8 mg/kg (BW ≥30 kg)
Ustekinumab (6/2018)	PsO (≥12 yo)	SC: 45 mg every 4 weeks × 2, then every 12 weeks (BW ≤100 kg); for BW >100 kg, 90 mg same regimen	SC: 0.75 mg/kg q4 weeks X2, then q12 weeks (BW <60 kg); for BW ≥60 kg, follow adult regimen

aHUS, atypical hemolytic uremic syndrome; ALL, acute lymphoblastic leukemia; BW, body weight; CAPS, cryopyrin-associated periodic syndromes; cHL, classical Hodgkin lymphoma; CRS, cytokine release syndrome; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulin D syndrome; HoFH, homozygous familial hypercholesterolemia; JIA, juvenile idiopathic arthritis; mAb/Fc, monoclonal antibody and Fc-fusion protein; MCC, Merkel cell carcinoma; MKD, mevalonate kinase deficiency; MRD, minimal residual disease; MSI-H, microsatellite instability-high cancer; MWS, Muckel Wells syndrome; pJIA, polyarticular juvenile idiopathic arthritis; PMBCL, primary mediastinal large B-cell lymphoma; PsO, plaque psoriasis; RA, rheumatoid arthritis; SC, subcutaneous; sJIA, systemic juvenile idiopathic arthritis; TRAPS, tumor necrosis factor receptor–associated periodic syndrome; UC, ulcerative colitis.

[a]The dosing chart and indications are abbreviated for this table. Please refer to full prescribing information.

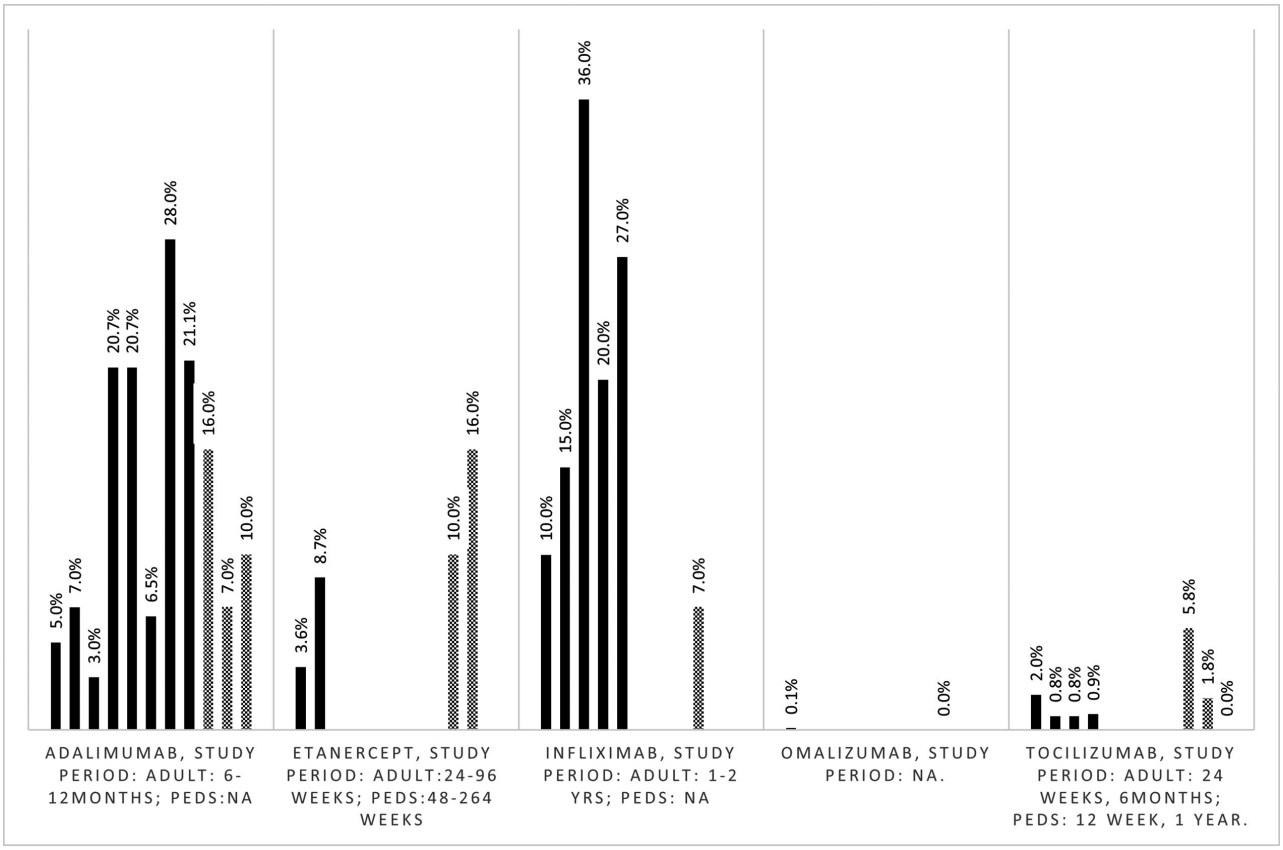

Figure 1. The percentage of patients developing antidrug antibodies in individual adult and pediatric trials. Only monoclonal antibody and Fc-fusion protein products that have both pediatric and adult immunogenicity rates are included. The solid bars represent adult studies, and the pediatric studies are represented by hatched bars. The immunogenicity rate (%) is listed at the top of the bar.

Table 3. Information on M&S Techniques Used in Drug Development of mAb/Fc Products Based on FDA Reviews and Labels

mAb/Fc[a]	No. of Individuals (Adult/ Pediatric Subjects)	Age Range (y)	Body Weight Range (kg)	Type of Model	Dose Selection[b]	Study Design[b]	Data Analysis/ Interpretation[b]	Analyzed Covariates[b]
Abatacept[64,65]	238/0	16-82	39-189	popPK, ER	x	NA	x	x
Adalimumab[66]	NA	NA	NA	popPK	x	NA	x	x
Avelumab[67,68]	1629/0	20-91	30.4-204	popPK	x	NA	x	x
Basiliximab[69]	NA	NA	NA	NA	NA	NA	NA	NA
Benralizumab[70]	2267/22	12-75	39.4-204.7	popPK, ER	x	NA	x	x
Blinatumomab[71,72]	322/76	18-80	44-134	popPK, ER, PBPK	x	NA	x	x
Canakinumab[73,74]	57/12	4-74	17-82	popPK	x	NA	x	x
Eculizumab[75]	NA	Adults	na	popPK, ER	x	NA	x	x
Etanercept[76]	NA*	NA	NA	popPK	x	NA	NA	NA
Evolocumab[77]	5474/0	20-80	41-175	popPK, ER	x	NA	NA	x
Infliximab[78,79]	NA	NA	NA	popPK, ER	x	NA	x	NA
Ipilimumab[80]	499/0	25-85	NA	popPK, ER	x	NA	x	x
Mepolizumab[81]	1216/7	12-82	40-162	popPK, ER	x	NA	x	x
Obiltoxaximab[82]	Animal study	Animal study	Animal study	popPK	x	NA	x	x
Omalizumab[83,84]	NA	NA	NA	popPK, ER	x	NA	NA	x
Pembrolizumab[85]	476/0	18-94	33.2-231	popPK, ER	x	NA	x	x
Raxibacumab[86]	Animal study	Animal study	Animal study	popPK	x	NA	x	x
Rilonacept[87]	333/17	NA	NA	popPK	x	NA	x	x
Tocilizumab[88]	1793/0	18-90	38-150	popPK, ER	x	x	x	x
Ustekinumab[89]	1963/0	18-86	37.4-195.1	popPK, ER	x	x	x	x

ER, exposure-response; mAb/Fc, monoclonal antibody and Fc-fusion protein; M&S, modeling and simulation; NA, not available; PBPK, physiologically based PK; popPK, population PK.

[a]The clinical pharmacology and some multidisciplinary reviews are referenced here, but all publicly available reviews were searched.[13]

[b]"x" denotes that modeling was apparently used for this purpose.

to therapy is increasingly understood. Also, the use of M&S is increasing to better utilize all of the drug experience available. Additionally, mAb/Fc products in oncology may be tested in pediatric patients more in the future under the FDA Reauthorization Act of 2017.

Study Population Size

Pediatric studies often have significantly fewer study subjects than their adult counterparts. Pediatric studies are often limited due to the difficulty in recruiting patients and the small patient population eligible for the study. Therefore, well-designed studies are crucial to offset the smaller sample size.

However, efforts have been made to mitigate this issue by better utilization of the data available using M&S techniques. Utilization of M&S techniques may increase the confidence in clinical data and results, even if the sample size is small.[16] M&S can contribute to dosing, efficacy, and safety assessments during pediatric drug development for mAb/Fc products. Drug safety remains a concern when only small numbers of pediatric patients have been studied, since the incidence of adverse drug effects is significantly different in pediatric patients in comparison to adults.[19] Postmarketing surveillance will also continue to be an important part of drug safety studies for the mAb/Fc products.

Dosing

The dosing strategy for mAb/Fc products is of concern in pediatric patients to maximize therapeutic efficacy while minimizing adverse effects. The clinical dose and dose regimen are dependent on multiple factors including PK, PD, ER relationships, genomics, disease progression, available concentration, and patient characteristics.[20] The rationale behind dose selection in pediatric patients for most mAb/Fc products was generally established by matching the pediatric exposure to the adult exposure, as ER is not routinely established in adult studies, and some models are developed on the basis of adult data only. Infliximab does represent one example where a similar ER between adults and pediatric patients with inflammatory bowel disease during the induction phase was used to establish pediatric dosing.[21] Similarity between the adult and pediatric disease is often unclear, and the ability to match exposures is often imprecise.[22]

A primary question is whether body weight–based, weight-tiered dosing, or body weight–independent (fixed) dosing should be used for dosing for pediatric

patients. Weight-tiered dosing was used frequently (9 of 20 products), but differing weight tiers for different products is an inconsistent observation among these mAb/Fc products. The effect of body size in pediatric patients has been an important factor in pediatric dose selection,[23] especially for products approved for use in young children. Dose selection is a critical step in pediatric development that requires leveraging prior knowledge from adult trials and conducting appropriate and well-designed pediatric trials.[23] Several dosing approaches have been employed to account for body size including weight-based dosing, body surface area–based dosing, weight-tiered dosing, and a combination of approaches. These dosing strategies have all been utilized in the 20 mAb/Fc products analyzed in this review as mentioned in the results section.

Immunogenicity

Immunogenicity is a unique and most often unwanted adverse effect of biologic products provoked by the body's immune reaction to a foreign antigen or epitope. The development of ADA can result in loss of efficacy, variable effects on PK, and adverse effects. Adverse effects include anaphylaxis, infusion reactions, and cross-reactivity to endogenous proteins.[1] Neutralizing ADAs can reduce the efficacy of the mAb/Fc product by binding to surface epitopes critical for efficacy. Nonneutralizing ADA binds to nonspecific functional domains of the mAb/Fc product, resulting in a range of effects. Both neutralizing and nonneutralizing ADAs may alter the PK of an mAb/Fc product, including enhancing the clearance of the mAb/Fc product.[24] Immune responses in infants and children are expected to be different than in adults. Our best prior examples come from the various B-cell responses in infants and children vs adults to immunization procedures. Multiple examples are available in the literature demonstrating different immune responses to immunizations in infants and children vs those in adults.[25,26]

As stated in the FDA-approved labels of these products, the detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody positivity, including neutralizing antibodies, in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, any comparison of the incidence of antibodies across therapeutic protein products in the adult or pediatric studies may be misleading. In comparing adult and pediatric immunogenicity data, a good understanding of the above-stated influencing factors would be critical for data interpretation.

The development and improvement of assays for detection of ADAs is critical for mitigating risk and understanding of immunogenicity. Detection of ADAs typically relies on ligand-binding assays in which the detection of ADAs depends on the binding of specific reagents to the specific ADA. However, drug molecules in the test sample can interfere with ADA assay detection. The "drug tolerance" of an assay is dependent on the experimentally determined maximum observed concentration not interfering with the detection of ADAs.[27] Many other factors contribute to accurate ADA detection including technological advancements and different detection techniques across biologic products. A lack of standardized procedures at the present time makes it impossible to accurately compare immunogenicity incidence across multiple products.

Of the studies analyzed, immunogenicity incidence rates are highly variable and inconclusive with regard to a pediatric and adult comparison. For example, the study results of adalimumab initially appeared to indicate a higher incidence of ADAs within the pediatric populations, but the assay used in pediatric studies for adalimumab detected ADAs with much greater sensitivity than that used in the adult studies. As seen in Figure 1, subsequent studies do not distinguish a difference between adults and pediatric patients for adalimumab immunogenicity.

High-quality ADA assays that can accurately detect ADA in the presence of therapeutic drug concentrations are critical for gathering immunogenicity data in order to improve the management of serious and chronic diseases or for comparing patient populations. Other variables that are being considered in present research on mAb/Fc immunogenicity include the change in ADA rate over time,[28] the effect of other drug therapy taken with the mAb/Fc product,[29] and the effect dose and drug concentration management.[30] As mentioned above, in January 2019 the FDA released a new Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products—Developing and Validating Assays for Anti-Drug Antibody Detection.[2]

Modeling and Simulation

Modeling and simulation techniques may contribute to reducing the uncertainty in dosing strategies of mAb/Fc products in pediatrics, with the exception of predicting immunogenicity. Population PK/PD models and PBPK/PD models are considered valuable in silico tools to help understand drug PK and PD and ultimately improve pharmacotherapy in special patient populations, such as children, in which clinical data are often unbalanced and sparse.[31,32]

Population PK/PD models were primarily used in the reviewed mAb/Fc products (Table 3), and are mathematical-statistical models that combine the description of drug PK with drug PD in a multicompartmental structural framework. The population

component refers to the stochastic model element that is incorporated in the PK/PD model and that accounts for the variability in model parameters between individuals. Additionally, these models can contain a covariate model element that allows the identification and quantification of sources and correlates of variability in drug concentrations and drug response among individuals, such as the subject's sex, age, demographics, biomarkers, disease status, or treatment-specific factors.

Despite various challenges, population PK/PD models for mAb/Fc products have the potential to be applied in pediatric drug development and clinical research. For pediatric patients, M&S techniques were frequently described in clinical pharmacology reviews, especially population PK studies (Table 3). While the information on the applied models given in clinical pharmacology reviews is generally limited to elementary information, more detailed examples of M&S techniques applied to pediatric patients can be found in the literature. Although not always used in the context of drug development and marketing authorization applications submitted to the FDA, these examples may provide important insights on how these models are developed and which research questions they can address. An overview of population PK/PD models for mAb products in pediatrics was provided in a previous publication.[33]

Two examples of pediatric population PK models from the literature illustrate the role and potential of these models in guiding drug development and optimizing dosing strategies in pediatrics. A previous study in pediatric cancer patients investigated the dosing strategy for bevacizumab, using a population PK model developed on the basis of pooled concentration data from 5 pediatric studies (comprising a total of 323 patients contributing 1971 plasma bevacizumab concentration data).[34] Covariate analysis indicated that changes in clearance and central volume of distribution between different age groups correlated well with body weight, thus supporting body weight–based dosing of bevacizumab across different age groups. In addition, clearance and central volume of distribution were significantly lower in children with primary central nervous system tumors than in children with sarcomas. However, in children with all tumor types, simulated bevacizumab steady-state maximum and trough concentrations ($C_{max,ss}$ and $C_{min,ss}$, respectively) following different body-weight dosing strategies fell within the 90% prediction interval of adult concentrations, suggesting that the same dose can be used for different tumor types in children. Bevacizumab currently does not have a pediatric FDA-labeled indication.

Another example is palivizumab, an mAb indicated for the prevention of serious lower respiratory tract disease caused by respiratory syncytial virus infection in infants who are at high risk of respiratory syncytial virus disease. A population PK/PD analysis was conducted on the basis of pooled clinical data from 10 pediatric studies involving preterm neonates born at ≤35 weeks of gestation and infants up to 24 months of age (comprising a total of 1684 patients with 4095 plasma palivizumab concentrations).[35] The results demonstrated that palivizumab clearance in children could not be estimated adequately by allometry alone. Therefore, a first-order function was developed to adequately describe palivizumab clearance indicating that, in addition to body weight changes, maturational effects also have a significant impact on palivizumab PK. Different dosing regimens were subsequently simulated to evaluate palivizumab exposure in infants. Simulation results indicated that a previously suggested reduction in the number of monthly doses would lead to a decreased and shortened palivizumab exposure over the respiratory syncytial virus season, hence confirming the label-indicated regimen of 5 monthly doses.

As highlighted by the published examples discussed above, pediatric population PK models for mAb/Fc products have largely focused on drug PK providing key insights into optimal dosing regimens, exposure in different pediatric age groups, and covariates affecting exposure. To strengthen the clinical importance of these findings, future modeling efforts with mAb/Fc products could elaborate the PK/PD relationship where a more thorough understanding in children is desirable. As described in the clinical pharmacology review for pembrolizumab, a population PK model indicated marked differences in the simulated steady-state exposure between different body weight categories. However, the review concluded that these differences in exposure were unlikely to lead to clinically significant efficacy responses because the ER relationship was found to be flat, supporting body weight–based dosing for pembrolizumab. One additional contribution of M&S in the future could be related to the development of ADAs and their impact on PK and PD. The first attempts to model this intricate ADA relationship have been summarized previously.[36]

Examples of the application of M&S and extrapolation can be found in the reviews of the current products. The efficacy of subcutaneous abatacept was extrapolated from the intravenous (IV) abatacept data in polyarticular JIA based on PK bridging. $C_{min,ss}$ was considered the relevant PK parameter for efficacy in rheumatoid arthritis, and a $C_{min,ss}$ >10 μg/mL was associated with a near-maximal effect based on ER analysis. With this information, the $C_{min,ss}$ for subcutaneous abatacept at day 113 was determined to be the primary PK end point to support efficacy extrapolation from IV abatacept. A similar situation was observed with tocilizumab when going from the IV formulation

to the use of the drug subcutaneously. In the case of tocilizumab, the efficacy and safety of the subcutaneous products was extrapolated from pediatric experience with the IV product, based on comparable PK/PD profiles and safety for systemic JIA.

In contrast to population PK/PD models, PBPK models were rarely used in the reviewed mAb/Fc products, and are mechanistic models consisting of a plethora of differential equations that simulate drug movements and drug effects in the body within a physiologically realistic structure, in which tissues and organs are compartmentalized with knowledge of their size and composition. While PBPK predictions can be conducted before initiating clinical trials, data from pediatric clinical trials may still be required to evaluate and verify the predictions. Also, these mAb/Fc products have rarely been indicated in neonates, where dosing predictions based on allometry generally are not applicable, and where PBPK models may find a use in the future.

As illustrated by the low rate of PBPK models included in clinical pharmacology reviews, more research is needed for developing pediatric PBPK models for mAb/Fc products. No PBPK model for mAb/Fc products in pediatric patients has been published to date. The current bottleneck for developing these models is the lack of robust data on relevant system-specific physiologic parameters pertaining to all PK processes. Additionally, the application scenarios of these models to mAb/Fc products are rather limited and not yet as established as for small-molecule drugs, where these models are routinely applied for such things as predicting the magnitude of drug-drug interactions, characterizing the in vivo absorption behavior, or scaling the PK to special populations such as children or renally impaired patients.

The disposition of mAb/Fc products is poorly understood in pediatric patients. The lymph flow rate is the key parameter driving the absorption kinetics, and lymphatic transit time and drug clearance during lymphatic transport are unknown in children. Distribution of mAb/Fc products is mainly confined to the plasma and extracellular fluid since mAb/Fc products are generally hydrophilic proteins with a large size and low membrane permeability. Therefore, the volume of distribution for most mAb/Fc products lies between the volume of the plasma and the extracellular fluid volume. Several studies have reported estimates for the plasma volume and extracellular space in children of different age groups suggesting that the weight-normalized volume increases progressively during childhood, whereas the extracellular space declines rapidly during the first months after birth.[37–41] Finally, the rate of distribution of mAb/Fc products into tissues is permeability limited. Since no information on these processes is available in children, they might be informed on the basis of other surrogate markers. In regard to distribution, a potential surrogate marker for the extravasation rates of mAb/Fc products is the transcapillary escape rate of albumin, which has been found to be 3 to 4 times higher in neonates and 1.5 to 2 times higher in children aged 8 to 14 years compared to adults.[37,42] The elimination of mAb/Fc products in pediatric patients is complex, but changes specific to pediatric patients have not been clearly identified. One hypothesis is that the increased weight-normalized clearance of mAb/Fc products in infants and young children can be mainly explained by the low neonatal Fc receptor expression, which normally prevents lysosomal degration.[43] In addition to these aspects, the disease state may have to be taken into account since inflammation may alter the expression of neonatal Fc receptor and concentration of immunoglobulin G.[44] A detailed overview of relevant physiologic system-specific parameters that affect mAb/Fc product disposition and their changes in childhood has been published recently.[43] Integration of this information in a PBPK framework could allow a more mechanistic extrapolation of drug disposition from adults to children and hence complement simple allometric scaling.

Model-informed drug development is advancing quickly under the Prescription Drug User Fee Act reauthorization for 2018 to 2022. The applications of M&S to mAb/Fc products will undoubtedly expand, and pediatric patients will benefit from these new approaches. In general, these applications can be broadly classified into 4 categories: dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy.[45] For the use of mAb/Fc products in pediatric patients, all 4 categories have a direct link to advancing drug development in this area in the future.

One limitation of this review was the restriction to publicly available information in the FDA reviews and labels. While this was not considered to be a major limitation to presenting this overview of mAb/Fc products in pediatric patients, individual aspects of a product could have been missed.

Conclusions

Only 20 of 68 approved mAb/Fc products have both adult and pediatric indications, but 13 of the 20 products received concurrent approval of the initial pediatric and adult indications. The number of patients in pediatric mAb/Fc studies was considerably lower than that in adult studies, which presents a concern due to limited safety information available. Technical differences present challenges to comparing immunogenicity profiles for mAb/Fc products between adults and pediatric patients, but current research into

immunogenicity may allow better management of drug response and immunogenicity in the future. An improved understanding of the physiologic processes entailing the requirement for differences in dosing regimens between adult and pediatric patients, and the application of advanced M&S methods such as PBPK for mAb/Fc products, may assist the future development of new mAb/Fc products for pediatric patients.

Disclaimer

The opinions expressed in this article are those of the authors and should not be interpreted as the position of the US Food and Drug Administration.

Declaration of Conflicting Interests

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The authors received no financial support for the research, authorship, and/or publication of this article.

Data Sharing

All of the data from this assessment are available online, and links to this material have been included in the references.

References

1. US Food and Drug Administration. Immunogenicity Assessment for Therapeutic Protein Products. https://www.fda.gov/downloads/drugs/guidances/ucm338856.pdf. Accessed January 31, 2019. 2014.
2. US Food and Drug Administration. Guidance for Industry: Immunogenicity Testing of Therapeutic Protein Products—Developing and Validating Assays for Anti-Drug Antibody Dectection. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm629728.pdf. Accessed on January 31, 2019. 2019.
3. Levy G. Pharmacologic target-mediated drug disposition. *Clin Pharmacol Ther*. 1994;56:248-252.
4. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokin Pharmacodyn*. 2001;28:507-532.
5. Laer S, Barrett JS, Meibohm B. The in silico child: using simulation to guide pediatric drug development and manage pediatric pharmacotherapy. *J Clin Pharmacol*. 2009;49:889-904.
6. Barrett JS, Della Casa Alberighi O, Laer S, Meibohm B. Physiologically based pharmacokinetic (PBPK) modeling in children. *Clin Pharmacol Ther*. 2012;92:40-49.
7. Huang SM, Abernethy DR, Wang Y, Zhao P, Zineh I. The utility of modeling and simulation in drug development and regulatory review. *J Pharm Sci*. 2013;102:2912-2923.
8. Leong R, Vieira ML, Zhao P, et al. Regulatory experience with physiologically based pharmacokinetic modeling for pediatric drug trials. *Clin Pharmacol Ther*. 2012;91:926-931.
9. US Food and Drug Administration. Guidance for Industry: Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Initial Pediatric Study Plans. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm360507.pdf. Published 2016. Accessed August 14, 2018.
10. US Food and Drug Administration. Guidance for Industry: Pediatric Rare Diseases—A Collaborative Approach for Drug Development Using Gaucher Disease as a Model. https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM587660.pdf Published 2017. Accessed August 14, 2018.
11. US Food and Drug Administration. Purple Book: Lists of Licensed Biological Products With Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/ucm411418.htm. Published 2018. Accessed June 30, 2018. 2018.
12. US Food and Drug Administration. FDA 101: Regulating Biological Products. https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm048341.htm. Published 2018. Accessed September 17, 2018. 2018.
13. US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. https://www.accessdata.fda.gov/scripts/cder/drugsatfda/ Published 2018. Accessed October 8, 2018.
14. US Food and Drug Administration. Tocilizumab (Actemra). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125276s125,125472s038lbl.pdf. Published 2018. Accessed February 3, 2019.
15. US Food and Drug Administration. Canakinumab (Ilaris). https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125319s088lbl.pdf. Published 2016. Accessed February 3, 2019.
16. Zhuang L, Chen J, Yu J, et al. Dosage considerations for canakinumab in children with periodic fever syndromes [published online ahead of print November 17, 2018]. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.1302.
17. Xu Y, Hijazi Y, Wolf A, Wu B, Sun YN, Zhu M. Physiologically based pharmacokinetic model to assess the influence of blinatumomab-mediated cytokine elevations on cytochrome P450 enzyme activity. *CPT Pharmacometrics Syst Pharmacol*. 2015;4:507-515.
18. US Food and Drug Administration. Guidance for Industry: How to Comply With the Pediatric Research Equity Act. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm079756.pdf Published 2005. Accessed February 3, 2019.
19. Liu XI, Schuette P, Burckart GJ, et al. A comparison of pediatric and adult safety studies for antipsychotic and antidepressant drugs submitted to the United States Food and Drug Administration [published online ahead of print January 21, 2019]. *J Pediatr*. https://doi.org/10.1016/j.jpeds.2018.12.033.
20. Bai S, Jorga K, Xin Y, et al. A guide to rational dosing of monoclonal antibodies. *Clin Pharmacokinet*. 2012;51:119-135.
21. Mehrotra N, Garnett C, Zhang L, Fang L, Wang YM, Fiorentino RP. Role of exposure-response analysis to guide dose selection in pediatric drug development when extrapolating efficacy from adults. *Inflamm Bowel Dis*. 2011;17(S2):5-6.
22. Mulugeta Y, Barrett JS, Nelson R, et al. Exposure matching for extrapolation of efficacy in pediatric drug development. *J Clin Pharmacol*. 2016;56:1326-1334.
23. Xu Z, Davis HM, Zhou H. Rational development and utilization of antibody-based therapeutic proteins in pediatrics. *Pharmacol Ther*. 2013;137:225-247.
24. Wang YM, Wang J, Hon YY, Zhou L, Fang L, Ahn HY. Evaluating and reporting the immunogenicity impacts for biological products—a clinical pharmacology perspective. *AAPS J*. 2016;18:395-403.
25. El-Madhun AS, Cox RJ, Søreide A, Olofsson J, Haaheim LR. Systemic and mucosal immune responses in young children and adults after parenteral influenza vaccination. *J Infect Dis*. 1998;178:933-939.

26. He XS, Holmes TH, Zhang C et al. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. *J Virology*. 2006;80:11756-11766.
27. Wang YM, Fang L, Zhou L, Wang J, Ahn HY. A survey of applications of biological products for drug interference of immunogenicity assays. *Pharm Res*. 2012;29:3384-3392.
28. Bian S, Dreesen E, Tang HT, et al. Antibodies toward vedolizumab appear from the first infusion onward and disappear over time. *Inflamm Bowel Dis*. 2017;23:2202-2208.
29. Balsa A, Sanmarti R, Rosas J et al. Drug immunogenicity in patients with inflammatory arthritis and secondary failure to tumour necrosis factor inhibitor therapies: the REASON study. *Rheumatology*. 2018;57:688-693.
30. Wong U, Cross RK. Primary and secondary nonresponse to infliximab: mechanisms and countermeasures. *Expert Opin Drug Metab Toxicol*. 2017;13:1039-1046.
31. De Cock RF, Piana C, Krekels EH, Danhof M, Allegaert K, Knibbe CA. The role of population PK-PD modelling in paediatric clinical research. *Eur J Clin Pharmacol*. 2011;67(suppl 1):5-16.
32. Bouzom F, Walther B. Pharmacokinetic predictions in children by using the physiologically based pharmacokinetic modelling. *Fundam Clin Pharmacol*. 2008;22:579-587.
33. Edlund H, Melin J, Parra-Guillen ZP, Kloft C. Pharmacokinetics and pharmacokinetic-pharmacodynamic relationships of monoclonal antibodies in children. *Clin Pharmacokinet*. 2015;54:35-80.
34. Han K, Peyret T, Quartino A et al. Bevacizumab dosing strategy in paediatric cancer patients based on population pharmacokinetic analysis with external validation. *Brit J Clin Pharmacol*. 2016;81:148-160.
35. Robbie GJ, Zhao L, Mondick J, Losonsky G, Roskos LK. Population pharmacokinetics of palivizumab, a humanized anti-respiratory syncytial virus monoclonal antibody, in adults and children. *Antimicrob Ag Chemother*. 2012;56:4927-4936.
36. Gomez-Mantilla JD, Troconiz IF, Parra-Guillen Z, Garrido MJ. Review on modeling anti-antibody responses to monoclonal antibodies. *J Pharmacokinet Pharmacodyn*. 2014;41:523-536.
37. Parving HH, Klebe JG, Ingomar CJ. Simultaneous determination of plasma volume and transcapillary escape rate with 131 I-labelled albumin and T-1824 in the newborn. *Acta Paediatr Scand*. 1973;62:248-252.
38. Anthony MY, Goodall SR, Papouli M, Levene MI. Measurement of plasma volume in neonates. *Arch Dis Child*. 1992;67:36-40.
39. Linderkamp O, Versmold HT, Riegel KP, Betke K. Estimation and prediction of blood volume in infants and children. *Eur J Pediatr*. 1977;125:227-234.
40. Friis-Hansen B. Water distribution in the foetus and newborn infant. *Acta Paediatr Scand*. 1983;305:7-11.
41. Battistini N, Virgili F, Severi S, et al. Relative expansion of extracellular water in obese vs. normal children. *J Appl Physiol*. 1995;79:94-96.
42. Brochner-Mortensen J, Ditzel J, Mogensen CE, Rodbro P. Microvascular permeability to albumin and glomerular filtration rate in diabetic and normal children. *Diabetologia*. 1979;16:307-311.
43. Malik P, Edginton A. Pediatric physiology in relation to the pharmacokinetics of monoclonal antibodies. *Expert Opin Drug Metab Toxicol*. 2018;14:585-599.
44. Gonzalez-Quintela A, Alende R, Gude F, et al. Serum levels of immunoglobulins (IgG, IgA, IgM) in a general adult population and their relationship with alcohol consumption, smoking and common metabolic abnormalities. *Clin Exper Immunol*. 2008;151:42-50.
45. Wang Y, Zhu H, Madabushi R, Liu Q, Huang SM, Zineh I. Model-informed drug development: current U.S. regulatory practice and future considerations [published online ahead of print January 17, 2019]. *Clin Pharmacol Ther*. https://doi.org/10.1002/cpt.1363.
46. US Food and Drug Administration. ORENCIA (abatacept). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125118s209lbl.pdf. Published 2017. Accessed February 3, 2019.
47. US Food and Drug Administration. Humira (Adalimumab). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125057s410lbl.pdf. Published 2018. Accessed February 3, 2019.
48. US Food and Drug Administration. Avelumab (Bavencio). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761049s003lbl.pdf. Published 2018. Accessed February 3, 2019.
49. US Food and Drug Administration. Basiliximab (Simulect). https://www.accessdata.fda.gov/drugsatfda_docs/label/2003/basnov010203LB.htm. Published 2003. Accessed February 3, 2019.
50. AstraZeneca. Benralizumab (Fasenra). https://www.azpicentral.com/fasenra/fasenra.pdf#page=1. Published 2017. Accessed February 3, 2019.
51. US Food and Drug Administration. Blinatumomab (Blincyto). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125557s013lbl.pdf. Published 2018. Accessed February 3, 2019.
52. US Food and Drug Administration. Eculizumab (Soliris). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125166s047s048lbl.pdf. Published 2018. Accessed February 3, 2019.
53. US Food and Drug Administration. Etanercept (Enbrel). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103795s5569lbl.pdf. Published 2018. Accessed February 3, 2019.
54. US Food and Drug Administration. Evolocumab (Repatha). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125522s017lbl.pdf. Published 2018. Accessed February 3, 2019.
55. US Food and Drug Administration. Infliximab (Remicade). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103772s5385lbl.pdf. Published 2018. Accessed February 3, 2019.
56. US Food and Drug Administration. Ipilimumab (Yervoy). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125377s096lbl.pdf. Published 2018. Accessed February 3, 2019.
57. US Food and Drug Administration. Mepolizumab (Nucala). https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/125526s004lbl.pdf. Published 2017. Accessed February 3, 2019.
58. US Food and Drug Administration. Obiltoxaximab (Anthim). https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125509s001lbl.pdf. Published 2016. Accessed February 3, 2019.
59. US Food and Drug Administration. Omalizumab (Xolair). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/103976s5231lbl.pdf. Published 2018. Accessed February 3, 2019.
60. US Food and Drug Administration. Pembrolizumab (Keytruda). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125514s037lbl.pdf. Published 2018. Accessed February 3, 2019.
61. US Food and Drug Administration. Raxibacumab. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125349s022lbl.pdf. Published 2018. Accessed February 3, 2019. 2018.
62. Regeneron Precribing Information. Rilonacept (Arcalyst). https://www.regeneron.com/sites/default/files/Arcalyst_FPI.pdf. Published 2016. Accessed February 3, 2019.
63. US Food and Drug Administration. Ustekinumab (Stelara). https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/125261s147lbl.pdf. Published 2018. Accessed February 3, 2019.

64. US Food and Drug Administration. Orencia (Abatacept): clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM552568.pdf. Published 2016. Accessed February 3, 2019.
65. US Food and Drug Administration. ORENCIA (Abatacept): clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM552570.pdf. Published 2016. Accessed February 3, 2019.
66. US Food and Drug Administration. Adalimumab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM529945.pdf. Published 2015. Accessed February 3, 2019.
67. US Food and Drug Administration. Avelumab (Bavencio): Office of Clinical Pharmacology memo. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000ClinPharmR.pdf. Published 2017. Accessed February 3, 2019.
68. US Food and Drug Administration. Avelumab (Bavencio): BLA multidisciplinary review and evaluation. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761049Orig1s000MultidisciplineR.pdf. Published 2017. Accessed February 3, 2019.
69. US Food and Drug Administration. Basiliximab: clinical pharmacology review of BLA 974251. https://web.archive.org/web/20170114041139/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm113364.pdf. Published 1998. Accessed February 3, 2019.
70. US Food and Drug Administration. Benralizumab: clinical pharmacology and biopharmaceutics review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/761070Orig1s000ClinPharmR.pdf. Published 2016. Accessed February 3, 2019.
71. US Food and Drug Administration. Blinatumomab: clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125557Orig1s000ClinPharmRedt.pdf. Published 2014. Accessed February 3, 2019.
72. US Food and Drug Administration. Blinatumomab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM629148.pdf. Published 2016. Accessed on February 3, 2019.
73. US Food and Drug Administration. Canakinumab: clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2009/125319s000_ClinPharmR.pdf. Published 2008. Accessed February3, 2019.
74. US Food and Drug Administration. Canakinumab: clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125319Orig1s085,086,087ClinPharmR.pdf. Published 2016. Accessed February 3, 2019.
75. US Food and Drug Administration. Eculizumab: Office of Clinical Pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/125166s0000_ClinPharmR.pdf. Published 2007. Accessed February 3, 2019.
76. US Food and Drug Administration. Etanercept: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM554676.pdf. Published 2016. Accessed February 3, 2019.
77. US Food and Drug Administration. Evolocumab: Office of Clinical Pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125522Orig1s000ClinPharmR.pdf. Published 2014. Accessed February 3, 2019.
78. US Food and Drug Administration. Infliximab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM557890.pdf. Published 2016. Accessed February 3, 2019.
79. US Food and Drug Administration. Infliximab: clinical pharmacology review of BLA 98-0012, cA2. https://web.archive.org/web/20170119061118/http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm107704.pdf. Published 1998. Accessed February 3, 2019.
80. US Food and Drug Administration. Ipilimumab: Office of Clinical Pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/125377Orig1s000ClinPharmR.pdf. Published 2011. Accessed February 3, 2019.
81. US Food and Drug Administration. Mepolizumab: Office of Clinical Pharmacology genomics and targeted therapy review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125526Orig1s000ClinPharmR.pdf. Published 2014. Accessed February 3, 2019.
82. US Food and Drug Administration. Obiltoxaximab: Office of Clinical Pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/125509Orig1s000ClinPharmR.pdf. Published 2015. Accessed February 3, 2019.
83. US Food and Drug Administration. Omalizumab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM393855.pdf. Published 2013. Accessed February 3, 2019.
84. US Food and Drug Administration. Omalizumab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM525863.pdf. Published 2015. Accessed February 3, 2019.
85. US Food and Drug Administration. Pembrolizumab: clinical pharmacology BLA review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125514Orig1s000ClinPharmR.pdf. Published 2014. Accessed February 3, 2019.
86. US Food and Drug Administration. Raxibacumab: clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/125349Orig1s000ClinPharmR.pdf. Published 2012. Accessed February 3, 2019.
87. US Food and Drug Administration. Rilonacept: clinical pharmacology review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2008/125249s000_ClinPharmR.pdf. Published 2007. Accessed February 3, 2019.
88. US Food and Drug Administration. Tocilizumab: NDA/BLA multidisciplinary review and evaluation. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM623326.pdf. Accessed February 3, 2019.
89. US Food and Drug Administration. Ustekinumab: clinical pharmacology review. https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM586124.pdf. Published 2016. Accessed February 3, 2019.