DOSE OPTIMIZATION AND BODY SIZE

By

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To my parents and my husband

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Therapeutic biologics and anticancer small molecules are often administered based on body size. A previous study has found that fixed dosing performs similarly to body size-based dosing in reducing intersubject variability in drug exposure across the monoclonal antibodies (mAbs) studied. A few studies have questioned body surface area (BSA) based dosing for anticancer drugs. This dissertation extends the evaluation from mAbs to other therapeutic proteins and peptides. This dissertation also for the first time evaluates fixed dosing and BSA-based dosing using population pharmacokinetic simulation. Eighteen therapeutic proteins and peptides as well as 28 anticancer drugs with published population pharmacokinetic (PK) models were selected for dosing approach evaluation. The relationships between body size and drug exposure were evaluated, and simulation studies were conducted to compare the performance of the 2 dosing approaches. The results showed that fixed dosing performed better for more selected biologics and anticancer drugs than body size-based dosing in terms of reducing intersubject variability in exposure at both population and individual levels. This result is consistent with the findings for mAbs, and previously published review for anticancer drugs. Therefore, fixed dosing is recommended for first-in-human studies of

proteins and peptides and small oncology drugs. The final dosing approach for Phase III studies should be determined based on a full assessment of body size effect on PK/PD when data are available and the therapeutic window of the drug. The pediatric dosing for protein and peptides was also discussed in this dissertation and selected proteins and peptides were reviewed for their body size-based dosing. Pediatric dosing is more complicated than adult dosing. For most of the evaluated proteins and peptides, body size-based dosing was appropriate. However, for certain biologics, a simplification can be made, such as one fixed dose for a range of body weight/age and another fixed dose for a different range of body weight/age.

CHAPTER 1
INTRODUCTION

Overview of Population Pharmacokinetics and Dose Optimization

During drug development, the concept of drug response in pharmacokinetic and pharmacodynamic (PK/PD) investigations has been confirmed for many decades. However, drug response is influenced by substantial interindividual variability. Individual patients given the same dose and dose regimen may present widely varied responses in onset, magnitude, and duration. Dose optimization and dose individualization is, therefore, the common goal for scientists who are involved in drug development, both in the pharmaceutical industry and regulatory agencies. To achieve this goal does not seems to be an easy journey, since the large between patient variability exists in pharmacokinetic, pharmacodynamic, physiological, physiochemical, and pathophysiological processes which ultimately effect the clinical outcomes of the medicines. The task of the late stage of drug development is to select dose or doses to be proposed for therapeutic use, and the purpose is to optimize the dosage and reduce the risk of failing to meet the safety and efficacy criteria. The focus of this dissertation is on the interindividual variability in pharmacokinetics and pharmacodynamics, mainly pharmacokinetics of the protein, peptides and anticancer drugs.

The factor that can contribute to the interindividual variability in pharmacokinetics and pharmacodynamics can be intrinsic factors such as the patients' biological characteristics (e.g. gender, race, age, weight, height, menopausal status, pregnancy); genetic differences (e.g. polymorphisms in metabolizing enzymes and transports); disease related characteristics (e.g. tumor type, cancer stages, surgery, liver function, renal function, albumin and alpha -1- acid glycoprotein levels); comedications (e.g.

antibiotics, herbal supplements, over the counter medications); and environmental factors such as patients' life style (e.g. adherence to medications, food, alcohol, smoking, coffee, exercise, stress). In order to optimize the dose and dosing regimen, study or studies may be needed to identify patients' intrinsic and environmental characteristics that have a significant effect on PK and PD, and ultimately on the clinical outcome.

The classic PK/PD analyses, in many cases, fail to identify the factors that are responsible for the interindividual variability. To individualize doses further for therapeutic agents with high interindividual PK or PD variability, the drug development team needs additional information of factors that might account for the intersubject variability. Population pharmacokinetics was originally proposed in the 1970s by Sheiner et al.[1] In early 1990s, population pharmacokinetics drew the attention due to the increasing activities in the field, and has expanded from a discipline mainly used for therapeutic drug monitoring to a critical tool in drug development. In February 1999, the FDA issued "Guidance for Industry: Population Pharmacokinetics", which laid out the mechanisms and theory of population pharmacokinetics and highlighted its usage during the drug development process.[2] Population pharmacokinetics was defined in the guidance as "The study of the sources and correlates of variability in drug concentrations among individuals who are the target patient population receiving clinically relevant doses of a drug of interest. Population pharmacokinetics seeks to identify the measurable pathophysiologic factors that cause changes in the dose-concentration relationship and the extent of these changes so that, if such changes are associated with clinically significant shifts in the therapeutic index, dosage can be

appropriately modified." In 1997, a survey of 206 new drug applications showed that 47 of the applications contained population pharmacokinetics and/or population pharmacodynamic reports, and early application of population PK provided helpful safety, efficacy and dose optimization information in 83% of the 47 applications.[3]

In the traditional pharmacokinetic studies, the main focus has been the average behavior of the group, such as the mean plasma concentration- time profile. The interindividual variability in pharmacokinetics is often investigated through complex controlled studies. Additionally, concentrating on one single variable in the traditional way of pharmacokinetic study makes it complicated when interactions among variables need to be understood.

Compared to traditional pharmacokinetic studies that are mainly focused on collecting plasma concentration of the drug at a series of time points, population pharmacokinetic studies collect any further information that might explain the interindividual variability in the patient population (e.g., gender, age, body weight, body surface area, race, smoking status, drug response phenotypes, etc.). Similar to traditional pharmacokinetics, population pharmacokinetics also estimates the average pharmacokinetic parameters (e.g. typical value of clearance or volume of distribution, which are called THETA (θ)). The focus of the population pharmacokinetic analysis process is identifying the factors that do have an effect on PK parameters or exposures, which is the major purpose of the analysis (e.g. body weight, gender, age, etc., which are called covariates in population pharmacokinetics or fixed effects on pharmacokinetic parameters). Population pharmacokinetics also quantifies the magnitude of unexplained (random) variability which is called "intersubject variability" or ETA (η). The greater the

percentage of the interindividual variability can be explained by covariates, the more control we have in ensuring that the dosing of the therapeutic drug is both efficacious and safe. In other words, the less the intersubject variability accounts for the overall interindividual variability, the more information we have to adjust dosing according to the covariates for different groups of patient population. Concentrations of the drug may vary between days or within a day due to the error of the analysis measurements. Samples taken in different clinical study locations may have variation as well. This kind of variability is called residual intrasubject variability and interoccasion variability, usually expressed as epsilon (ε). Estimation of such variability is also important for therapeutic drug monitoring. Finding the optimum dose for a population, subpopulation, or individual patient requires knowledge of the variability mentioned above. The siginificance and usefulness of the population PK in drug development has been recognized more and more nowadays, it should be integrated as broad as it can be when appropriate.

As early as in pre-clinical studies, population PK can be applied to allometric scaling and toxickinetic studies in small and large animals, as well as more importantly to guide the first in human (FIH) doses for clinical Phase I trials. In Phase I (usually healthy volunteers) studies, population PK can be applied to understand the structural model with the mean PK parameters and potential covariates for healthy subjects, as well as the foundation to evaluate the difference between patient and healthy populations. Phase II studies data provides the best situation to uncover the dose response of PK and PD for the product in patient population, and propose dose strategies that maximize the benefits and minimize the adverse effects. Phase III and IV

studies can provide opportunities to further explore the population PK model and find correlation of new appeared responses.

Population Pharmacokinetic Approach

In 1972, Sheiner et al. first proposed the theory of population pharmacokinetics, and suggested using computer programs to find the optimal dose for a number of drugs for individual patients.[4] In order to conduct population PK analysis, Lewis B. Sheiner and Stuart Beal developed NONMEM (non-linear mixed effect model) software during the 1970s at University of California San Francisco. The difference between NONMEM and other statistics softwares that can also be used to conduct non-linear mixed effect model is that there are numerous model libraries and specific terms that are easier for clinical pharmacologists and pharmacokineticists to adapt as a tool. It has been used mainly in the academic research in the 1980s, and regulatory agencies began to take notice of population PK in the late 1980s. Since the FDA issued the guidance for population PK in 1999, NONMEM (Globomax) has been the gold standard for pharmaceutical companies and regulatory agents.

The goal of this part of the chapter is introduce the concept of nonlinear mixed effects modeling, the mechanics of NONMEN and the utility of population PK in drug development. We all understand that individuals vary in the pharmacokinetic and pharmacodynamic responses to the administration of certain doses of drugs. Population PK is the tool to understand why there are variations and to what extent are the variations. The simplest way to describe population PK is the PK in a certain patient population. The goal is to estimate mean PK parameters and between-subject variability, estimate individual PK parameters, and estimate residual variability, in order

to understand measurable sources of variability in PK and describe their relationship to PK parameters.

The reason that industry and regulatory agencies conduct population PK is to understand factors that cause variability in PK. It is a highly efficient way to screen a large number of diverse individuals from the certain target population. The advantage of population PK is to investigate multiple factors (e.g. disease status, demographics (body weight, age, gender, etc.), drug interactions, food effects, etc. and combinations of all these factors at once instead of designing and conducting multiple clinical trials according.

Nonlinear mixed effects model. Nonlinear mixed effects model is a suitable tool to analyze repeated measurements data. The clinical PK/PD data is usually repeated measurements over time. The functions to fit the PK/PD data are also very common to be nonlinear in the parameters. This is the reason why nonlinear mixed effects model became popular in PK/PD modeling. The nonlinear mixed effects model simultaneously estimates parameters relating fixed effects and random effects to observed data. Fixed effects are observed or measured variables (e.g. dose, time, weight, age, gender, genetic difference, etc.), and random effects are unexplained random variability (e.g. interindividual or residual errors). Based on the premise, the individual pharmacokinetic parameters of a patient population arise from a distribution which can be described by the population mean and the interindividual variance. Each pharmacokinetic parameter can be expressed as a population mean and a deviation for that individual. Nonlinear mixed effects model is a one stage analysis that simultaneously estimates mean

parameters, fixed effect parameters, interindividual variability and residual random effects.

The concept of mixed effects model can be explained by a schematic approach as it applies to analysis of PK data. Let us take the example of concentration – time profiles of a group of subjects.[5] In Figure 1-1, each data point is identified using the subject ID in the concentration- time profile. The red line is the mean concentration time profile using a 1 compartment model that provides the best fit to all of the data in the figure. This mean profile is a result of a mean clearance as shown in Figure 1-1C, the clearance-CrCL (creatine clearance). The horizontal line indicates that there is only one clearance value across the whole patient population, and the volume of distribution has a similar case.

We all know that individuals vary. We will focus on subject 2 in the concentration–time profile, Figure 1-1D. If only data from subject 2 were fit alone, a higher clearance will be predicted. The blue line indicates the best fit for this particular subject due to a higher clearance. It is assumed that the individual pharmacokinetic parameters arise from a distribution which can be described by the population mean and the interindividual variance. The deviation (the difference between the population mean and the individual parameter) is assumed to be a random variable with an expected mean of zero and variance ω^2. This variance describes biological population variability. Therefore, in order to fit each subject, we sample an ETA (η) for each subject from this distribution shown in green (Figure 1-1, C and D). However, we still have not predicted the concentrations for subject 2 accurately. This is where we should consider the second level of random variable. This random variable represents assay error, within

subject error (or the intraindividual variability), and model specification error. It is also assumed that the distribution of the random variable epsilon (ε) is zero with a variance of sigma squared. In a word, there are two levels of random variability (one for inter individual variability and one for residual variability).

The next step is to identify any possible covariates that can explain the interindividual variability of the parameters. For example, suppose this compound is predominantly eliminated via the kidney, and assume there is a strong relationship between CL of the drug and CrCL. In Figure 1-1 D, since subject 2 having lower concentrations, the subject's clearance is higher than the clearance value of the red line. As a result a particular typical value can be assigned to this subject (instead of everyone has the same typical clearance value); here is the green line indicates the typical concentration time profile of a subject with a certain CrCL (Figure 1-1 C and D). As can be seen, the predicted concentrations are much closer to the individual's data compared to the mean profile in red. However, there is still a difference between the typical concentration time profile for subject 2 with a certain CrCL (in green) and the individual predicted profile (in blue). This difference is the interindividual variability in the new model that incorporates CrCL as a covariate for clearance. The reason for this difference between the two profiles (also two models) is that CrCL has attributed some of the intersubject variability in CL, but CrCL cannot explain all the interindividual variability in CL. The grey shaded area is now an area where we could explain the variability from subject to subject using CrCL. The goal would be to have this grey area as big as possible. In order to achieve this goal, all the possible covariates (e.g. body

weight, gender, age, genetic polymorphism, etc.) that could contribute to the interindividual variability should be evaluated carefully during the analysis.

The covariates, eta and epsilon can be better explained by Figure 1-2. In Figure 1-2 C, the clearance-CrCL profile, instead of everyone having the same clearance, the typical value of clearance can be expressed by TVCL=θ1+CrCL*θ2, and the typical clearance of the whole population depends on the value of CrCL. The individual clearance for a particular subject is expressed as CL_i, and CL_i = TVCL+η. The red profile is corresponding to TVCL, and blue profile is corresponding to CL_i. Even after corrected for the covariate CrCL and interindividual variability η, there is still a difference between the observed concentration points to the profile, and this is the random variable epsilon (ε) attributed by assay error, within subject error, and model specification error.

As mentioned before, fixed effects are observed or measured variables (e.g. dose, time, weight, age, gender, genetic difference, etc.), and incorporating them into equations can be shown for example: TVCL=θ1+CrCL*θ2 or CL=TVCL*(CrCL/median CrCL)^ θ2. To describe the population PK model using equations, the two levels of random effects can be expressed by the following equations.In this example, I.V infusion administration is used

Interindividual variability:

$$CL_i = TVCL \cdot e^{\eta_{CL,i}}$$

Where CLi is individual clearance for the ith subject, TVCL is the typical value of clearance for the population, and $\eta_{CL,i}$ is the interindividual variability on clearance for the ith subject.

Residual variability:

$$y_{ij} = \frac{k_0}{CL_i}\left(1 - e^{-\frac{CL_i}{V_i}\cdot T_{ij}}\right)\cdot e^{-\frac{CL_i}{V_i}\cdot t'_{ij}} + \varepsilon_{ij}$$

Where y_{ij} is the response, the concentration of ith subject at jth time point, CL_i is individual clearance for the ith subject, k_0 is the infusion rate, V_i is individual volume of distribution for the ith subject, T_{ij} is the infusion duration of ith subject at jth time point, t'_{ij} is the time after infusion of ith subject at jth time point, ε_{ij} is error term of the intraindividual variability of ith subject at jth time point.

Nested random effects:

$$y_{ij} = \frac{k_0}{TVCL\cdot e^{\eta_{CL,i}}}\left(1 - e^{-\frac{TVCL\cdot e^{\eta_{CL,i}}}{TVV\cdot e^{\eta_{V,i}}}\cdot T_{ij}}\right)\cdot e^{-\frac{TVCL\cdot e^{\eta_{CL,i}}}{TVV\cdot e^{\eta_{V,i}}}\cdot t'_{ij}} + \varepsilon_{ij}$$

where :

$\eta \sim N(0,\omega^2)$

$\varepsilon \sim N(0,\sigma^2)$

TVV is typical value of volume of distribution for the population, $\eta_{V,i}$ is the interindividual variability on volume of distribution for the ith subject.

A simple case in population PK nonlinear mixed effects model is explained above. There are different scenarios in PK that can be analyzed using nonlinear mixed effects model if the variability is the interest. Population PD and population PK/PD are widely adapted in drug development as well. Since the same theory applies to population PK/PD models, there won't be examples given here. As long as the data is repeated – measurements, and the goal is to understand not only the structure model but the variability nonlinear mixed effects model is the ideal candidate tool.

Population Pharmacokinetics in Dose Optimization during Drug Development

The application of population PK can be involved in all phases of clinical drug development: the transition from Phase I to Phase II/III, dose selection for Phase III, dose adjustment in special populations, confirm drug interaction studies, support for confirmatory efficacy/safety, pediatrics studies and dosing, bridging to different ethnic groups, results incorporated in product package insert, and also applied in preclinical development.

Sheiner [6] first introduced the learning and confirming concept to the drug development process. In the first learning and confirming cycle (traditional Phase I and Phase IIa), the purpose of Phase I is to find out what is the biggest short – term dose that maybe given to human without introducing side effects; and the purpose of Phase IIa is to confirm that the dose resulted from Phase I provide promising efficacy in selected group of patients. The decision after the first learning and confirming cycle is the go or no go call for continuation of the investment of the drug after reviewing whether there is strong enough indication of efficacy and absence of toxicity. In the second learning and confirming cycle, the purpose of the Phase IIb is to find a good, if not ideal, dosing and dosage regimen to provide a promising clinical outcome; and the purpose of the Phase III is to get the compound approval by confirming via a randomized clinical trial in a large number of target patient population using the selected dosing and dosage regimen from Phase IIb to achieve reasonable benefit – risk ratio.

The application of population PK in the modeling and simulation in different phases and the learning and confirmation cycle is summarized as below.

Phase I: PK/PD simulations in preclinical studies are very helpful in deciding the first in human dose. The PK data in Phase I is characterized by rich data at different

dose levels and relatively consistent PK profile for each individual. The structural population PK model is usually best identified due to the intense sampling in Phase I. In addition, related demographics for PK parameters as well as PD models can also be done in this step to be better prepared for Phase II designs. Since the Phase I studies are usually carried out in healthy volunteers, the PKPD difference between healthy population and patient population can be studied later. Especially, for the PD models, if the difference is established between healthy and patient population for one of the compounds used previously for the same indication for the disease, then these models can be used for another compound via simulation to better guide the design of the Phase II studies. The importance of the population PK in this phase is no doubt, since this is the first time ever in human, for the new compound estimates of the basic structural model parameters and demographic covariates effects on the parameters could be evaluated. The estimation of inter- and intra individual variability could provide valuable information for designing robust Phase II studies.

Phase IIa: It is the confirming step of the first learning and confirming cycle. Phase IIa studies are done in patients at different dose levels. Phase II has more cohorts than Phase I and more dose levels than Phase III, which provides the greatest opportunity to apply population PK modeling and simulation knowledge for dosing strategies with promising benefit – risk ratio. The population PK models give an overall idea of fixed effects and random effects in healthy population. In Phase IIa, the learning and confirming steps go along together. The goal of this stage is the proof of concept. The concentration in this learning step is usually sparse sampling. After the proof of concept, the PK/PD steps in to analyze the relationship between dose, concentration and effects.

The population PK/PD models then could estimate for patients certain demographic characteristics will/will not achieve the targeted exposure that corresponds to final clinical outcome.

Phase IIb: Phase IIb is the dose finding step. The knowledge about variation in PK and PD in patient population will be improved. The previous knowledge about PK and PD will help to design the dose finding studies via simulations. The data observed will further improve the population PK/PD models. An optimized dose for Phase III will be proposed using simulations with latest updated population PK/PD models in order to achieve the ultimate goal of maximizing the beneficial effects while minimizing adverse effects.

Phase III: The purpose of the Phase III is to confirm efficacy in a larger patient population as well as learning side effects about this population. It is usually better to use sparse sampling design in a small group with exposure data, because sometimes confirmation of efficacy fails. Using the data from this small group, we can validate the population PK model. The demographic information in Phase III (e.g. body size, gender, disease status, age, etc.) is richer than previous phases. This information will provide more improvement for the population PK model. Simulations from the updated models could provide good recommendation for new Phase III to confirm the efficacy. The simulations can also help dose adjustment with special populations to be indicated in the drug label.

Overall, in the past decade, population PK/PD has been applied more and more in drug development by pharmaceutical industry. The theories, methods and applications of population PK/PD modeling and simulation has been actively published in clinical

pharmacology journals and international conferences, such as American College of Clinical Pharmacology, American Association of Pharmaceutical Scientists, American Society for Clinical Pharmacology and Therapeutics, Population Approach Group in Europe which is more focused on population PK and PD started in Europe, and the new emerging American conference that focused only on PK/PD modeling the American Conference on Pharmacometrics (ACOP, the first ACOP meeting was hold in 2008). The guidance by FDA in 1999 speeded up the growth of population PK/PD in drug development. It is and has been shown to be a great tool that needs to be integrated in the modern drug dosing finding studies to build more efficient, robust, informative, and cost effective clinical studies at different stages. It is more encouraged to be implemented throughout the entire drug development process including the preclinical animal studies. The early the implementation is the more information and benefits it can provide.

Body Size Measurement and Body Size Effect on Pharmacokinetics

Although with not sufficient scientific evidence, body size-based dose is usually used for biotherapeutic molecules and small oncology drugs. Flat fixed dosing is most commonly used for small chemical molecules in adults. Whether body size-based dosing should be used in patients, mainly depends on whether body size has a significant effect on PK and PD of the drug, as well as its therapeutic index. If the drug has a wide therapeutic window, a flat fixed dose for every adult patient is chosen, regardless of the effect of body size on PK and PD. The reason of this decision is because flat fixed dosing provide a series of advantages than body size-based dosing: 1) it is easier for pharmacists to prepare and easier for nurse to administer; 2) patients usually have better compliance; 3) there is less risk for medical errors, since no

calculation is needed for dosing each patient; 4) it costs less, since there is no drug wasted. On the other hand, if the drug has a narrow therapeutic index, not only the body size effect, but all the other possible factors that can affect PK/PD of the drug should be systemically evaluated for an appropriate dosing strategy that provides the optimal clinical outcomes. The goal of evaluating the factors that could affect the PK/PD of the drug is to optimize a dosing strategy to achieve low interindividual variability in the patient population by adjusting the dose when necessary according to the factors (e.g. body size, gender, pharmacogenomics differences), and most importantly achieve the optimal risk/benefit ratio.

If the interindividual variability cannot be explained by any obvious factor, then flat fixed dosing should be chosen during drug development and clinical practice. If there is enough evidence showed that the drug be dosed according to the patients' body sizes, then the drug development team needs to choose a body size measurement for the dosing in this case. Pinkel has suggested using body surface area (BSA) instead of body weight as the dosing criterion for anticancer chemotherapy.[7] Body weight has long been used in the dosing criterion, and it is a straight forward measurement that is easier to observe than body surface area. However, BSA was believed to be better correlated with basal metabolic rate as well as blood volume than body weight across difference species (e.g. rabbits, guinea pigs, and mice) and humans.[7] BSA-based dosing has been extensively used in chemotherapy. The history of BSA and BSA formulas will be discussed in detail in Chapter 4.

Besides body weight and BSA, there are other body size measurements, such as body mass index (BMI), ideal bodyweight (IBW), percent IBW, adjusted bodyweight,

lean bodyweight (LBW). The body size measurements and body size effect on pharmacokinetics as well as obesity pharmacokinetics are reviewed in this section.

Measurements of Body Size

Since it is hard to measure body fat and fat free mass directly, many methods have been used to indirectly measure body composition. These indirect measures of body composition are often derived from readily measurable body size, thus body weight, height, and gender.

Body mass index. Body mass index (BMI), or Quetelet's Index was first proposed by Quetelet in 1869.[8] It was intuitively suggested that body size should depend on a person's weight and height. At first Quetelet proposed that body volume would be ideally explained by height to the third power (HT^3). This idea was introduced by Keys et al. to describe the incidence of coronary heart disease in men.[9] Keys then reported that the ratio of total body weight to HT^2 (named as Quetelet's Index) was the best to describe the result. Quetelet's Index was later renamed as body mass index (BMI). BMI is currently the WHO's preferred and recommended measure to classify obesity. It is used to separate people into four major groups: underweight, BMI < 18.5 kg/m^2; normal weight BMI18.5–24.99 kg/m^2; overweight, BMI 25 – 30 kg/m^2, and obesity BMI > 25 kg/m^2. Obesity is then further classified as moderate, BMI30–34.99 kg/m^2; severe, BMI 35–39.99 kg/m^2; and morbid BMI > 40 kg/m^2. Although BMI is widely used by medical professionals, it is not that helpful in pharmacokinetics and dosage calculations. The biggest limitation for BMI is that it does not differentiate between the fat tissue mass and lean muscle mass. If BMI is used, then the patient with a large muscle mass would be given the same dose as a patient with a large fat

mass. As a result, BMI is unlikely to become a good body size measurement for dosing.

Ideal body weight. Ideal body weight (IBW) was a size measurement first derived from insurance data collected by the Metropolitan Life Insurance Company of New York. The company reported evidence that relates size to mortality in woman and man, respectively in 1942 and 1943.[10, 11] This finding was updated in 1959 [12] and 1960 [13] using the data obtained during the Build and Blood Pressure Study.[14] The study recruited more than 4.5 million people; however, ideal body weights for height were derived based on only 360 000 people. This version of IBW from was reported unrelated to total body weight (TBW), and is an estimate of weight corrected for height, gender, and body frame size. Equations for estimation was reported by Blackburn in 1977.[15] However, the empirical estimate of IBW that is often used in pharmacokinetics was derived by Devine in 1974 in a case study of gentamicin [16]. The Devine formula was not related to the Metropolitan Life Insurance Company data, even though they are similar. The Devine formula is expressed as: IBW (kg) = 45.4 kg (49.9 kg ifmale) + 0.89 · (height in cm– 152.4). Unlike BSA and BMI mentioned before, IBW introduced gender into the equations. The Devine equation is the most common citation in the PK studies. IBW also seems to not be an ideal metric for dosing calculation, since it basically suggests that patients with the same gender and height should be given the same dose regardless of body fat and muscle composition.

Adjusted body weight. In order to improve IBW as dosing calculation for size, the concept of adjusted body weight (ABW) came into the picture in the pharmacokinetics. ABW was the first body size measurement that was derived for the purpose of

pharmacokinetics studies. ABW was introduced to the field as part of a noncompartmental analysis for aminoglycoside dosing in 1983 by Bauer.[17] The mean correction factor (CF) was estimated to be 0.45 for gentamicin, 0.37 for tobramycin and 0.42 for admikacin, and later and average value of 0.4 were used for aminoglycoside generally. The equation of ABW (kg) = ideal body weight + [0.4 * (actual body weight - ideal body weight)] was incorporated into basic pharmacokinetics text books.[18, 19] ABW overcome the drawback by introducing total body weight into the equation and utilizes the difference between total body weight and IBW for dosing adjustment. In clinic practice, ABW is often used for aminoglycoside dosing calculation.[20] Since the CF is determined on case-by-case base, so far ABW is used mainly for aminoglycosides.

Fat free mass. Fat free mass (FFM) was first reported by Rathbun and Pace in 1945 to validate the relationship between weight and fat mass.[21] FFM was derived using live weight, eviscerated wet weight and eviscerated dry weight of guinea pigs in order to find out the total fat mass. Since direct measure of human body fat is difficult, several indirect methods were proposed: derivation from height and total body weight,[22] skinfold thickness measurement,[23] underwater weighing (density test),[24] and total body potassium test.[24] Bioelectrical impedance analysis (BIA) has been combined with height, total body weight and gender to determine FFM.[25-27] Garrow and Webster presented the regressed FFM equations to evaluate the effect of obesity on the pharmacokinetics of glibenclamide.[28] The study used the fat mass estimated by skinfold thickness, underwater weighing and total body potassium tests, and derived equations to evaluate how BMI correlates with fat mass.

Lean body weight. Fractional fat mass (FM_{frac}) has been used by James for obesity report for the Department of Health and Social Security Medical Research Council in the UK.[29] It was then used to estimate lean body weight (LBW), where LBW is the difference between total body weight and fat mass weight.[30] LBW concept relates closely to the concept of FFM, and it consists of bone, muscle, extracellular fluid and vital organs.[31] The often used equations by James to estimate LBW are: for males, LBW (kg) = 1.10 x TBW- 0.0128 x BMI x TBW; females, LBW (kg) = 1.07 x TBW- 0.0148 x BMI x TBW.[29] Green and Duffull have reported that the formulae may not be physiologically accurate when estimating the extremes of height and weight.[32]
A semi-mechanistically-derived equation for estimating LBW was reported in 2005, using bioelectrical impedance data.[31] The equations for this LBW estimation are: for male: LBW (kg) = (9270 x TBW)/ (6680 + 216 x BMI); for female: LBW (kg) = (9270 x TBW)/(8780 + 244 x BMI). These LBW estimates do not decrease with increasing total body weight; it was suggested to be a more appropriate method of calculating LBW in obese and normal weight individuals.

Predicted Normal Weight. Predicted normal weight (PNW) was derived by Duffull to predict the normal weight estimate for dosing obese patients.[33] This weight descriptor was developed to better describe the pharmacokinetics properties of the drugs. PNW was developed to describe the expected normal body weight of obese patients as the sum of the obese patient's lean body weight and their predicted normal fat mass (excluding the excess portion of the fat mass) according to the patient's gender and height. For males, PNWT (kg) = 1.57 x TBW- 0.0183 x BMI x TBW- 10.5. For female, PNWT (kg) = 1.75 x TBW - 0.0242 x BMI x TBW - 12.6. However, because that

PNWT is derived using the previous equations for LBW, its accuracy was also questioned at the extreme values of height and weight.[33]

The estimation of body composition in elderly patients is more complex because of the fact that the ratio of adipose tissue and lean tissues increases with increasing age.[33, 34] The semimechanistic LBW was suggested to account for changes related to age due to the fact that it was derived using bioimpedance data.[31] The changing of pediatric body composition is even more complicated than in elderly individuals, and the effect of body composition on pharmacokinetics will be discussed in Chapter 3 in detail.

Body Size Effect on Pharmacokinetic parameters

The prevalence of obesity has been rising dramatically in the last decade. Due to the fact that obese patients often have other diseases such as type 2 diabetes mellitus and heart disease, more and more physicians are facing the dosing adjustment challenges for obese patients. Since there is not much pharmacokinetic information of obese patients available in the literature for most of the drugs, finding the right dose for a new obese patient could be difficult. Green and Duffull have summarized the impact of different size descriptors on the pharmacokinetic parameters clearance (CL) and volume of distribution (Vd) in obese patients.[35] The size descriptors included TBW, height, IBW, LBW, ABW, BMI, BSA, FFM, PNWT. All available size descriptors' effect on CL and Vd were evaluated using either regression of the parameter against a size descriptor or as part of population PK model. Green and Duffull concluded that none of the single size descriptor is dramatically better than others in terms of explaining the variability of pharmacokinetic CL and Vd in obese patients. However, they suggested that since there is a strong empirical and mechanistic theory that supports the use of LBW for CL and TBW for Vd, if the drug does not degrade in fat tissue, the clearance

was believed to be related more to LBW than TBW. Vd was concluded to consistently increase with excess adipose tissue and TBW is more related to the physicochemical properties of drugs, especially for lipophilic drugs.

Volume of distribution. Volume of distribution (Vd) is a theoretical term that relates total drug amount in the body and plasma or tissue drug concentration. Vd presents roughly to what extent a drug distributes into extravascular spaces. As a result, drugs with larger tissue uptake usually have larger volumes of distribution. However, with only the information of Vd it is not sufficient to determine the sites of distribution. The way to find out the site of distribution is to measure directly the tissue concentration at certain sites which is usually not readily observed in the clinical studies.

The emerging technology microdialysis made direct measurement of tissue concentration possible.[36] Though the brain and lung microdialysis is not often conducted in human, skin microdialysis including adipose tissue and skeletal muscle is readily performed in patients to measure endogenous compound and free drug concentration at the sites. Hollenstein, Brunner et al. has reported that obese and non-obese subjects presented very different drug plasma concentration but very similar free tissue concentration measurable by microdialsys when given weight adjusted dose of ciprofloxacin [37]. Barbour, Derendorf et al. reported the microdialysis measured concentrations in the interstitial space fluid of soft tissues following a standard 1.5 g cefuroxime dose may be high enough to prevent infections with Gram-positive organisms in morbidly obese patients undergoing abdominal surgery.[38]

In general, increase of body weight leads to increasing of body water, muscle mass, adipose tissue and organ blood flow, which all may contribute to the increase of

volume of distribution. Followed by drug administration in a patient, the Vd of a drug will depend on both the physicochemistry of the drug and physiology of the patient. The physical and chemical properties of the drug determine the rate and extent of the drug distribution to the body, such as the molecular size, ionization degree, lipophilicity, and the permeability to the biological membranes. The physiological conditions that affect the distribution of the drug includes degree of tissue perfusion, tissue size, permeability of the tissue and very importantly protein binding and tissue binding.

The lipophilicity can be assessed by the partition (octanol/water) coefficient of the drug. It makes sense that Vd of lipophilic drugs is usually larger in obese patients than normal weight subjects, since obese patients have an excess amount of adipose tissue compared with non-obese patients. However, the proportion and amount of fat tissue is not the single factor for even lipophilic drugs that affect Vd, Vd varies due to the affinity of the drugs to the tissue as well.

Physiological changes in obesity can significantly change the drug distribution in obese patients. These changes include increased cardiac output, increased blood volume, larger organ mass, larger lean body mass, significant absolute amount and proportion of adipose tissue mass, as well as altered plasma or tissue binding. The adipose tissue has smaller proportion of water than lean muscle which leads to a smaller proportion of water per total body weight in obese subjects. Hydrophilic drugs distribute poorly to the adipose tissue, the Vd changes little in obese patients compared to non – obese patients. In this case, obese patients might be overdosed if water soluble drugs are given per body weight.

Tissue perfusion and plasma protein binding could potentially change the volume of distribution. Tissue perfusion was reported to decrease in obese subjects by Summers et al. after evaluating the subcutaneous abdominal tissue blood flow.[39] Abel et al. summarized the obesity influence on cardiac structure and function.[40] In terms of plasma protein binding, it does not seem that obesity has a big impact on drug binding to albumin for alprazolam, triazolam and phenytoin.[41, 42] Contradictory conclusion was drawn from different studies evaluating drug binding to α1-acid glycoprotein in obese subjects.[43-46]

Vd plays an important role in dosing obese patients, since it is an essential parameter for determining load dose for a lot of drugs. A good understanding of obesity impact on Vd is therefore the key information. In many pharmacokinetic analyses, Vd can be expressed as an absolute value with a unit of liter or a weight/BSA – normalized value with a unit of liter per kilogram (L/kg) or liter per square meter (L/m^2). For hydrophilic drugs, there is little change in absolute Vd (L) in obese compared with non-obese subjects, but decreased body weight normalized Vd (L/kg). For extremely lipophilic drugs, both the in absolute Vd (L) and body weight normalized Vd (L/kg) are increased in obese patients. There are some advantages body weight normalized Vd(L/kg) to absolute Vd (L). By comparing the body weight normalized Vd (L/kg) values in obese and non-obese subjects, one can get some information about the drug distribution to the excess adipose tissue. For some drugs, body weight – adjusted dose is often used for dosing obese patients assuming the body weight normalized Vd (L/kg) is constant in both obese and non- obese subjects. But in the reality, body weight normalized Vd (L/kg) is not always the same for both obese and non- obese

populations. Especially for hydrophilic drugs, the absolute Vd increased in the obese but not much, body weight normalized Vd (L/kg) is much lower in obese patients than in non-obese subjects. This indicates that the drug does not distribute much to the fat tissue. Therefore, IBW or LBW might be a better method than TBW when dosing obese patients. If the absolute Vd does not increase much, then a flat dose could be given to both obese and non-obese subjects for the loading dose. Additionally, if the adipose tissue is not the site of target or the site of adverse events, then distribution might not be the interest of dosing strategy. Different dosing methods might have different effect on distribution, but the one that benefits other important pharmacokinetic properties should be chosen in this case.

Clearance. Clearance (CL) is often considered to be the most important pharmacokinetic parameter when finding the right dose regimen. Maintenance dose regimen needs the clearance information to be determined. CL mainly depends on the physiological properties of the patients when compared with Vd which is affected by both the physiochemical properties of the drugs and physiological properties of the patients. For a given organ, CL can be seen as the volume of blood being removed in a certain time, or the rate of blood volume removed from the organ.

One of the main organs for drug elimination is kidneys. Renal clearance depends on glomerular filtration rate (GFR), tubular reabsorption, and tubular secretion. The influence of obesity on renal functions is still not well known.[47] According to the Cockcroft-Gault formula developed in 1976, if controlling for the gender and age of the patients, then creantinine clearance is increased with increasing body weight.[48] However, in the published studies when obesity effect on GFR is investigated, it has

been shown GFR increased, decreased, or remain unchanged when comparing obese and non- obese subjects. In 2007, Pai et al. investigated the influence of morbid obesity on daptomycin and reported that GFR values were found to be 60% higher in the morbidly obese patients than non-obese patients.[49] However, there was no difference found for the two groups for Vd, total clearance, renal clearance or protein binding.

For many drugs, hepatic elimination in liver plays an important role in the total drug clearance. Obese individuals have been reported to have higher risk of developing nonalcoholic fatty liver disease.[50] Impairment of hepatic microcirculation has been found in fatty liver.[51] Thus, these changes in obese individuals might change their hepatic blood flow and hepatic function, and as a result changed the hepatic clearance of the drugs. Emery et al. has reported increased cytochrome P450 2E1 activity in morbidly obese subjects with nonalcoholic fatty liver disease, and recovery after weight loss.[52]

Green and Duffull have summarized different size descriptors for clearance for various drugs. They concluded that there is no single best size descriptor for determining clearance and reported that 35% of the studies in which LBW was considered. It was suggested from a physiological standpoint that, LBW should be used generally, due to the more close relationship with liver/kidneys to LBW than TBW.[35]

In a more recent publication, Han, Duffull et al. emphasized further the correlation between LBW and clearance by suggesting a simple solution when dosing obese patients.[53] It was proposed that obese subjects have higher absolute drug clearance than non-obese subjects; clearance does not linearly increase with increasing total body weight; and clearance and LBW are linearly correlated. With the first two points

generally accepted, the third point has been challenged by Mathijssen and Sparreboom who claimed that BSA is a good size describer for the summarized anticancer drugs.[54] Soon after the report, Han et al. responded to the publication by suggesting LBW and BSA calculated for patients of 40–120 kg and 150–190 cm are highly correlated.[55] However the weight range seem not be able to represent obese and non- obese populations.

Overall, currently, there is no single, well-proven size descriptor to present drug CL in obese and non–obese individuals. Green and Duffull's comment on size descriptor requires the consideration of all the factors that are height, weight and gender. When CL is incorporated in the population pharmacokinetics analysis, gender could be included as a covariate, and as a result, the size descriptor does not necessarily describe the gender difference; the same method can be applied to age effect on size.

It is true that no single size descriptor can be the tool to provide constant exposure to the whole patient population. We should not expect the size measurement to be able to explain all the interindividual variability as well. As the population PK analysis is raising rapidly in the pharmaceutical industry and regulatory agencies, the overall picture (all factors that could affect PK/PD including size, genetic polymorphisms, gender, age, disease) needs our attention when finding the optimal dose for patients instead of only focusing on size effect. With the blooming of pharmacogenomics, combined with population PK/PD modeling and simulation, pharmacokinetics and pharmacodynamics stand more and more critical roles in dose optimization.

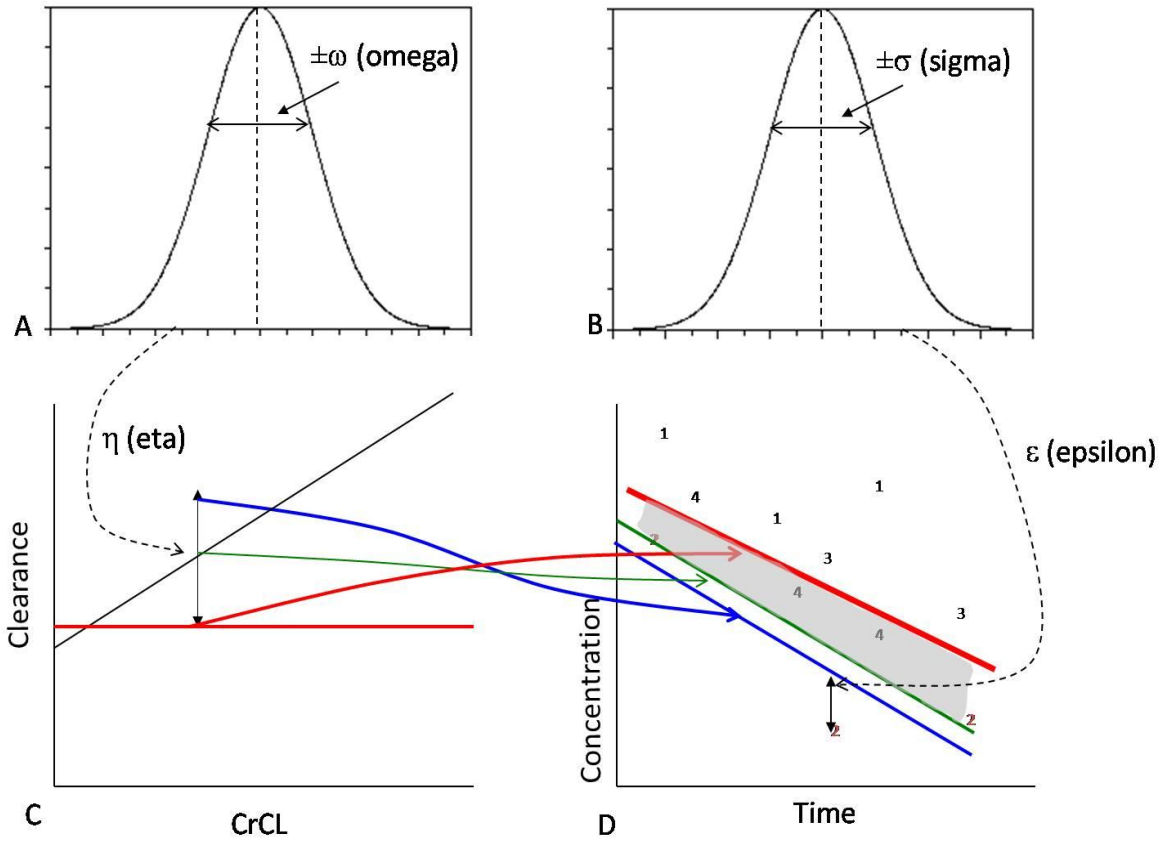

Figure 1-1. Schematic diagram of relation between observed concentration, interindividual variability, intraindividual variability and errors

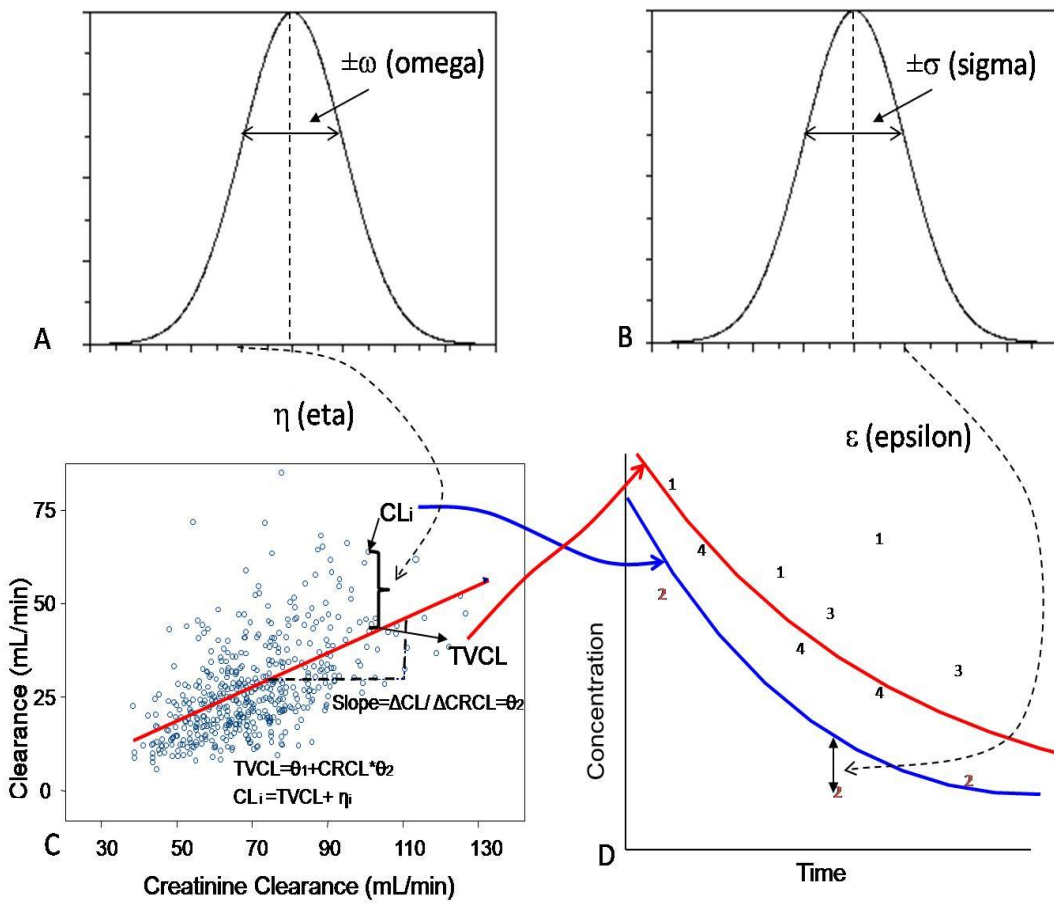

Figure 1-2. Schematic diagram of relation between typical clearance, individual clearance, interindividual variability, intraindividual variability, and errors

CHAPTER 2
FIXED DOSING VERSUS BODY SIZE-BASED DOSING OF THERAPEUTIC PEPTIDES AND PROTEINS IN ADULTS[1]

Background

In contrast to small-molecule drugs, which are commonly dosed with fixed doses, therapeutic biologics are often administered based on patients' body size, such as body weight (BW) and body surface area (BSA). It has been generally perceived that dosing biologics based on patients' body size would reduce interpatient variability in pharmacokinetics (PK) and/or pharmacodynamics (PD) and thereby optimize their therapeutic outcomes, based on the theory that patients with larger body size would have a larger volume of distribution and a higher elimination capacity. The validity of the above perception, however, has recently been challenged for dosing of mAb therapeutics.[56] Through simulation studies of 12 approved mAbs with published population PK and/ or PD models, Wang et al.[56] compared the performance of fixed and body size-based dosing with regard to reducing intersubject PK and/or PD variability in adult patients. In contrast to the expectation that body size-based dosing should produce less intersubject variability, their results showed that fixed dosing performed similarly to body size-based dosing across the 12 mAbs evaluated, with fixed dosing being better for some mAbs (7 of 12) and body size-based dosing being better for the others (5 of 12). The study indicated that determination of body size as a significant covariate on clearance (CL) parameter does not necessarily justify body size-based dosing as a better approach than fixed dosing even when the only consideration is to reduce PK and/or PD variability, because simple body size correction as mg/kg or

[1] Reprinted with permission. Zhang S, Shi R, Li C, Parivar K, Wang DD. Fixed Dosing Versus Body Size-Based Dosing of Therapeutic Peptides and Proteins in Adults. *J Clin Pharmacol* 2011

mg/m^2 could overcorrect the effect of body size on exposure. The determinant factor is the value of the exponent (α) when the effect of body size on CL is described by a power function, as shown in equation below:

$$CL = CL_{typical} \bullet (\frac{bodysize}{bodysize_{typical}})^{\alpha} \quad (2\text{-}1)$$

In terms of reducing intersubject variability in the area under the concentration-time curve (AUC), body size-based dosing would work the best when CL is body size proportional (α = 1), and fixed dosing would work the best when CL is not affected by body size (α = 0). The 2 dosing approaches would perform similarly when the α value is close to 0.5. Fixed dosing is expected to produce less variability in AUC when the α value is less than 0.5, and the opposite is true when α values are greater than 0.5 (Figure 2-1).

The contribution of body size effect to overall PK and/or PD intersubject variability was also evaluated, as many other factors, besides body size, could also contribute to the intersubject variability in PK and/or PD of a given drug. These factors include intrinsic factors (eg, age, gender, disease states, and genetic polymorphism) and environmental factors (eg, concomitant medication and smoking). Depending on the contribution of body size effect to the overall intersubject variability, body size-based dosing may or may not be necessary even when it significantly reduces intersubject variability in certain PK and/or PD parameters.

On the basis of the findings from this analysis, the authors recommended (1) using fixed dosing in first in human (FIH) adult studies for mAbs because of its convenience, better compliance, less risk for medical errors, and cost-effectiveness and (2) selecting

the final dosing approach for Phase III trials based on a full evaluation of the effect of body size and other influential factors on PK and PD of the study mAb along with its therapeutic window after sufficient data become available during drug development.[56]

As a continuation of the mAb study,[56] the present study was set out to evaluate the clinical benefit of body size-based dosing for other therapeutic biologics—namely, therapeutic peptides and proteins. These biologics should be examined separately considering that the sources of the variability in exposure are likely to be different between mAbs and therapeutic peptides and proteins since they do not necessarily share the same distribution and elimination mechanisms. In contrast to mAbs, which usually share the same IgG structure with a molecular weight of ~150 kDa, therapeutic peptides and proteins comprise a much more diverse group of molecules. Large therapeutic proteins may share similar distribution and elimination mechanisms to mAbs. They are generally distributed via convection and eliminated via intracellular catabolism following fluid-phase or receptormediated endocytosis. However, mAbs differ from most therapeutic proteins in that a significant fraction of mAbs is protected from protein catabolism by FcRnmediated recycling, whereas most of the therapeutic peptides and proteins do not have such protective mechanism with the exception of fusion proteins containing the Fc region of IgGs.[57, 58] For smaller therapeutic peptides and proteins, depending on the molecular size and physicochemical properties (eg, charge and lipophilicity), renal excretion and diffusion into tissues may play an important role in their overall elimination and distribution mechanisms in addition to catabolism and convection.[59] With increased amount of PK and PD information of this class of therapeutics accumulated in recent years, it is time to compare the clinical benefits of

the 2 dosing approaches for therapeutic peptides and proteins. The objectives of the present study are therefore to 1) systemically evaluate the performance of fixed dosing and body size-based dosing for therapeutic peptides and proteins in adults and 2) recommend a dosing strategy for clinical trials conducted in adults at different stages of the development of therapeutic biologics other than mAbs.

Methods

Data Collection

Data used in this simulation study were collected from the population PK/PD studies of therapeutic peptides and proteins published in peer-reviewed journals. The selection criteria included the availability of population PK and/or PD models for adult patients or healthy volunteers and adequate assessment of the effect of body size on the PK (and/or PD) parameters.

Population PK and PD Models

The population PK and/or PD models of the selected peptides and proteins (see Table 2-1) were obtained from published reports. General properties of these population PK and PD models and the effect of body size, such as BW or BSA, on the PK and/or PD parameters are summarized in Table 2-2. Mixed-effect models were used to describe the PK and/or PD of all the selected therapeutic peptides and proteins. The jth observation for the ith individual was given by

$$Y_{ij} = f\left(\theta_i, t_{ij}\right)\left(1+\varepsilon_{1ij}\right)+\varepsilon_{2ij}$$

where θ_i is a set of PK and/or PD parameters for the ith individual, and ε_{1ij} and ε_{2ij} are the residual errors following normal distributions with a mean of zero and variance of σ_1^2 and σ_2^2, respectively. θ_i can be further described by

$$\theta_i = g(z_i, \theta) + \eta_{ij}$$

where z_i is a set of fixed effects on the PK or PD parameters, θ is a set of typical population values of PK and/ or PD parameters, and η_i is the intersubject variability following a normal distribution with a mean of zero and variance of Ω^2. Simulation analysis was conducted using NONMEM (version VI; GloboMax, Hanover, Maryland).

PK and/or PD Simulation

Population performance. Simulations to evaluate population performance of a dosing approach were conducted in the same way as previously described.[56] Briefly, Monte Carlo simulation was conducted using the final PK and/or PD model reported for each peptide or protein to obtain the concentration-time profiles following both fixed dosing and body size-based dosing approaches. The dose used for simulation was the dose recommended in the labeling for marketed products or the dose used in the reported clinical trials for biologics under development. The median value of body size (BW or BSA) was used as the conversion factor for dose determination so that the dose used in the fixed-dosing approach is the same as the dose for the participants with median (typical) body size in the body size-based dosing approach. For all simulation studies, 1000 participants were simulated per dosing approach. The sampling points were chosen based on the PK or PD properties of therapeutic peptides and proteins, and the same sampling schedule was used for both dosing approaches.

For each simulation study, with the exception of BW, values of influential covariates were randomly generated using S-PLUS 7.0 (TIBCO, Palo Alto, California) assuming normal or lognormal distribution. The values of parameters used for generating these covariates were selected by trial and error, with a goal of reproducing

the patient population by matching the median, standard deviation, or the range of covariates to those reported in the corresponding population PK/PD study. BSA was generated assuming normal distribution with a median of 1.82 m^2 and a range of 1.2 to 2.4 m^2. [56]

BW values were generated as previously described.[56] Historical data have shown that BW does not follow normal distribution, whereas transformation of BW by a power function Z = BW−0.5 was shown to give a better approximation to normal distribution and can adequately describe the right tail of natural BW distribution.[60] Therefore, the BW values were generated assuming a normal distribution of Z (Z = BW−0.5). The randomly generated BW (1000 participants) has a median of 75.7 kg and a range of 38.8 to 187.2 kg, which in general covers the range of those reported in the population PK/PD studies for selected peptides and proteins (Table 2-2).

Individual performance. To evaluate the individual performance, we simulated the PK profiles for the participants with typical, low extreme, and high extreme body size. The typical, low extreme, and high extreme BW/BSA used in this study were 75.7 kg/1.8 m^2, 40 kg/1.3 m^2, and 140 kg/2.3 m^2, respectively. For covariates other than BW/BSA, typical values were used. The intersubject variability and residual errors were all set to zero for the simulations conducted for both dosing approaches.

Calculation of α Values

A simple way to assess whether fixed dosing or body size-based dosing may be better in reducing intersubject variability in AUC is to look at the α value of the body size effect on CL, as defined in Equation (2-1), obtained from covariate analysis. However, the covariate models used to characterize the effect of body size on CL for the selected molecules are not all in the form of Equation (2-1) (Table 2-2). Therefore, an effort was

made to obtain the α values for all biologics evaluated. For those whose α values were not reported, the following steps were used to obtain the α value for each molecule: (1) generate a series of CL values over the range of body size reported based on the reported original covariate model and (2) fit the generated CL versus body size data using equation (1) to obtain the α value using WinNonlin 5.2 (Pharsight, Mountain View, California).

AUC calculation. The AUC for each participant was calculated as dose/CL if the molecule exhibited a linear PK. When the molecule exhibited a nonlinear PK, the AUC was calculated by integration of the concentration-time curve by the trapezoidal method using S-PLUS.

PK C_{max} (PD C_{max} or C_{min}) determination. The maximum concentration (C_{max}) for each participant was determined as the maximal concentration from the simulated concentration-time profile of the participant. For PD measurements, C_{max} or the minimum concentration (C_{min}) of the PD marker, whichever reflects the maximal drug effect, was determined from the PD marker-time profile of the participant.

Performance Evaluation

The performance of a dosing approach in terms of reducing intersubject variability in AUC was assessed by evaluating the α value of the CL versus body size relationship as described by Equation (2-1) based on the following criteria:

α < 0.5—fixed dose is better.
α = 0.5—fixed and body size-based dosing are similar.
α > 0.5—body size-based dosing is better.

These criteria apply to both population and individual performances. To be consistent with the mAb paper1 and to confirm the predictive performance of the α

value, results from simulation studies for the comparison of the 2 dosing approaches were also presented as described below.

Population performance was assessed by comparing the intersubject variability (expressed as % coefficient of variation [CV %]) in the exposure (AUC and C_{max}) of 1000 participants simulated following the 2 dosing approaches. The dosing approach that produced less intersubject variability provides a better population performance.

Individual performance was evaluated by comparing the percentage difference in the exposure between participants with extreme body size and typical body size following the 2 dosing approaches. The dosing approach that resulted in a smaller difference in PK or PD exposure between participants with extreme body size and those with typical body size has a better individual performance.

Contribution of Body Size Effect to Overall Intersubject Variability of Relevant PK Parameters

A simulated PK data set of 100 participants was generated using the published "final" PK models, including all influential covariates following a fixed dose. The relevant covariate values were randomly generated as described above. This simulated data set was then fitted using both the "final" model and the "reduced" model, which excluded body size as covariate(s) for any PK parameters. The percentage change in the intersubject variability of relevant PK parameters by the "final" model in comparison to the "reduced" model was calculated to determine the contribution of body size effect to the overall intersubject variability of the relevant PK parameters.

Results and Discussion

Data Collection

A total of 18 therapeutic biologics were identified based on the data collection criteria specified in the Methods section (Tables 2-1 and 2-1), including 7 therapeutic peptides and 11 therapeutic proteins. The effect of body size on various PK parameters, including CL, intercompartment clearance (Q), volume of the central compartment (V or V1), and volume of the peripheral compartment (V2), is summarized in Table 2-1. Body size has been found to be covariate(s) of 1 or more of the PK parameters for 11 therapeutic biologics (Table 2-2). The effect of body size on PK parameters of these 11 biologics was generally well estimated with a couple of exceptions. The relative standard error (RSE) or 95% confidence intervals of the parameters that describe the body size effect on CL and/or volume of distribution (V/V1 or V2) are summarized below to help the interpretation of these simulation studies. The RSE ranged from 16% to 26% for CL and 12% to 33% for volumes of distribution except for octreotide (89.5% for V). In the case of darbepoetin alfa, where standard error of the estimate was not reported, 95% confidence intervals were (0.172, 1.07) for CL and (−0.01, 1.29) for V.

It should also be pointed out that for 4 of the selected biologics—namely, degarelix, hematide, recombinant factor VIIa, and rhGH—although body size had been found not to be covariates of their PK parameters, the population PK models were developed based on data from fewer than 30 patients (Table 2-2). Therefore, some caution needs to be exercised in interpretation of the following results.

Among these 18 selected biologics, 12 are administered based on their body size in adult patients (Table 2-1). Interestingly, for some products that are administered using body size-based dosing, such as hematide and onercept (Table 2-1), body size

measures (BW) had been shown not to be a covariate of their PK parameters (Table 2-2).

Dosing Approach Performance

Performance evaluation based on AUC

As discussed in the mAbs work, [56] the comparative performance of the 2 dosing approaches based on AUC can be simply assessed by the α values, the exponent of the power function as defined in equation (2-1), with α value of 0.5 as the separation point. As such, the α values that describe the body size effect on CL were obtained for all the 18 selected therapeutic biologics and listed in Table 2-1. These α values were either directly obtained from the published reports or obtained in such a way as described in the Methods section. For products with body size found not to be a covariate of CL, a zero value was assigned to α. As shown in Table 2-2, 12 of 18 molecules had α values less than 0.5, 1 molecule had an α value equal to 0.5, and 5 molecules had α values greater than 0.5. These results suggested that fixed dosing would perform better for 12 molecules ($\alpha < 0.5$), body size-based dosing would perform better for 5 molecules ($\alpha > 0.5$), and the 2 dosing approaches would perform similarly for 1 molecule ($\alpha = 0.5$).

The results of the simulation studies for comparing the performance of these 2 dosing approaches at the population level are presented in Figure 2-2A. Consistent with the prediction based on the α values, 5 therapeutic biologics with $\alpha > 0.5$ exhibited less intersubject variability in AUC when body size-based dosing was adopted, whereas the other 12 biologics with $\alpha < 0.5$ exhibited less variability in AUC when fixed dosing was used. For the molecule with $\alpha = 0.5$ (enfuvirtide), the variability was similar for the 2 dosing approaches. Similar results were also obtained for individual performance

(Figure 2-3A). For all therapeutic biologics investigated, the dosing approach that had better population performance also had better individual performance. It should be noted that the zero difference in AUC between patients with extreme body size and typical body size following a fixed dose for daptomycin, degarelix, emfilermin, lanreotide autogel, octreotide acetate, onercept, recombinant factor VIIa, and rhGH is a result of the lack of BW effect on their CL (Figure 2-3A).

The consistent conclusions obtained based on the α values and from the simulation studies further reconciled the recommendation of using the α value to select the optimal dosing approach if AUC is the exposure parameter of the main concern. This approach can also be used for comparative performance evaluation based on C_{max} if body size is only a covariate for the V/V1 but not for any other parameters, as is the case for emfilermin and octreotide. However, if the body size variable is a covariate on more than one PK parameter that could affect C_{max}, simulation needs to be conducted to evaluate the performance of the 2 dosing approaches in terms of reducing C_{max} variability.

Performance evaluation based on C_{max}

The population and individual performances of the 2 dosing approaches based on Cmax were evaluated by simulation studies and shown in Figures 2-2B and 2-3B, respectively. At the population level, body size-based dosing resulted in less intersubject variability in Cmax for 7 of 18 biologics, whereas fixed dosing produced less variability in Cmax for the other 11 biologics (Figure 2-2B). At the individual level, body size-based dosing produced a smaller percentage difference in C_{max} between participants with extreme and typical body sizes for 6 of 18 biologics, whereas fixed dosing produced a smaller percentage difference for the other 12 biologics (Figure 2-

3B). The results from both population and individual level evaluations are again very consistent with the only exception of enfuvirtide, for which body size-based dosing was shown to have better individual performance but worse population performance.

It was noted that body size-based dosing tends to overdose patients with large body size and underdose patients with small body size. The opposite is true for fixed dosing, that is, overdose patients with small body size but underdose patients with large body size (Figure 2-3A, B).

Performance evaluation based on Pharmacodymanics

Among the 18 selected biologics, PD models, in addition to the PK models, have been reported for 3 products (abatacept, darbepoetin alfa, and etanercept).[61-63] Therefore, the 2 dosing approaches were also evaluated for their performance in reducing PD variability. The PD response of abatacept—namely, IL-6 levels—was described by an indirect response model, in which the IL-6 degradation rate was stimulated by abatacept according to an Emax model.[63] The PD response of darbepoetin—namely, the hemoglobin levels—was described by a modified indirect response model, wherein serum darbepoetin stimulated the production of hemoglobin through an Emax model after weekly administration of darbepoetin.[61] A logistic regression model was adopted to describe the exposure-response relationship for etanercept.[62] The cumulative AUC of etanercept was used as the exposure variable, and the American College of Rheumatology response criterion of 20% improvement (ACR20) was used as the binominal clinical outcome. Body size measures were not identified as covariates for any PD parameters in any of these PD models. The results of PD performance for all 3 biologics are shown in Figure 2-4. Although the comparative performance of 2 dosing approaches in reducing PD variability is in the same order as

that in reducing drug exposure variability, the difference between the performances of the 2 dosing approaches based on PD is smaller than that based on the PK for all these 3 therapeutic agents (Figures 2-2, 2-3, and 2-4). For example, the intersubject variability in drug exposure of etanercept following the 2 dosing approaches was shown to be 47.5% (fixed dosing) versus 45.7% (body sized-based dosing) for AUC and 37.4% (fixed dosing) versus 31.4% (body size-based dosing) for C_{max} at the population level. However, the intersubject variability in its PD measures was 82.2% (fixed dosing) versus 81.9% (body size-based dosing) for AUC and 70.8% (fixed dosing) versus 70.3% (body size-based dosing) for C_{max} of the PD effect.

As the ultimate goal of a clinical trial is to achieve its efficacy and safety endpoints, efficacy data, safety data, and data of surrogate PD markers, when available, are more important than PK data alone. The smaller difference in intersubject PD variability between the 2 dosing approaches suggested that the clinical benefit, if any, of body size-based dosing could be further "diluted" in terms of drug response or PD measurements, as shown in this study for abatacept, darbepoetin alfa, and etanercept.

Contribution of Body Size Effect to Overall Intersubject Variability in PK Parameters

The contribution of the effect of body size to the overall intersubject variability of relevant PK parameters was evaluated for 8 therapeutic biologics, and the results are summarized in Table 2-3. It was observed that the effect of body size had a small and, in some cases, moderate contribution to the overall intersubject variability of major PK parameters, ranging from 1.8% to 18.4% for CL and from 0.42% to 26.9% for V/V1 (Table 2-3). Interestingly, the α values for the body size effect on relevant PK parameters appear to correlate with the relative contribution of body size to the overall

variability, although the rank orders of the two are not exactly the same. This discrepancy may be due to the difference in the extent of the contribution of other identified and unidentified factors, such as demographic characteristics and disease conditions.

When body size only explains a very small percentage of the intersubject variability—for example, in the case of darbepoetin alfa and PEG-interferon alpha-2b—adjusting the dose based on body size would lead to a minimal reduction in the variability in AUC. On the other hand, if body size is a major source for intersubject variability, body size-based dosing may provide a clinical benefit when supported by other factors, such as a narrow therapeutic window.

Relationship between the Type of Therapeutic Biologics and Body Size Effect on Pharmacokinetics

The therapeutic biologics investigated for this analysis included 7 therapeutic peptides and 11 therapeutic proteins. Among the 11 therapeutic proteins, including 3 fusion proteins and 1 pegylated protein, no apparent correlation between either the type or the size of therapeutic proteins and the body size effect on their PK was observed. However, it was noted that the α values of body size effect on CL for the 7 peptides were all less than 0.5, with 6 having α values equal to 0. As a result, fixed dosing would work better for all the peptides evaluated. Whether this can be generalized to other peptides remains a topic for further investigation when more data become available.

Summary

As a continuation of the mAb work,[56] body size-based dosing and fixed dosing were evaluated for 18 nonmAb therapeutic biologics in terms of their population and

individual performances in reducing intersubject PK and/or PD variability in adult patients.

The results demonstrated that body size-based dosing did not always result in less intersubject variability in drug exposure and PD measurements. In fact, fixed dosing showed better performance for 12 of 18 evaluated biologics based on both AUC and C_{max} assessments. Even if the 4 biologics whose population PK models were developed based on data from fewer than 30 patients were excluded from the analysis, fixed dosing would still show better performance for 8 of 14 evaluated biologics. Therefore, the recommendations made for mAbs dosing1 also apply to non-mAb biologics. For adult FIH studies, fixed dosing is recommended because it offers advantages in ease of dosing preparation, reduced cost, and reduced chance of dosing errors. When sufficient data become available, a full assessment of body size effect on PK and/or PD should be conducted. The final dosing approach for Phase III trials in adults should be selected based on the established body size effect on the PK and PD, the therapeutic window of the therapeutic products, and other factors that may affect the outcome of the study.

Table 2-1. Selected therapeutic peptides and proteins and their dosing approaches for adult patients

Generic name	Brand name	Approval date	MW (Da)	Type	Target	Dosing approach
Abatacept	Orencia®	2005	92,300	fusion protein	CD80/CD86	mg/kg
Daptomycin	Cubicin®	2004	1,620	peptide	LTA synthesis	mg/kg
Darbepoetin alfa	Aranesp®	2001	37,100	protein	EpoR	μg/kg
Degarelix	Firmagon®	2008	1,632	peptide	GnRHR	mg
Emfilermin		Discontinued	22,007	protein	LIFR	μg/kg
Enfuvirtide	Fuzeon®	2003	4,492	peptide	gp41	mg
Erythropoietin alpha	EPOGEN®	1989	30,400	protein	EpoR	Units/kg
Erythropoietin beta	NeoRecormon®	1993	30,000	protein	EpoR	μg/kg
Etanercept	Enbrel®	1999	150,000	fusion protein	TNF	mg
Hematide		In development	NR[1]	pegylated peptide	EpoR	mg/kg
Lanreotide autogel	Somatuline®	2007	1,096	peptide	IGF-1	mg
Octreotide acetate	Sandostatin®	1988	1,019	peptide	SSTR2/5	μg
Onercept		Discontinued	18,000	fusion protein	TNFR	mg/kg
PEGinterferon alpha-2b	PEG-Intron A®	2001	19,271	protein	IFNAR1/2	μg/kg
Plitidepsin	Aplidin®	2004	1,110	peptide	EGFR	mg/m^2
Recombinant Factor VIIa	NovoSeven®	1999	50,000	protein	TF	μg/kg
rhGH[1]	Norditropin®	1987	22,000	protein	GH receptor	mg/kg
u-hFSH[1]	Metrodin HP®	Discontinued	30,000	protein	FSH receptor	IU

[1]Abbreviation: NR: not reported; rhGH: recombinant human growth hormone; u-hFSH: Urinary human follicle stimulating hormone.

Table 2-2. Population pharmacokinetics/pharmacodynamics (PK/PD) models for the selected therapeutic peptides and proteins

Generic name	Type	MW (Da)	Dosing	Structure Model	Covariates, Mean (SD or range)	Covariate model	N	α on CL	Ref
Abatacept	fusion protein	92,300	mg/kg	2-CMT, linear	BW: 78.3 (21.0)	CL=CL0+CL1x(BW/78.3)	388	0.4	[63]
Daptomycin	peptide	1,620	mg/kg	2-CMT linear	BW : 75.1 (48.2-152.8)	CL=[CLr+0.14(Temp(°C) - 37.2)]*y Q=3.46+0.0593x(BW-75.1) V2=[3.13+0.0458x(BW-75.1)*z	282	0	[64]
Darbepoetin alfa	protein	37,100	μg/kg	2-CMT, linear	BW: 70.8 (36,123)	CL=TVCLx(0.737)[a]x(BW/70)$^{0.623}$ V=TVVx(BW/70)$^{0.639}$	140	0.623	[61]
Degarelix	peptide	1,632	mg	3-CMT linear	no info	WT is not a covariate	24	0	[65]
Emfilermin	protein	22,007	μg/kg	1-CMT linear	BW: 62 (48-83)	TV=V+6.7x(WT-62)	64	0	[66]
Enfuviride	peptide	4,492	mg	1-CMT, linear	BW: 72.2 (12.7)	CL/F=CL0+CL1x(BW/70)	534	0.5	[67]
Erythropoietin alfa	protein	30,400	Units/kg	1-CMT, linear	BW: 72.2 (18.96)	CL=TVCLx(BW/70)$^{0.75}$ V=TVVx(BW/70)$^{1.37}$	48	0.75	[68]
Erythropoietin beta	protein	30,000	μg/kg	1-CMT, linear	BW: 62.0 (51.0-79.0)	ka=TVkaxBW $^{-1.92}$ ke=TVkex(CrCL)$^{-0.542}$ x AGE $^{-1.13}$ V=TVVx(BW)$^{0.776}$	48	0.776	[69]
Etanercept	fusion protein	150,000	mg	1-CMT, linear	BW:73.6 (19.2)	CL=TVCLx(BW/70)$^{0.75}$ V=TVVx(BW/70)	182	0.75	[70]
Hematide	PEGylated peptide	76,000	mg/kg	1-CMT linear & nonlinear	BW: 76.9 (59 - 96)	WT is not a covariate	28	0	[71]
Lanreotide autogel	peptide	1,096	mg	3-CMT linear	BW:67.1 (12.4)	WT is not a covariate	50	0	[72]
Octreotide acetate	peptide	1,019	μg	1-CMT linear	BW: 77.1 (51-103)	V=TVVx(BW/81)$^{0.362}$	59	0	[73]
Onercept	fusion protein	18,000	mg/kg	2-CMT linear,	BW: 73.1 (11.2)	WT is not a covariate	48	0	[74]

Table 2-2. Continued

Generic name	Type	MW (Da)	Dosing	Structure Model	Covariates, Mean (SD or range)	Covariate model	N	α on CL	Ref
PEG-interferon alpha-2b	protein	19,271	μg/kg	1-CMT, linear	BW: 80 (41-149)	$CL=TVCLx(BW/70)^{0.455}$	817	0.455	[75]
Plitidepsin	peptide	1,110	mg/m^2	3-CMT nonlinear	BSA:1.78 (1.29–3.32)	WT is not a covariate	283	0	[76]
Recombinant Factor VIIa	protein	50,000	μg/kg	2-CMT linear	no info	WT is not a covariate	28	0	[77]
rhGH	protein	22,000	mg/kg	1-CMT nonlinear	BW:77.9	WT is not a covariate	21	0	[78]
u-hFSH	protein	30,000	IU	1-CMT, linear	BW: 59 (7.4)	CL/F=TVCL/Fx(1+0.017x(BW-58.5))	62	0.99	[79]

[1]Abbreviation: rhGH: recombinant human growth hormone; u-hFSH: Urinary human follicle stimulating hormone.

Table 2-3. Percentage contribution of body size measurements to the overall intersubject variability of pharmacokinetics (PK) parameters in selected proteins and peptides

Biologics	% contribution of BW to the intersubject variability		α value	
	CL	V1	CL	V1
u-hFSH	13.6	NA	0.99	0
Etanercept	18.4	26.9	0.75	1
Erythropoietin alfa	8.48	11	0.75	1.37
Darbepoetin alfa	1.80	0.42	0.623	0.639
Enfuviride	3.17	NA	0.5	0
PEG-interferon alpha-2b	2.12	NA	0.455	0
Abatacept	3.46	NA	0.4	0
Emfilermin	NA	4.16	0	1.66

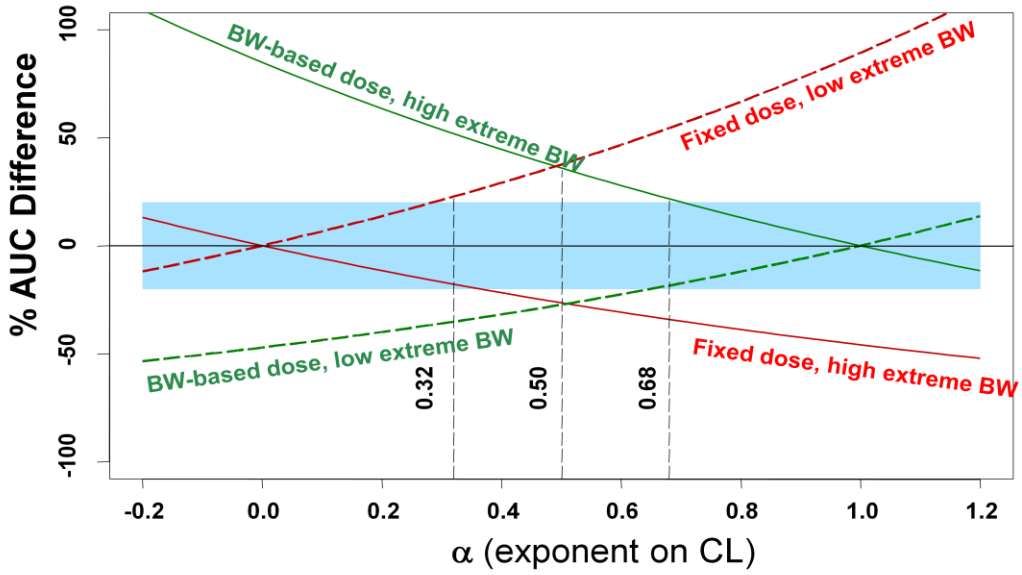

Figure 2-1. The % difference of AUC for patients with extremely low body weight (BW) (40 kg, colored broken lines) and extremely high BW (140 kg, colored solid lines) from those for patients with a median BW of 75 kg as a function of the α values following a fixed (red) and a BW-based (green) dose, assuming $CL = CL_{typical} \bullet (\frac{BW}{BW_{typical}})^{\alpha}$ The shaded area represents AUC values within100 ± 20% of typical AUC. Reprinted from[56] with permission.

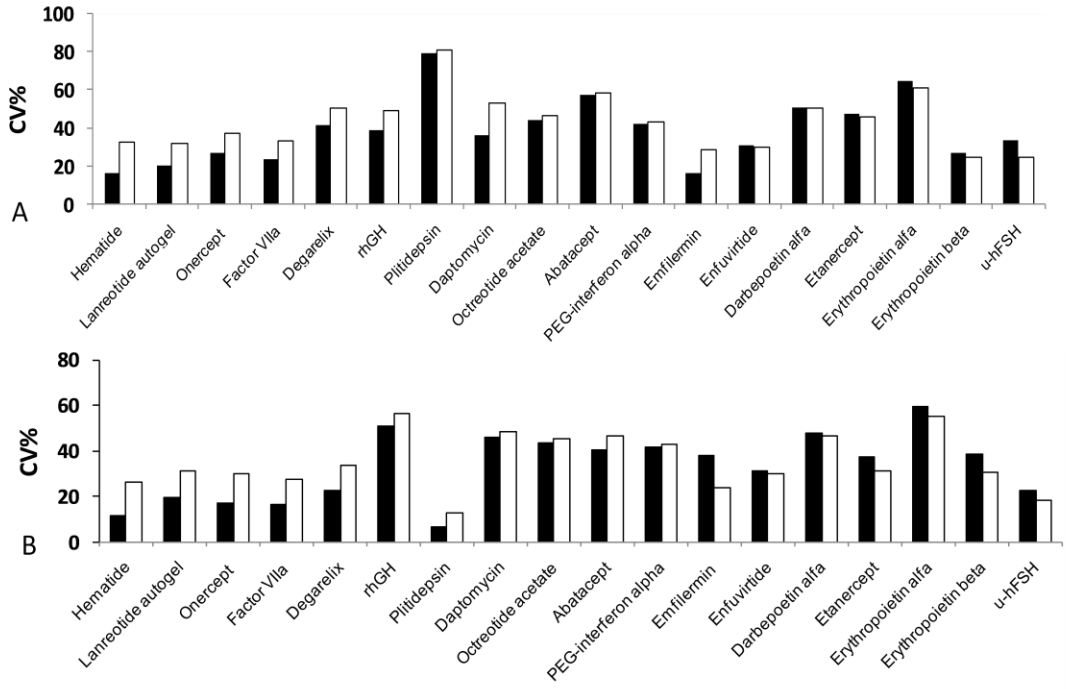

Figure 2-2. Comparison of the inter-subject variability of simulated AUC (A) and Cmax (B) of 1000 subjects after receiving a single fixed (solid bar) dose or a body size (BW/BSA)–based dose(open bar) for selected proteins and peptides

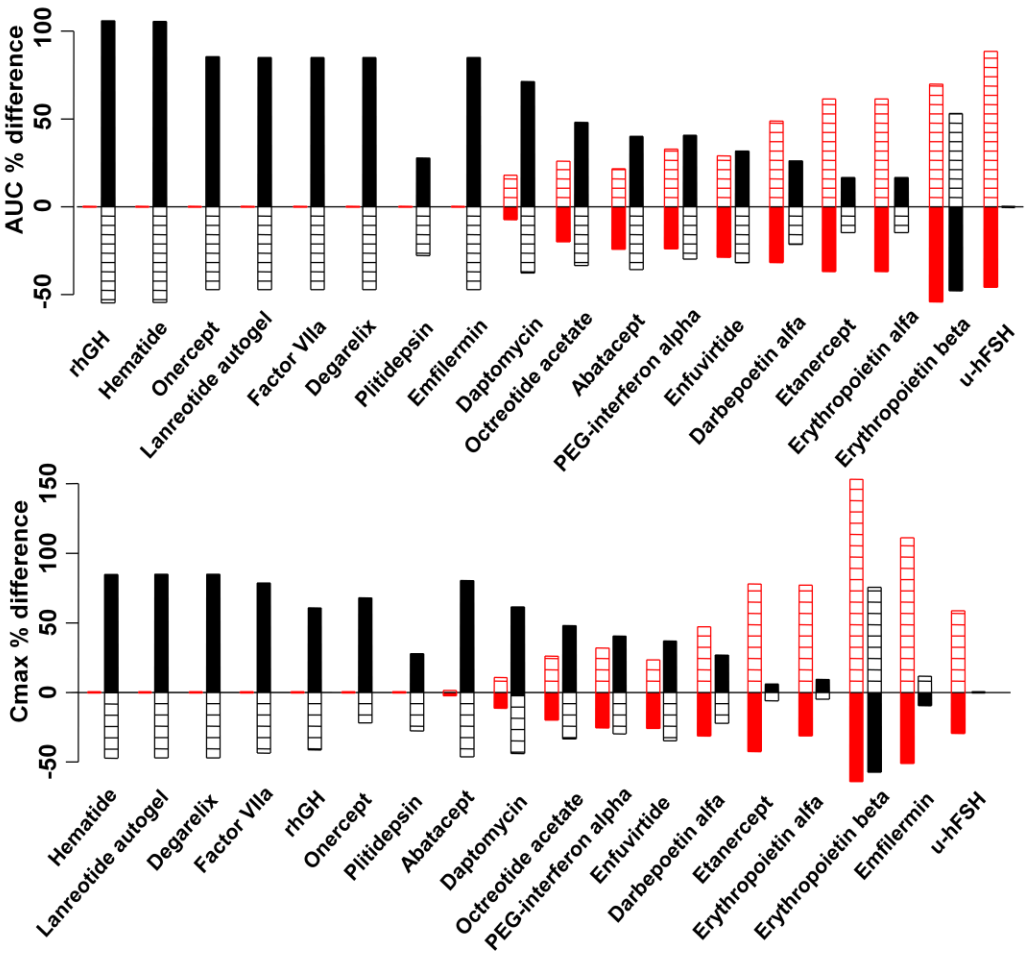

Figure 2-3. Comparison of the deviation (% difference) of AUC (A) and Cmax (B) for subjects with low (open bar) and high (solid bar) extreme body size (BW/BSA) measurements from the typical values (AUC and Cmax for subjects with median body size measurements after a fixed dose (red) or a body size (BW/BSA)–based dose (black) for selected proteins and peptides

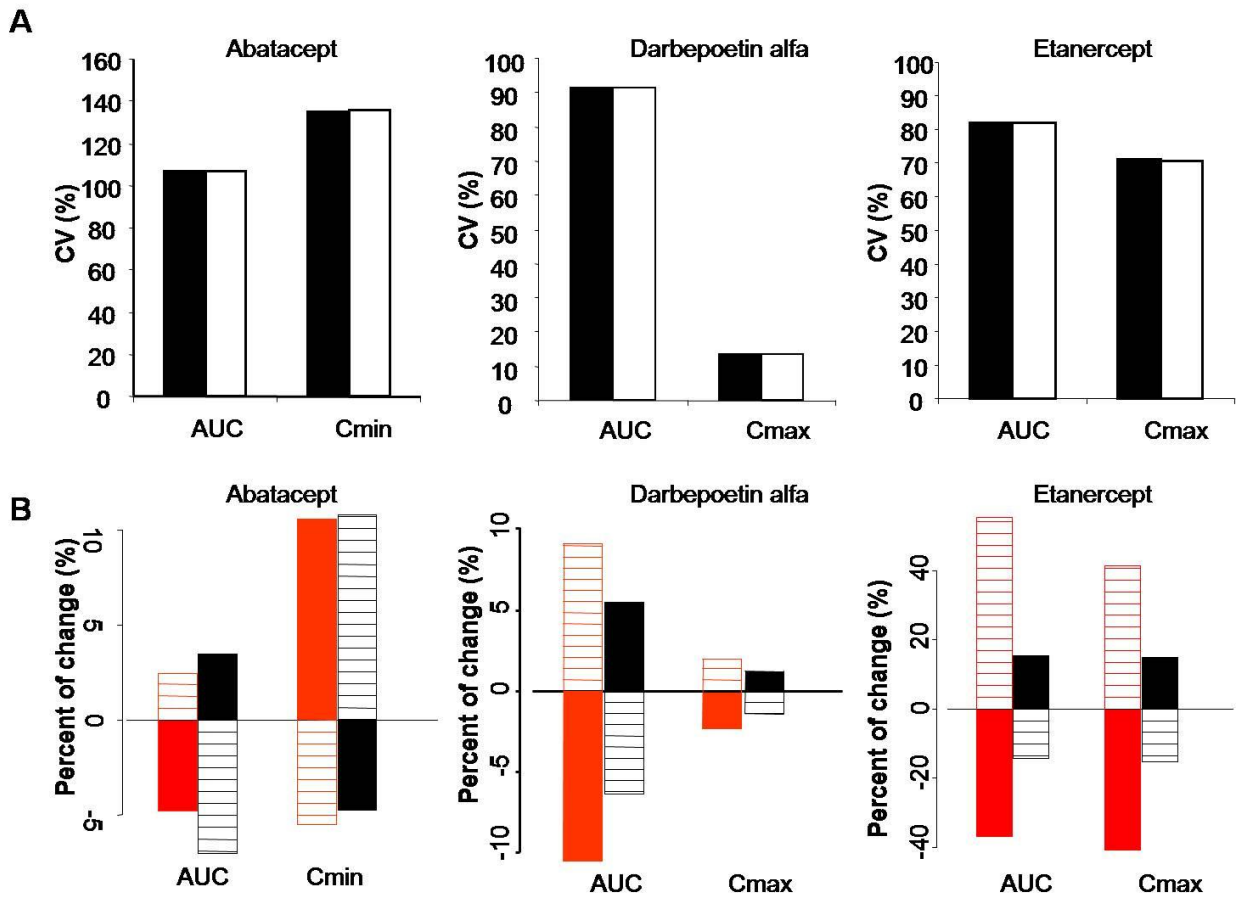

Figure 2-4. (A) The intersubject variability of AUC and Cmax (or Cmin) of the PD markers for abatacept, darbepoetin alfa and etanercept across 1000 subjects after fixed (solid bar) and body size-based (open bar) dosing. (B) Deviation of AUC and Cmax (or Cmin) of the PD markers for subjects with low (open bar) and high (solid bar) extreme BW from the typical value after a fixed (red) and body size-based (black) dose of abatacept, darbepoetin alfa and etanercept

CHAPTER 3
PEDIATRIC DOSING AND BODY SIZE IN BIOTHERAPEUTICS[1]

Background

Due to the complexity and costs of pediatric safety and efficacy studies, pharmaceutical companies are somewhat reluctant to study drugs and biological products in children. Without safety and efficacy studies in children, physicians are often forced to make empirical assumptions to treat children on a trial-and-error basis.[80] The clinical outcomes of such treatments in children can be promising, marginal or harmful. Physiological development during childhood can produce significant effects on drug absorption, distribution, metabolism and excretion. After birth, the changes in gastrointestinal absorption, secretion, motility, metabolism and transport, as well as first-pass effects will affect the absorption of the drug; the changes in body composition, tissue perfusion and plasma protein binding will affect the distribution of the drug; maturation in cytochrome P450 enzyme-mediated metabolism and Phase II metabolism will affect hepatic clearance; and maturation of glomerular filtration and renal tubular function will affect renal clearance.[81] In general, all the effects of maturation of the pharmacokinetics of a given drug are not well understood. Usually, drugs are given with two types of dosing strategies: flat fixed dosing and body size-based dosing (Figure 3-1 a and b). The most common dosing approach for pediatrics is body surface area (BSA) / body weight adjusted dosing. Small children are rarely given the same dose as adults (Figure 3-1a). However, a convenient dosing approach that sometimes provides accurate dosing and less intersubject variability is often overlooked by body size-based

[1] Reprinted with Permission. Shi R, Derendorf H. Pediatric Dosing and Body Size in Biotherapeutics. *Pharmaceutics* 2010; **2**: 389-418

dosing. This dosing approach provides a fixed dose for a certain age or certain body size group (Figure 3-1c). Fixed dosing for a patient group provides quite a few advantages compared to body size-based dosing: ease of preparation and administration, less risk of medical errors, better patient compliance, and cost effectiveness. When body weight or body surface area adjusted pharmacokinetic parameters can explain the difference between pediatrics and adults, body weight or BSA dose adjustment can provide comparable exposure in pediatrics as in adults. However, this is not always the situation. More often, the trend and extent of the pharmacokinetic difference between pediatrics and adults across different age groups are not predictable. Clearance and volume of distribution of drugs can be higher but also possibly lower in younger children, compared with older children or adults.[82] Therefore, simply adjusting the pediatric dose according to the body weight/BSA may not be an accurate dosing approach. Age should also be accounted for the maturation in pediatrics. Sometimes, even when taking age into consideration for dose determination, it might still not accurately account for all variables related to the different stages of maturation as well as the physiological differences between pediatrics and adults. More importantly, any dose adjustment should decrease the variability in the resulting exposure, which would be the proof of if it makes sense to apply the dose adjustment.

General Pharmacokinetics in Pediatrics

The definitions of pharmacokinetics in children are as follows:

- Premature: gestational age < 36 weeks
- Full-term: gestational age ≥ 36
- Neonates: 0-1 months
- Infants: 1-12 months

- Children: 1- 12 years
- Adolescent: 12-16 years

Unlike adults, the pharmacokinetics in pediatrics is remarkably affected by the growth and development of children. Body composition and organ function change over the development of childhood. The total body water, extracellular fluid and intracellular fluid constitution of the body weight in fetuses, premature or full-term neonates, infants, adolescent and adults are shown in Table 3-1.[83, 84] The total body water and extracellular fluid decrease dramatically among premature, full-term and infants. Additionally, fat contributes to 3% of the total body weight in premature neonates, and 12% of the total body weight in full-term neonates; and it is more than 20% by the age of 4-5 months. Protein mass in infants before they start walking is around 20% and increases to 40% in adults. Lean muscle tissue contains about 75% water by weight. Therefore, total body water, fat and muscle change at different ages may produce significant changes in volume of distribution and systemic concentration of the drug. Different organs such as the heart, liver, and kidney account for more body weight than adults in percentage (Table 3-2 [83]). This can explain the cases when infants or children have a faster body weight normalized clearance than adults, since infants or children have relatively larger liver or kidney per body size compared with adults. The glomerular filtration rate (GFR) is an important factor in clearance. Table 3-3 lists the GFR and renal plasma flow (RPF) change by age. Infants to children from 1-10 days, 1 month and 6 months roughly double the GFR in the three stages.[83] GRF reaches maturation at age 1 and stays almost constant from the age of 1 to 70 years. GRF/vECF(extracellular fluid volume) ratio and GRF/BSA ratio was studied in 130 patients (age range 1-80 years; 40 patients < 12 years). Neither GFR measurement

showed a significant correlation with age in children. In adults, GFR/vECF significantly decreased with age; however, no significant association was shown between age and GFR/BSA.[85] Besides GFR and RPF, the cardiac output (Q, the volume of blood being pumped by the heart in the time interval of one minute) may change by body weight (per kg) or by body surface (cardiac index= Q/BSA) in children at different ages. The cytochrome P450 enzymes constitute the major system for Phase I metabolism, and some CYP enzymes appear to be switched on by birth, while in others onset was later than birth.[86, 87] However, for proteins and peptides, endopeptidase or receptor mediated transport processes are involved in hepatic metabolism instead of CYP enzyme.[88, 89] The guidance for general industry considerations for pediatric pharmacokinetic studies for drugs and biological products by the FDA has summarized the effect of age and growth on ADME and protein binding in pediatrics.[90] The guidance has also pointed out that "In the pediatric population, growth and developmental changes in factors influencing ADME also lead to changes in pharmacokinetic measures and/or parameters. To achieve AUC and C_{max} values in children similar to values associated with effectiveness and safety in adults, it may be important to evaluate the pharmacokinetics of a drug over the entire pediatric age range in which the drug will be used. Where growth and development are rapid, adjustment in dose within a single patient over time may be important to maintain a stable systemic exposure."

Pharmacokinetics of Proteins and Peptides

Generally, pharmacokinetic principles are equally applied to the large molecule proteins and peptides and small conventional molecules. The underlying mechanisms for absorption, distribution, metabolism and excretion (ADME) of biologics are usually quite different from that of small molecules.[91, 92] Therefore, in order to interpret and

apply the pharmacokinetics of biologics, a thorough understating of ADME in these proteins and peptides is required. With few exceptions, almost all proteins and peptides are administered with intravenous, subcutaneous, or intramuscular dosage forms.

Distribution

The volume of distribution of a molecule is affected by its physiochemical properties (such as lipophilicity and charge), protein binding, and possibly active transporters. Due to the large size of proteins and peptides, they usually exhibit small volume of distribution, limited by the volume of extracellular space because of their mobility and inability to pass through membrane. [93, 94] However, binding to the intravascular/extravascular proteins or active tissue uptake can significantly increase the volume distribution of biologics.[95] The pharmacokinetics of proteins and peptides are usually described by a two compartment model, and volume of distribution of the central compartment as well as the steady-state volume of distribution (Vss) are usually reported.[96] The typical volume of distribution of the central compartment is equal or slightly bigger than the plasma volume of 3-8 L, and the Vss usually falls in the range of 14- 20 L. It should be noted that the assumption to obtain Vss is not suitable for many biologics, since proteolysis in peripheral tissues may contribute a significant portion of overall elimination process for these drugs.[92] Therefore, caution should be taken when interpreting Vss for proteins and peptides. Take antibodies for example. The Vss values reported in the literature for antibody pharmacokinetics studies are usually based on noncompartmental analysis which assumes that the site of elimination reaches rapid equilibrium with plasma and that elimination is only through the central compartment. These assumptions do not necessarily apply to antibodies since antibodies also degrade in the tissues.[92] Protein binding has been reported to affect the transport and

regulation of some proteins and peptides such as growth hormone, recombinant human growth factor, cytokines and fusion proteins (e.g. enfuvirtide).[97-100]

Elimination

Peptides usually have short elimination half-lives, which is desirable for drugs like hormones, while large proteins like antibodies have an elimination half-life of around 21 days.[92] Biotechnological peptides and proteins are almost exclusively metabolized through the same catabolic pathways as dietary proteins and endogenous biologics. With few exceptions, renal or biliary excretions are generally negligible for most peptides and proteins. Proteases and peptidase are widely available throughout the body. Therefore, besides metabolism in liver and kidneys, blood and other tissues are also the sites of extensive metabolism for proteins and peptides. Renal elimination was reported in small proteins and peptides through predominantly three routes. Glomerular filtration of interleukin-11, growth hormone, and insulin was described previously.[101-103] Some of the small linear peptides are eliminated through hydrolysis by brush border enzymes on the luminal membrane, such as angoitensin I/II, glucagons and luteinizing hormone-releasing hormone.[104-106] Peritubular extraction of immunoreactive growth hormone and insulin has also been reported.[101, 107] Several proteins and peptides were reported to be the substrates for hepatic metabolism including insulin, glucagon, epidermal growth factor, and antibodies.[89, 108] Endopeptidase or receptor mediated transport processes were observed in the liver as well.[88, 89] Many therapeutic proteins and peptides are endogenous molecules; receptor-mediated uptake followed by intracellular metabolism can take place in the organs that express receptors for these molecules. Since the number of receptors is limited, saturation can happen within the therapeutic concentration range. This saturation of the receptor-mediated elimination

contributes a major source for nonlinear pharmacokinetics of many proteins and peptides.[109] Nonlinear pharmacokinetics due to receptor-mediated drug disposition has been often reported for monoclonal antibodies.[110, 111]

In the current review, we summarize the effect of body size (body weight or body surface area) or age on pharmacokinetic parameters of selected biological products in pediatric patients such as clearance, volume of distribution, area under the curve (AUC), maximum concentration (C_{max}), half-life, etc. Comparison of these parameters and the relationship of the parameters with body weight and age between pediatrics and adults are also included. The current review selectively includes the original clinical pharmacokinetic safety studies in pediatrics that have recorded body weight/BSA or age and/or incorporate body size and age in pharmacokinetic analysis. The dosing strategy of biologics in pediatrics is discussed accordingly.

Results and Discussion

An overview of pharmacokinetics of selected FDA-approved proteins and peptides is presented in Table 3-4. Comparisons of the pharmacokinetic parameters between pediatrics and adults, as well as the effect of body size and/or age on these parameters are discussed in the following section.

Monoclonal Antibodies (mAbs)

Basiliximab. In a pharmacokinetic and dosing rational study, 39 pediatric renal transplant patients were enrolled.[112] In part 1 of the study, pediatric patients were given 12 mg/m^2 of basiliximab; in study part 2, infants and children received two 10 mg doses and adolescents received two 20 mg doses. Basiliximab clearance in infants and children (n = 25, 17 ± 6 mL/h) was reported approximately half that of adults (n = 169, 37 ± 15 mL/h) from a previous study,[113] and was independent of age (1–11 years), body

weight (9–37 kg), and body surface area (0.44–1.20 m^2). Clearance in adolescents (12–16 years, n =14, 31 ± 19 mL/h) was comparable to the adult values.

A similar designed study was done in liver transplant pediatric patients,[114] and together; these data support a simple dosing algorithm for basiliximab in pediatric transplant patients. An adjusted fixed-dose of two 10 mg is recommended for pediatric patients less than 35 kg, and a dose of two 20 mg is recommended for pediatric patients weighting 35 kg or more just like for adults.

In another study of basiliximab in pediatric renal recipients on comedication with mycophenolate mofetil, patients were classified by age as 16 children (3–11 years) and 27 adolescents (12–18 years).[115] This study confirmed that the dosing strategy mentioned by the studies above provides consistent exposure for children and adolescents. Body surface area adjusted basiliximab clearance was reported to be significantly higher in children. However, children were given higher dose than adolescents (0.54 ±0.18 vs. 0.42 ± 0.08 mg/kg). Similar total AUC were observed in the two groups (101 ± 68 µg d/mL in children vs. 102 ± 42 µg d/mL in adolescents) which resembled those of adults (107 ± 44 µg d/mL) from a previous study.[116] Significantly larger central and steady-state volumes of distribution were reported in children and adolescents than in adults, whereas half-lives were similar, 10.1 ± 7.6, 12.1 ± 5.0 and 11.5 ± 4.3 days respectively in children, adolescents and adults. All the data implies that the body surface area adjusted dosing approach does not offer any apparent advantage over the simpler fixed-dose approach.

Daclizumab. In a study of daclizumab, pediatric renal transplant recipients were divided into different age groups (≤ 5 years (n = 18), 6 – 12 years (n = 18), and 13 –17

years (n = 25), and the analysis indicates that bodyweight and race (black vs. nonblack) were found to be significant influences on the pharmacokinetics of daclizumab in pediatric patients.[117] A 4.2-fold range in clearance (CL) (4.50–19.0 mL/h) and a 7.4-fold range in central volume of distribution (V1: 0.64–4.71 L) were less proportional than a 12-fold range of bodyweight (7.5–89.5 kg). As a result, body weight adjusted dosing leads to lower exposure in the younger patient group (<5 years), and higher exposure in patients with larger body weight. The pharmadynamic results showed that the difference in exposure did not affect the safety and extent of daclizumab saturation in different age groups.

Palivizumab. Intramuscular humanized monoclonal antibody palivizumab in premature infants and infants with bronchopulmonary dysplasia was studied using body weight adjusted dosing.[118] Sixty-five infants (ages 4.6 to 7.6 months) were enrolled of whom 11 (17%) received 5 mg/kg, 6 (9%) received 10 mg/kg and 48 (74%) received 15 mg/kg palivizumab. Mean serum palivizumab concentrations (ranges) measured at 2 days and were 28.4 (13.0-41.1) and 91.1 (52.3-174.0) µg/mL for the 5 mg/kg and 15 mg/kg dose groups, respectively, and at 30 days the palivizumab levels were 12.5 (4.2 to 26.2) and 49.2 (13.5 to 132.0) µg/mL. The study concluded that monthly injections of 15 mg/kg were able to maintain mean serum concentrations above 40µg/mL. The safety and pharmacokinetics of palivizumab was studied in 59 children ≤ 2 years with respiratory syncytial virus infection.[119] Mean palivizumab levels were 61.2 and 303.4 µg /mL at 60 min after infusion and 11.2 and 38.4 µg/mL at 30 days, after the infusion of 5 and 15 mg/kg palivizumab respectively. The mean half-life was 22.6 and 16.8 days after the infusion of 5 and 15 mg/kg palivizumab, respectively. The mean area under the

curve was 487µg/mL after 5 mg/kg and 2386 µg/mL after 15-mg/kg. No significant differences in clinical outcomes between placebo and palivizumab 5 or 15 mg/kg were observed.

Infliximab. Infliximab has been studied for the first time in a clinical trial in patients younger than 12 months (6 infants and 10 children).[120] The pharmacokinetics of infliximab (5 mg/kg) did not differ as age increases. Standard body weight adjusted dosing provided peak concentrations similar to those reported previously, regardless of subject age. The peak concentrations were similar to those observed in the study with peak and trough levels reported after a dose of 6 mg/kg in 62 children (ages 4 to 17 years) with pauciarticular juvenile rheumatoid arthritis.[121] The single dose of 5 mg/kg used in the study with infants and children exhibited comparable systemic infliximab exposure to that reported previously for therapeutic drug monitoring of infliximab in adolescents and adults.[122] The estimated pharmacokinetic parameters median (CV) in the 5 pediatric patients were volume of distribution (V) 3.0L (13%), clearance (CL) 0.0083 L/h (40%), and half-life (t1/2) 10.9 days (20%)[43]. The parameters are consistent with a study that reported a median t1/2 of 9.5 days and a median CL of 0.0098 L/h by Cornillie [123], and another study reported a t1/2 of 8 to 12 days (n=108, 1,5,10,20mg/kg)[45]. In yet another study, 21 pediatrics, ages 8 -17 years, were given an infliximab dose of 1, 5, and 10mg/kg, serum infliximab concentrations were reported to be proportional to dose, and the pharmacokinetic profile in pediatric patients was similar to that in adults.[124]

Gemtuzumab. Gemtuzumab is derived from the murine anti-CD33 antibody hP67.6. In a pediatric pharmacokinetic study of gentuzumab, twenty nine patients were

grouped into three age categories: infant (0-2 years), children (3-11 years), and adolescents (12-16 years).[125] Dosages of 6, 7.5, and 9 mg/m2 gentuzumab were given to the pediatric patients. Pharmacokinetic parameters of hP67.6 antibody for the first dose are consistent and statistically different from that of the second dose. Increases in AUC and decreases in CL and Vss from the first dose to the second dose in pediatrics agree with those of the adults. Reported mean pharmacokinetic parameters in pediatrics are similar to the values reported in adults.[126] Children given the dose of 9mg/m^2 had the hP67.6 parameters of: C_{max}, 3.47 ± 1.04 mg/L; AUC, 136 ± 107 mg•h/L; CL, 0.12 ± 0.15 L/h/m^2; Vss, 6.5 ± 5.5L; and t1/2, 64 ± 44h after the first dose. Concentration vs. time profiles of hP67.6 was similar for the first dose among age. The mean C_{max} for infants was a bit lower than the children, and the C_{max} for children was 22.8% higher than the adolescents. Infants and children AUC are 2.3% and 33.5% higher than adolescents AUC. CL in infants and children was 80.9% lower and 72.0% lower than in the adolescents. The CL (L/h) values after administration of 9 mg/m^2 gentuzumab in infants, children, adolescents and adults were 0.03 ± 0.02, 0.06 ± 0.03, 0.26 ± 0.30 and 0.27 ± 0.23, respectively. The body surface area adjusted CL (L/h/m^2) values in infants, children, adolescents and adults were 0.05 ± 0.02, 0.05 ± 0.05, 0.17 ± 0.21 and 0.15 ± 0.13, respectively. Therefore, both absolute CL (L/h) and body surface area adjusted CL (L/h/m^2) increase from infants to adults. Volume of distribution showed the same trend: lower in infants and children than in adolescents. Body weight adjusted Vss (L/kg) was larger in adults and infants than children and adolescents. There was no statistically significant correlation observed between hP67.6 CL and body weight or CL and age. Intersubject variability within age groups was relatively large for the

pharmacokinetic parameters. Overall, the body surface area adjusted dose provides comparable exposure for pediatric patients.

Alemtuzumab (Campath-1H). In a Phase II study, Campath-1H 0.6 mg/kg (max 30mg) was administered in 13 (8 male) pediatric patients, median (range) age 8 (3–20) years.[127] The study concluded that Campath-1H exposure in pediatrics with acute lymphoblastic leukemia (ALL) tends to be lower than that in adults with chronic lymphocytic leukemia (CLL),[128] and this observation may be due to the more rapid clearance in children. That indicated that children may have higher body weight normalized clearance than adults. Mould et al. reported that adult patients with a Campath-1H trough concentrations >13.2 mg/mL had a 50% chance of achieving either complete remission or partial remission,[128] while Montillo et al. reported that all patients with a Campath-1H $AUC_{0–12}$>5 mg hr/mL achieved a complete remission. [129] In a study of 30 CLL patients, mean peak and trough plasma concentration was 10.7 mg/mL (2.8–26.4 mg/mL) and 5.4 mg/mL (0.5 to 18.3 mg/mL). It was found that not all patients showed beneficial clinical response, and higher blood peak concentrations correlate with better clinical outcomes.[130]

Cetuximab. In a Phase I study, twenty seven children (ages 1-12 years) and 19 adolescents (ages 13- 18 years) received escalating weekly doses of cetuximab (75,150,250 mg/m^2).[131] In the dose range studied, cetuximab exhibited nonlinear pharmacokinetics, since the AUC does not increase proportionally as dose increases. The clearance after non-compartmental analysis decreased with increasing dose in both children and adolescents. In children, clearance decreased from 0.057 to 0.015 L/h•m^2 as cetuximab dose increased from 75 to 250 mg/m^2. Similar results were reported in

adolescents. The receptor-mediated clearance might explain this dose-dependent elimination of cetuximab, and the receptors are likely to be saturated at higher doses. The mean steady-state volume of distribution across all doses and age groups was around 2 L/m^2, indicating limited distribution of cetuximab into the extracellular space. Overall, cetuximab exhibits nonlinear pharmacokinetics and similar profiles among age groups. Estimates of the pharmacokinetic parameters (clearance, area under the curve, and volume of distribution) at steady state in both the children and adolescent subgroups were comparable to those previously reported in adults.[132] The body surface area adjusted dosing seems to provide consistent exposure in children and adolescents compared to that of adults and the pharmacokinetics does not seem to correlate with age in pediatric patients.

Bevacizumab. In a Phase I study of 20 pediatric cancer patients, ages 1 to 20 years (median 13 years), 10 females and 10 males, bevacizumab exposure was proportional to dose (5, 10, 15 mg/kg).[133] The study showed a large degree of interpatient variability in children, and it was similar to that observed in adults.[134] Bevacizumab exhibits linear pharmacokinetics at the dose range of 1 to 20 mg/kg in adults [56]. Median clearance and mean residence time in children and adults are 4.1 vs. 3.9 mL/d/kg and 16.3 vs. 12.4 days, respectively.[133, 134] In a population pharmacokinetic study of bevacizumab, gender difference was found in adult patients, [135] but with a limited number of pediatric patients, the gender analysis was not performed in the study.[128]

Natalizumab. In a pediatric study, 38 adolescent patients (ages 12–17 years) with active pediatric Crohn Disease received 3 intravenous infusions of natalizumab (3

mg/kg) at 0, 4 and 8 weeks.[136] The natalizumab peak level and half-life after the first and third infusions are 61.0 vs. 66.3 mg/mL and 92.3 vs. 96.3 h. Natalizumab showed time-invariant pharmacokinetics and no accumulation on repeated monthly dosing. The C_{max} and half-life of natalizumab (3 mg/kg) in the adolescents were reported to be lower and shorter compared with those in adults after a fixed dose of 300 mg. The study showed that the dose of 3 mg/kg in adolescent patients may reduce the symptoms of severe or moderate Crohn Disease. Overall, the study concluded that the magnitude of the clinical benefit to adolescent patients is unknown, because the body weight-based dosing 3 mg/kg did not provide adequate receptor saturation in adolescents. This study is an example where simple body weight adjustment for dose in adolescents has the potential of underdosing the population.

Growth Factors

Epoetin alfa and delta. In a pharmacokinetic and pharmacodynamic study, twelve children with cancer were enrolled, and six (median age 15.2 years; range 9.3–18.6 years) were randomized to receive erythropoietin (EPO).[137] In this study, children were randomized to receive i.v. EPO 600 IU/kg (max dose 40,000 IU) or placebo weekly for 16 weeks. Doses for all children were increased to 900 IU/kg (max dose 60,000 IU) due to not observing a 1 g/dl increase in hemoglobin by study week 3 or 4. EPO clearance after the first dose showed relatively big intersubject variability (0.19–1.08 L/h/m^2), but the clearance after the 10th and 11th dose showed much less intersubject variability (0.15 to 0.25 L/h/m^2). Additionally, the AUC0–24 of EPO increased proportionally with EPO dose in these children.

In a previous study in adults, the mean half-life and clearance after the first EPO dose were 7.7 h (range 3.5–12.6 h) and 0.4 L/h (range 0.3–0.7 L/h), respectively.[138] If

adjusting for BSA, the study exhibits similar pharmacokinetic parameters as the above study in children with cancer. For example, an adult with a typical BSA of 1.73 m^2 has clearance of 0.4 L/h which equates to 0.2 L/h/m^2. Another intravenous EPO (40 IU/kg) study in children (ages 9-16 years) reported mean half-life and clearance of 5.6 h (range 4.4–6.7 h) and 10.1 mL/h/kg (range 7.1–14.9 mL/h/kg).[139] The study also concluded that, after i.v. administration, clearance in pediatrics was two-fold of that in adults, and after s.c. dosing, bioavailability was two-fold of that in adults. This study showed similar clearance to the cancer children study when adjusting the clearance in cancer children for body weight (12.4 mL/h/kg). Unlike children, premature infants (birth weight <1.25kg) showed greater serum erythropoietin clearance and larger volume of distribution than adults [140] Two more studies have reported greater clearance in preterm infants than adults after continuous intravenous or multiple subcutaneous EPO administration, and larger bioavailability was reported in preterm infants than adults given subcutaneous EPO.[140, 141]

A population pharmacokinetics of intravenous and subcutaneous epoetin delta in pediatric patients with chronic kidney disease discussed the covariate effects on epoetin delta and epoetin alfa pharmacokinetic parameters.[142] Sixty patients, 47 of them received i.v. or s.c epoetin delta and 13 of them received i.v. or s.c. epoetin alfa. In the population pharmacokinetic modeling building, V and CL were allometrically scaled by body weight by fixing the power exponents to 0.75 for CL and 1 for V. Age was included in the final model by a power function, normalized by the reference age of 10 years for children order than 10; sex, dialysis type, and drug type were also included in the model. The typical pharmacokinetic estimates were CL (0.268 L/h), V (1.03 L), Ka

(0.0554 h–1), and bioavailability (0.708) for a 35 kg male ≤10 years who was given s.c. epoetin delta and on predialysis. The epoetin delta pharmacokinetic parameters were similar in children as compared with those in adults when normalized by weight.[143] The subcutaneous epoetin alfa reported lower bioavailability than subcutaneous epoetin delta.

Darbepoetin alfa. This is a randomized, open-label, crossover study in pediatric patients with chronic kidney disease (CKD) , mean age 11 (range 3-16 years).[144] Twelve patients with CKD were randomized to receive a single dose of 0.5 μg/kg i.v. or s.c darbepoetin alfa. The mean clearance and half-life of darbepoetin alfa was 2.3 mL/h/kg and 22.1 h after i.v. administration. Absorption was shown to be the rate limiting step after s.c. darbepoetin alfa; the mean half-life was 42.8 h and mean bioavailability was 54%. Beside slightly faster absorption for s.c. administration, darbepoetin alfa disposition in pediatrics were shown to be similar to that in adults patients.[145] Darbepoetin alfa exhibited roughly two to four fold longer terminal half-life than previously reported in epoetin in pediatric patients.[139] Previous studies in adult patients with CKD showed darbepoetin alfa half-life was approximately 3 fold longer than that of i.v. epoetin (25.3 h v.s. 8.5 h) and around 2 fold longer than s.c. epoetin (48.4 h v.s. 24 h).[145-147] In another study in pediatric patients with chemotherapy-induced anemia (CIA), sixteen patients (mean age 12 years, range 5- 18 years) were given darbepoetin alfa 2.25 μg/kg subcutaneously.[148] After a single dose of s.c. darbepoetin alfa, the mean (SD) terminal half-life of 49.4 (32) h was found to be similar to the 48.2 h in pediatric CKD patients.[144] The lack of dose-proportionality in the C_{max} between the 0.5 μg/kg in the CKD patients and 2.25μg/kg in the CIA patients is likely due to population

differences rather than nonlinear pharmacokinetics. Darbepoetin alfa showed linear pharmacokinetics in adults patients.

In a study in neonates, a single i.v. dose (4 mg/kg) of darbepoetin was given to 10 neonates who had a hemoglobin ≤ 10.5 g/dl. The birth weight of the neonates was 1128g (median, ranged from 704 to 3025 g), and were 26.0–40.0 weeks old (median, 29.2 weeks). The mean (range) half-life, V and CL in the preterm neonates were 10.1 h (range 9.0–22.7 h), 0.77 l/kg (range 0.18–3.05 l/kg), and 52.8 mL/h/kg (range 22.4–158.0 mL/h/kg) respectively. In preterm neonates, there was no significant correlation between age and darbepoetin pharmacokinetic parameters. V was found to be correlated with both age and gestational age in the term and near-term neonates. Darbepoetin i.v. pharmacokinetics in neonates was compared with children, and neonates had a shorter half-life, a larger V and larger CL than children.[149]

Filgrastim. A different dosage adjustment besides body weight or age based dose was used for granulocyte-colony stimulating factor (G-CSF) in pediatric patients, ages 2 to 17 years.[150] Because G-CSF clearance increases with increasing absolute neutrophil count (ANC), the dose optimizing study of G-CSF was conducted by giving 8 patients filgrastim at a single dose of 10 mg/kg/day subcutaneously for peripheral blood progenitor cell (PBPC) mobilization. This preliminary pharmacokinetics of G-CSF seems to indicate that an ANC-adjusted G-CSF dosing adjustment might improve PBPC mobilization in pediatric patients.

Interferon. In a Phase I pharmacokinetic study of interferon-αnl (IFN-αnl), twelve children, ages 3-15 years, with relapsed acute lymphocyte leukemia (ALL) were given IFN-αnl intravenously or intramuscularly for over 25 days.[151] Single doses of 2.5 to 15

MU/m^2 (total doses of 60 to 200 MU/m^2) were given to the subjects. The serum levels of IFN and the AUC are similar to those reported in adult cancer patients, but slightly lower. [152] The study did not discuss the body surface area, body weight or age effect on pharmacokinetic parameters. The individual AUC was reported, but due to the unknown information of the total dose, the relationship of age or body size with dose adjusted AUC could not be evaluated.

A safety and pharmacokinetic study of PEG-interferon alpha2a was done in 14 children 2 to 8 years (mean age 4.4 years) with chronic hepatitis virus infection (HCV).[153] Mean (range) weight was 20.1 kg (13.3-45.3 kg). The drug dose was calculated based on patients' body surface area (BSA) using the formula BSA (m^2)/ (1.73 m^2) x180 µg. BSA was found as a linear covariate for apparent clearance and body weight was found to be a linear covariate for apparent volume of distribution of the central compartment. The study showed wide intersubject variability with the apparent clearance range of (6.6-35.5 mL/h) in the 14 pediatric patients, which suggested the necessity of individualized dosing. When compared with data from a Phase III 48 weeks adult study, the mean Ctrough in children was comparable to that in adults.[154] The mean AUC0-168h was 25% higher in pediatrics than in adult. Standard interferon (INF) has shown better efficacy in pediatric patients; additionally, children seem to tolerate pegylated INF better than adults. As a result the study concluded that the higher drug exposure in pediatric patients may have potentially good efficacy outcomes.

Among the 56 pediatric patients (ages 3-16 years) who participated in the multiple-dose pharmacokinetics of interferon alfa-2b study, 20, 19, and 17 subjects received ribavirin 8, 12, and 15 mg/kg/d, respectively.[155] Median (range) body weight of the

subjects was 40.4 kg (10-95). The pharmacokinetics of interferon alfa-2b in children was approximately twice that of adults on a body surface area basis. The dose normalized AUC0-12h and C_{max} are similar to the multiple-dose pharmacokinetics in adults.

Blood Factors

Factor VII. Pharmacokinetics of activated recombinant coagulation factor VII (NovoSeven) was compared in children vs. adults with haemophilia A.[156] Twelve children (2–12 years) received rFVIIa at one single dose of 90 and 180 µg/kg. In children, the plasma FVII concentration is dose proportional in the dose range of 90-180µg/kg. Direct comparison of the results for adults (ages 18–55 years) and children (2–12 years) reflects that plasma clearance was significantly higher in pediatrics than in adults for both the FVII: C and FVIIa clot activity assays. The total body weight normalized clearance was significantly faster in children than in adults with both assays (rFVII:C, 58 vs. 39 mL/kg/ h and rFVIIa, 78 vs. 53 mL/kg/ h). This difference suggests a higher metabolic activity per kg body weight in children than in adults and is likely correlated with age-related differences in body composition, such as different liver volume per kg body weight, as previously described.[157] This difference also suggested a higher dose of rFVII might be needed for children to achieve the comparable levels as in adults. The relationship between clearance and weight was illustrated by a linear regression in a review as CL (mL/kg/h) =76.8-0.488 x (Weight-43.6kg) ($p<0.002$).[158] Volume of distribution at steady state tends to be larger in children than in adults, but not significantly (196 vs. 159 mL/kg). The dose-normalized AUC0-12 was 30% lower in children than in adults. This study is important for pediatric dosing of FVII as it provides predictable pharmacokinetics in children.

Factor VIII. A study for the first time analyzed the effect of age and BMI on pharmacokinetic parameters in young children for prediction of dosage regimen.[159] Pediatric patients (52 boys, one girl, mean ± SD age 3.1 ± 1.5 years) were given an intravenous bolus dose of rAHF-PFM (recombinant anti-haemophilic factor--protein-free method) 50 IU/ kg. Body mass index (BMI) was a significant predictor of Factor VIII distribution. Vss decreased linearly as BMI increases, and age was a significant covariate for half-life and MRT. In another study of rAHF-PFM with 111 subjects, median age of 18, rAHF-PFM mean (±SD) half-life was 12.0 ± 4.3 h.[160] A study in a premature infant showed the half-life of Factor VIII was 6.43 h, and 6-20 h in children from other studies.[161]

Twenty one patients (ages 8-42 years), including 12 pediatric patients, received single doses of 24-51 U/ kg.[162] The pharmacokinetic parameters were CL: 81-606 mL/h, V: 1.6-9.7 L, half-life: 7.8 to 18.3 h. Weight was found to correlate with clearance and Vss, and a positive correlation of age and half-life was reported. It was shown that when body weight increased from 40 to 80 kg, this 100% increase in body weight corresponds to an increase of 42% in clearance and an increase of 60% in Vss. Clearly this increase of clearance and Vss is not proportional to the weight change. Normalization of clearance and Vss for total body weight will therefore not correctly explain the interindividual differences but rather over-correct them. Additionally, body weight adjusted clearance in mL/h/ kg and Vss in L/ kg seems to decrease with age. The half-life of FVIII tended to be shorter in pediatrics than in adults.

In a retrospective study, patients 7 to 77 years old (one child, 16 teenagers, and 44 adults, body weight 21 to 120 kg) were given FVIII to determine the

pharmacokinetics of FVIII.[163] The body weight normalized pharmacokinetic parameters of pediatrics were comparable with those observed in adults. Covariate analysis showed that V1 is significantly related to body weight and BSA. Including BSA in the model decreases substantially the unexplained V1 variability (from 34.1% to 21.1%).

In a study of factor VIII (FVIII), 34 patients (ages 7- 74 years), including 16 children, were used for model building.[164] Body weight and age were found to be significant covariates. FVIII was administered at around 60 U/kg in the small children, decreasing to 10 U/kg or less in middle age patients. The dose requirements after obtaining individual PK data showed a much greater variation than the dose range used. Weight normalized clearance (CL/kg) of FVIII has been reported to decrease with age and/or body weight during growth from infancy to adulthood, and half-life showed the opposite trend. [162, 165, 166] Pharmacokinetics of FVIII was well described by a two-compartment model. In the model building process, the exponent on clearance and volume of distribution was set to 0.75 for the clearance parameters (CL and Q) and to 1 for the volume (V1 and V2) terms. In addition to the influence of body weight on clearance, age showed a significant effect only on weight-adjusted CL, which decreased by 1.5 mL/h per year of age with a reference age of 24. Age had showed no significant correlation with weight-adjusted V1, which was in line with a previous observation that age was not correlated with in vivo recovery (C_{max} divided by dose).[167] The study concluded that the right dosage of FVIII cannot be only calculated from body weight and/or age, and suggested that starting doses for most patients to be 1,000 U every other day. Individual FVIII concentrations should then be checked for further dose adjustment.

Factor IX. A 6-year follow-up study was done for coagulation factor, Factor VIII and Factor XI, in children and adults with haemophilia.[168] The median CL of FVIII: C was 3.0 (range, 1.1– 9.9) mL/h/ kg, the Vss was 0.050 (0.028–0.129) L/kg, and the half-life was 11 (5.1–33) h. Clearance increases with increasing body weight in this patient population. A 100% increase in weight, from 40 to 80 kg, corresponds with a 39% increase in CL for FIX. The median CL of FIX: C was 3.9 (2.9–4.5) mL/h/ kg, the Vss was 0.14 (0.08–0.20) L/kg, and the half-life was 32 (26–49) h. The prophylactic dose of coagulation factor, in U/kg, was higher for children, especially small children, because of the higher weight-adjusted CL in children than adults.

Pharmacokinetics of Factor IX was studied in 56 patients, ages 4-56 years.[169] FIX: C clearance and volume of distribution at steady state increased linearly with body weight, with a faster increase in children and adolescents but remaining relatively constant during adulthood. The body weight adjusted CL and Vss, shown as functions of age, indicated a decrease of 0.68% of CL/body weight per year, and CL/lean body mass decreased by 0.40% per year. The slope between the two regressions was not statistically different, which indicates that dose adjustment of rFIX (recombinant FIX) to lean body mass did not reduce this variability compared to body weight dose adjustment. Vss/body weight decreased by 0.68% per year, while Vss/lean body mass decreased by 0.38% per year, and they were not statistically different. The terminal half-life of FIX: C exhibited no correlation with age, nor MRT. The high intersubject variation in disposition and required doses of rFIX suggests the need for individual dose titration.

Drotrecogin alfa. In the first study reporting the use of drotrecogin alfa (activated) in pediatric patients, the overall mean weight adjusted clearance was 0.53 L/h/kg across

all infusion rates and age groups (n =63).[170] No correlation was found between infusion rate and age group. Weight-normalized clearance decreases significantly with age in patients <18 years old, although combined pediatric and adult weight-normalized clearance was not found to depend significantly on age or body weight. The mean weight-normalized CL in patients <3 months (n=11) (0.608 L/h/kg) was 22% higher than that in all patients 3 months or older (0.497 L/h/kg) and 19% higher than that in adult patients (18 years or older). The higher CL in the small children was expected to have slightly lower steady-state concentration than in the older patients.

Hormone

Insulin hormones. A trial enrolled 32 children and adolescents (19 girls and 13 boys; ages 13±2.5 years, range 6–17 years) to compare the pharmacokinetics of detemir and glargine.[171] BMI was 15–24 kg/m^2 for children ages 6–12 years and 18–29 kg/m^2 for adolescents ages 13–17 years, but the study did not mention weight or age effect on variability of the two drugs. Pediatric patients were randomized to receive a sequence of 0.4 U/kg of detemir and glargine. The study concluded that the intersubject variability in pharmacokinetic was significantly lower for detemir than for glargine in type 1 diabetes mellitus (T1DM) children and adolescents. The smaller pharmacokinetic variability was most likely due to the smaller variability in absorption with detemir, which is also likely to be associated with a more predictable therapeutic range.

An insulin comparison study in pediatrics reported that insulin aspart had a quicker onset and shorter duration of action compared with human insulin, meaning aspart is more appropriate to be injected immediately before a meal, which makes it a more practical product.[172] In this study, postprandial plasma glucose increments did not differ between the human insulin and insulin aspart. Slightly higher blood glucose

concentration observed after breakfast and dinner with insulin aspart administration. In another study, subcutaneous insulin aspart or human insulin (0.15 IU/kg body weight) was given 5 min before breakfast in 9 children (ages 6-12 years) and nine adolescents (ages 13-17 years) with T1DM.[173] Insulin aspart exhibits significantly higher C_{max} ±SD than human insulin (881±321pmol/L vs. 422±193 pmol/L, $p < 0.001$). C_{max} and AUC of insulin were found to be related with age in the study. The change of glucose AUC and C_{max} are smaller for insulin aspart than human insulin in children. It was surprising for the investigators to find higher levels of both insulin aspart and human insulin in the adolescents than in children. Additionally, the insulin dosage in this study does not reflect the usual dosage of insulin in adolescents (1.0±1.5 U/kg per 24 h) and smaller children or adults (0.5±1.0 U/kg per 24 h). There is not much comparison of pharmacokinetic study in children and adults in the literature. Pharmacokinetic study was done to compare insulin glulisine and regular human insulin analogous in children and adolescents with T1DM.[174] Ten children (ages 5–11 years) and 10 adolescents (ages 12–17 years) were enrolled. The concentration time profile for insulin glulisine is similar for children and adolescents, whereas human insulin exhibits 64% higher concentration in adolescents. The higher concentration in adolescents of human insulin is in line with the previous study.[173] The difference is suggested to be caused by disparities in residual endogenous insulin secretion in adolescents and children or simply the fact that adolescents were given a larger meal than the children.

Exenatide (5 and 10 μg twice daily (BID)) was approved as an incretin mimetic in adults with T2DM. Thirteen adolescent patients (ages 10–16 years, 7 females, 6 males, body mass index, 32.5± 5.0 kg/m^2) were given 2.5 μg exenatide, 5 μg exenatide, or

placebo followed by a standardized meal 15 minutes later.[175] There is no demographic effect, such as age, sex, race, or degree of obesity, found on exenatide pharmacokinetics in adults during clinical development. The exenatide AUC was found to be dose proportional in these adolescent patients. Postprandial plasma glucose levels were significantly decreased with both doses of exenatide compared with the placebo from 1 to 3 hours after administration. The geometric mean±SE exenatide AUC0–∞ and C_{max} are 339.5±39.6 pg•h/mL and 85.1±11.5 pg/mL after 5 µg exenatide (n = 12) and 159.2 (23.1) pg•h/mL (n = 6) and 56.3 (10.1) pg/mL (n = 9) after 2.5 µg exenatide. Not all exenatide levels were detectable in patients who received 2.5 µg exenatide. After 5 µg of exenatide was given to these patients, the geometric mean±SE AUC0–360min (195.9 ±25.5 pg•h/mL) and geometric mean C_{max} (85.1±11.5 pg/mL) are comparable to those in adults with T2DM (n = 39) (AUC0–360min, 232.2±30.3 pg•h/mL and C_{max}, 113.0±12.2 pg/mL).[142, 176, 177] With this finding, the study suggested that the recommended adult dose of 5 µg and the maximal recommended adult dose of 10 µg should be explored in adolescent patients.

Growth hormone. Somatropin inhalation powder and subcutaneous humatrope pharmacokinetics were compared in pediatrics with growth hormone deficiency, ages 6–16 years, weighted 18.0 - 52.0 kg, and mean BMI 17.5 kg/m^2.[178] Participants were randomized to one of three dose levels: 1) 8.4 mg/d somatropin or 0.5 mg/d humatrope; 2) 16.8 mg/d somatropin or 1.0 mg/d humatrope; 3) 33.6 mg/d somatropin or 2.0 mg/d humatrope. At least two subjects were assigned to each dose level within each of the weight ranges: 18.0–29.9, 30.0–39.9, and 40.0–52.0 kg. The mean serum growth hormone area under the curve of somatropin was dose proportional. There was no

significant effect of weight and age on somatropin and humatrope pharmacokinetic parameters. Height was found to be a significant covariate for somatropin AUC, somatropin C_{max}, and humatrope AUC, respectively, which indicates taller subjects tended to have higher AUC and C_{max}.

A novel sustained-release recombinant human growth hormone, LB03002 once-a-week s.c. injection was studied in 37 children (24 boys, 13 girls, ages 6.5±2.1 years), at doses of 0.2, 0.5 or 0.7 mg/kg.[179] C_{max} and AUC was dose proportional in the dose range of 0.2–0.7 mg/kg, and was comparable with the levels in adults.[180] This study shows body weight adjusted dosing of LB03002 gives comparable exposure in pediatrics as in adults.

Nutropin Depot was administered subcutaneously in 138 pediatrics, and the C_{max} and total growth hormone (AUC0–28 d) were approximately proportional to the dose administered (0.75 mg/kg twice a month and 1.5 mg/kg once a month).[181]

Zomacton 2 IU/m^2 jet-injected and needle-injected was studied in 18 pediatric patients, and the AUC, C_{max} and T_{max} are similar in both groups.[182] The study reported the individual BMI, age and sex information for the subjects, but due to the limited number of patients, no correlation was demonstrated with its pharmacokinetic parameters.

Other Proteins and Peptides

Interleukin. In a dose escalation study in children, adolescents and young adults of recombinant human interleukin-11 (rhIL-11), C_{max} and AUC are dose proportional, with mean C_{max} level (range, 7.6–25.5 ng/mL) and AUC (range, 56.7–208.6 ng•h/mL) at a dose range of 25–100 μg/kg.[183] The pharmacokinetics of intravenous and subcutaneous rhIL-11 at a dose range of 3-50 μg/kg was studied in 30 healthy male

adults.[184] The adult mean C_{max} and AUC was reported to be dose proportional, which is similar to the pediatric study. At their overlapping dose levels 25 μg/kg and 50 μg/kg in children and adults, it did not seem to show a difference between the C_{max} and Tmax in adults and pediatrics, but the half-life and AUC were significantly shorter and lower in children, indicating higher rhIL-11 clearance in pediatrics than adults. The AUC in children and adults were 56.7 vs. 115 ng•h/mL at 25 μg/kg and 117 vs. 242 ng•h/mL at 50 μg/kg, respectively, and the half-life were 4 vs. 8 h at 25 μg/kg and 4.4 vs. 8.1 h at 50 μg/kg. The maximum tolerated dose (MTD) of rhIL-11 in children and adolescents was found to be 50 μg/kg/day, which is similar to that reported in adults.

Etanercept. In a population pharmacokinetic study, 69 patients with juvenile rheumatoid arthritis(JRA), aged 4 to 17 years, received twice weekly subcutaneous etanercept 0.4mg/kg.[185] Sex was a covariate for CL/F, and power exponent of body surface area was found to be 1.41 when normalizing BSA by the typical BSA of 1.071 m^2. Body weight was found to be a significant covariate for V/F with typical body weight of 30.8 kg. This analysis justified the body weight based dose adjustment for etanercept in JRA patients. Age (<17 years) was identified as one of the most important covariates on CL in the population pharmacokinetic analysis of pooled data obtained from 10 clinical studies.[186] The correlation between age and CL is no longer apparent when age is 17 years and older. Body weight was also found as a significant covariate for both apparent clearance and volume of distribution in rheumatoid arthritis patients.[70] Gender difference was found in apparent clearance in these adults with a mean level of 0.117 L/h in female and 0.138 L/h in male, but the difference was not statistically significant. A similar trend was found in JRA patients with the population mean CL/F of 0.0576 L/h

(95%CI: 0.0525-0.0657 L/h) in females and 0.0772 L/h (95% CI: 0.066-0.0870 L/h) in males.[185] Elimination mechanism of etanercept is not known much, and there was no appropriate explanation for the gender difference reported both in children and adults. In this JRA patients study, simulation was conducted to find out whether body surface area (BSA) or body weight adjustment would be a better dosing regimen.[185] To calculate the dose for the BSA based regimen, it was assumed that a patient with the weight of the population median (i.e., 30.8 kg) and a patient with the BSA of the population median (i.e., 1.071 m^2) received the same total dose of etanercept. Therefore, for example, 11.5mg/m^2 (= 0.4mg/kg × 30.8 kg/1.071 m^2) was chosen to be the dose-per-unit BSA for the BSA based dosage in the simulation. In the middle 2 quartiles, the body surface area and body weight dosing adjustment yielded similar PK profiles. Interestingly, the simulated PK profiles of the BSA-based dosing were slightly higher than body weight-based dosing, and the opposite was observed in the higher quartile. The study also concluded that the current body weight-based dosing in patients weighing equal to or less than 23 kg may have less drug exposure compared to patients weighing more than 23 kg. But the pharmacokinetic difference of etanercept was not known to lead to clinical difference in JRA patients.

Enfuvirtide. Enfuvirtide is approved for HIV treatment in adults and dosage recommendations exist for children ages 6 years or older. The safety and efficacy study of 2.0 mg/kg (maximum 90 mg) subcutaneous enfuvirtide twice daily for 48 weeks was conducted in 52 treatment-experienced, HIV-1-infected pediatric patients (ages 3 to16 years).[187] There was no significant difference observed in enfuvirtide mean±SD pharmacokinetic parameters in children (n=12, ages 5 to 11 years) and adolescents

(n=13, ages 12 to16 years): steady-state C_{max} 6.43±2.15 vs. 5.88±2.81 µg/mL; Ctrough 2.87±1.49 vs. 2.98±1.66 µg/mL; AUC0-12h 56.1±19.4 vs. 52.7±27.4 h•µg/mL. There was no meaningful difference in the pharmacokinetic values between children and adolescents. In treatment-experienced HIV-1-infected children (3–12 years), 60 mg/m^2 subcutaneous enfuvirtide twice daily reported mean single dose AUC0-12h of 56.4 h•ug/mL, which is comparable to AUC0-12h of 55.8 h•µg/mL in adults and also similar to AUC0-12h of 48.7 h•µg/mL in adults after s.c. BID 90 mg enfuvirtide.[188, 189] The pediatric study showed that the body weight adjusted dosing in children was independent of age, body weight, body surface area, and sexual maturity. In a population pharmacokinetic analysis study by Zhang et al., 43 patients (20 adolescents and 23 children) were included, mean age was 11 years, and mean body weight was 35.7 kg.[113] Body weight was a covariate for CL/F but not V/F. The population parameters CL/F, V/F, and Ka for a 33 kg patient were 1.31 L/h, 2.31 L, and 0.105 h-1, respectively. Age did not seem to affect the enfuvirtide exposure. This analysis approves the body weight based enfuvirtide dosing in pediatrics. In HIV-1-infected adults, enfuvirtide reported a small volume of distribution (5.48 L), low clearance (1.4 L/h), and high plasma protein binding (92%). Body weight-based dosing (2 mg/kg BID) provides similar pharmacokinetic profiles to those observed with 90 mg BID.[190] Pharmacokinetic parameter CL/F (1.31 L/h for a 33 kg patient) from the pediatric study is comparable to the reported value from a previous study in HIV-1-infected pediatric patients (CL = 1.42 L/h and F = 0.90 for a 21.3 kg patient),[20] and also comparable to the adult population analysis with CL/F of 1.82 L/h for a 70 kg male patient and 1.45 L/h for a 70-kg female patients.[191] The mentioned pediatric enfuvirtide study by Soy et al

involved 26 children (mean age 8.2 years and range 4.0-12.1 years).[99] Patient weight was found to have an effect on CL and V, but the effect was not statistically significant. However, their predicted "adult" PK parameters are not comparable with those observed in adults by Zhang et al.[190] Additionally, in the plot of CL (L/h) vs. weigh, even the data covers a large weight range, but it does not seem to necessarily capture all differences between children and adults. However, if plotting the Soy et al data as CL/kg (L/h/kg) vs .weight, the trends seem to be decreasing, but it is unknown whether the trend is statistically significant.

L-Asparaginase. In a study of pediatrics with acute lymphoblastic leukemia, 271 patients were given 500, 750, 1000, and 2500 IU/m^2 PEG- L-Asparaginase.[192] After adjusting dose by body surface area, neither the patients' age (1 to 17 years) nor the body surface area had any influence on the distribution of Asparaginase activity. The study concluded that normalization of dose based on body surface area was appropriate in the pediatric patients studied. A statistical analysis using linear regression was done to compare chemotherapy dose modifications in obese and non-obese pediatric patients with acute lymphoblastic leukemia (ALL).[193] Obese ALL children were reported to have a 7% decrease in the mean relative modification of L-asparaginase compared with non-obese children. The result was statistically significant even after taking into consideration gender, age, race, and study center. It is found that the difference of dose modifications was greater among older children (10–18 years) than small children (2–9 years). It is pointed out that the obesity-driven dose modification among older children is possibly because of higher BSAs and the chemotherapy doses.

Summary

Most of the studies in the current review showed that body weight or BSA dose adjustment produced comparable exposure for proteins and peptides. However, not all pharmacokinetic studies result in promoting dosing adjustment. For basiliximab, a fixed dose of two 10 mg doses for patients less than 35 kg and a fixed doses of two 20 mg dose for patients more than 35 kg was recommended for pediatrics.[112] Children should not be treated as “small adults”. Changes in clearance of proteins and peptides in pediatric patients cannot always be explained by changes in body size. Simply adjusting dose linearly according to the body weight/BSA cannot always achieve desirable exposure in pediatrics.

Anderson and Holford have proposed that growth and development can be evaluated using readily observable demographic information such as weight and age.[194-196] Weight was suggested to be an essential covariate for determining dose in pediatrics. The range of body weights in children is much greater than that in adults and can range 200 fold (0.5 – 100 kg). An established framework was believed to support the allometry used in pediatric pharmacokinetics. The coefficient exponent of body weight/typical body weight was suggested to be 0.75 for clearance and 1 for volume. Fat free mass may be better than total body weight when variations in fat affect body composition. A sigmoid Emax model was used to describe gradual maturation of clearance from small children to adults. Future issues were suggested in pediatric pharmacokinetics and pharmacodynamics.[191] 1) Determination of in vivo maturation of clearance enzyme pathways; 2) Analysis of the placenta concentration to total clearance; 3) Investigation of elimination pathway triggered by birth; 4) Understanding the impact of hormonal changes on clearance pathway in adolescents; 5) Refining

PBPK models for children; 6) Further understanding of pharmacodynamic difference between children and adults.

Overall, the difference of pharmacokinetics of proteins and peptides in pediatric patients is due to catabolic enzymes, changes in body composition, elimination organs, and receptor mediated endocytosis. The differences lead to the changes in volume of distribution, clearance and absorption of proteins and peptides. The above factors can be dramatically affected by body weight, BSA, height, age, and these covariates may be highly correlated and not mutually exclusive. Due to the complexity of the contributors evolved, the direction and extent of the difference are not always readily predictable. Clearance and volume of distribution of proteins and peptides can be higher but also lower when the comparisons are done in children and adults or younger children and older children. In the current review, most of the proteins and peptides show a more rapid body size adjusted clearance (e.g., L/h/kg) in children than in adults, such as alemtuzumab, epoetin, factor VII, factor VIII, and factor XI, while both absolute CL (L/h) and body surface area adjusted CL (L/h/m2) of gemtuzumab are smaller in infants in adults. Enfuvirtide does not have consistent conclusions from different studies. One pediatric study showed that the pharmacokinetics of body weight adjusted enfuvirtide in children was independent of age, body weight, body surface area, and sexual maturity,[187] but from the figure of CL (L/h) vs. weight reported by Soy et al, the decreasing CL/body weight does not seems to support the body weight adjusted dose of enfuvirtide. Some of the studies showed that body size adjusted dose for certain proteins and peptides produce comparable exposure in children and adults, and the

pharmacokinetics of these products are not affected by age, for example, infliximab, cetuximab, drotrecogin alfa, L-Asparaginase.

Though there is not much obvious similarities for drugs that should not follow simple body size linear adjustment, quit a few monoclonal antibodies are among them. This may due of the fact that monoclonal antibodies often are reported to have nonlinear pharmacokinetics. Basiliximab has less PK variability if use 10mg (weight<35kg) and 20mg (weight>35kg) in pediatrics. Daclizumab tends to underdose younger patient and over dose larger children. Alemtuzumab and natalizumab underdose children and followed by not desired clinical outcomes.

Eating disorders such as anorexia and bulimia are rising in adolescent girls in the United States. On the other side, the rate of obesity in adolescents is also increasing. Anorexia related hospitalizations in children younger than 12 surged 119 percent between 1999 and 2006.[197] As the pharmacokinetic parameters may be even more complex, simple body weight adjusted dose might not be suitable for such particular population.

The finding from this review suggests the need to continue the study of proteins and peptides in this particular population, and mechanism based population pharmacokinetic and pharmacodynamic models with consideration of body size and maturity might be helpful in explaining and extrapolating the pharmacokinetics and pharmacodynamics of the studies. Dose adjustment in pediatrics should lead to not only consistent exposure compared with adults, but also decreased intersubject variability in the exposure; only then does it make sense to apply the adjustment.

Table 3-1. Total body water change by age

Age	Total body water (%)	Extracellular fluid (%)	Intracellular fluid (%)
Fetus (<3 months)	90	65	25
Neonate (Premature)	85	50	35
Neonate (Full-term)	75	40	35
Infant (4-6 months)	60	23	37
Adolescent	60	20	40
Adult	60	20	40

Table 3-2. Tissue distribution comparison of newborn and adults (Organ weight expressed as % of total body weight)

Organ	Newborn	Adults
Muscle	25	40
Skin	4	6
Heart	0.5	0.4
Liver	5	2
Kidney	1	0.5
Brain	2	2

Table 3-3. Renal function: glomerular filtration rate (GFR) and renal plasma flow (RPF) by age

Age	GFR (mL/min)	RPF (mL/min)
1-10 days	15-45	20-125
1 month	30-60	100-400
6 months	50-100	400-500
1 years	80-120	500-600
1-70 years	80-140	500-700
70-80 years	70-110	250-450
80-90 years	45-85	200-400

Table 3-4. Pharmacokinetics of selected proteins and peptides in pediatrics

Generic Name	Class	Route	Pharmacokinetics
Alemtuzumab	mAbs	i.v.	More rapid clearance in children than in adults.
Basiliximab	mAbs	i.v.	CL (ml/h) in infants and children is about half that of adults. Use 35kg as a cut off weight for 10 or 20mg in pediatrics.
Bevacizumab	mAbs	i.v.	BW based dose exhibits similar PK parameters in children and adults, and large variability in both populations.
Cetuximab	mAbs	i.v.	Dose-dependent nonlinear elimination. BSA based dose provides similar exposure in children and adults, and age has no effect on PK.
Daclizumab	mAbs	i.v.	The 4.2-fold range in CL, 7.4-fold range in V are less proportional than a 12-fold range in body weight
Darbepoetin Alfa	Growth factor	i.v., s.c.	The lack of dose-proportionality is likely due to pediatric population rather than nonlinear PK; neonates have a shorter half-life, larger V and CL than children.
Drotrecogin alfa	Blood factor	i.v.	Weight-normalized clearance decreases significantly with age in patients <18 years old.
Enfuvirtide	Peptide	s.c.	One study justified body weight (BW) based pediatric dosing.
Epoetin Alfa	Growth factor	i.v., s.c.	CL (mL/h/kg) and bioavailability in pediatrics were two-fold of that in adults.
Epoetin Delta	Growth factor	i.v., s.c.	BW adjusted PK parameters are similar in children and in adults.
Etanercept	Fusion protein	s.c.	The analysis justified the body weight based dose adjustment for etanercept in JRA patients; gender difference was reported both in children and adults.
Exenatide	Incretin	s.c.	The max recommended adult dose instead of half of the max dose was suggested to be explored in adolescent patients.
Factor VII	Blood factor	i.v.	Total body weight normalized clearance was significantly faster in children than in adults.
Factor VIII	Blood factor	i.v.	BW adjusted clearance in mL/h/ kg and Vss in L/ kg seems to decrease with age.
Factor VIX	Blood factor	i.v.	Higher weight-adjusted CL in children than adults.
Filgrastim	Growth factor	s.c.	ANC-adjusted G-CSF dosing adjustment might improve PBPC mobilization in pediatric patients.
Gemtuzumab	mAbs	i.v.	Both faster CL (L/h) and CL (L/h/m2) in adults than children and infants.

Table 3-4. Continued

Generic Name	Class	Route	Pharmacokinetics
Humatrope	Growth hormone	s.c.	No significant effect of weight and age on humatrope pharmacokinetic parameters.
Infliximab	mAbs	i.v.	BW based dose provides similar exposure in children and adults; PK of infliximab does not differ as age increases.
Insulin aspart	Insulin	s.c.	In pediatrics, insulin aspart had a quicker onset than human insulin; aspart has a higher exposure in adolescents than in children.
Insulin detemir	Insulin	i.v.	Less PK variability in insulin determir than glargine.
Insulin glulisin	Insulin	i.v.	The profile of insulin glulisine is similar for children and adolescents, whereas human insulin exhibits higher level in adolescents.
Interferon-α2a	Interferon	s.c.	Higher drug exposure in pediatrics; wide intersubject variability suggests further individualized dosing.
Interferon-α2b	Interferon	i.v.	BSA based PK parameters in pediatrics is about twice that in adults.
Interferon-αnl	Interferon	i.v., i.m.	No BW/BSA or age effected was discussed. Slightly lower exposure in pediatrics than in adults.
Interleukin	Cytokines	i.v., s.c.	Higher rhIL-11 clearance in pediatrics than adults
Asparaginase	Enzyme	i.m, i.p.	After adjusting dose by BSA, neither age nor the BSA had any influence on the distribution.
LB03002	Growth hormone	s.c.	Body weight adjusted dosing gives comparable exposure in pediatrics as in adults.
Natalizumab	mAbs	i.v.	BW base dose tends to underdose adolescents.
Nutropin	Growth hormone	s.c.	Drug exposure was approximately proportional to the dose.
Palivizumab	mAbs	i.v., i.m.	BW based dose for palivizumab, but body weight effect not discussed; no significant clinical outcome between placebo, 5 and 15 mg/kg were observed.
Somatropin	Growth hormone	Inhaled	No significant effect of weight and age on somatropin pharmacokinetic parameters.
Zomacton	Growth hormone	s.c.	No BW/BSA or age correlation was analyzed for its pharmacokinetic parameters.

Abbreviations: i.v.: intravenous, s.c.: subcutaneous, mAbs: monoclonal antibodies, CL: clearance, PK: pharmacokinetics, BSA: body surface area, V: Volume of distribution, JRA: juvenile rheumatoid arthritis, ANC: absolute neutrophil count, G-CSF: granulocytecolony simulating factor, PBPC: peripheral blood progenitor cell, rhIL-11: interleukin-11.

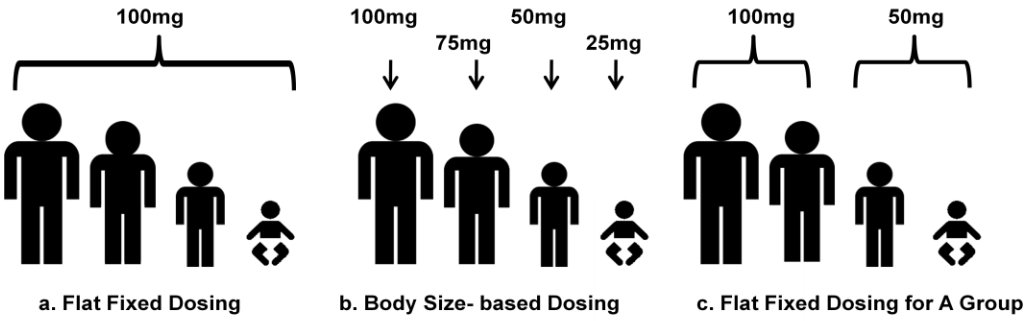

Figure 3-1. (a) An example of fixed dosing (b) An example of body size-based dosing (c) An example of fixed dosing by different age groups or different body size groups

CHAPTER 4
FIXED DOSING VERSUS BODY SIZE-BASED DOSING OF THERAPEUTIC ANTICANCER DRUGS IN ADULTS

Background

The classic cytotoxic anticancer molecules are widely known for their narrow therapeutic window. It was perceived that since patients with larger body size have a bigger metabolizing capacity, faster clearance, and a larger volume of distribution, a higher dose should be given to larger patients. As a result, anticancer drugs are usually administered based on the patients' body surface area (BSA), and it was believed that BSA-based dosing provides precise and accurate dosing even though there was no solid scientific support. BSA was used mainly for the purpose of allometric scaling at the beginning. In the 1950s, BSA was introduced to dose oncology drugs in pediatric patients.198 In 1958, Pinkel first proposed that the maximum tolerated dose (MTD) when adjusted by BSA (mg/m2) was similar in different animals and humans.7 The anticancer agents Pinkel reviewed were mechlorethamine, methotrexate, 6-mercaptopurine, actinomycin D and triethylenethiophosphoramide (thiotepa). In 1966, Freireich et al. compared the observed human MTD with the predicted MTD by preclinical animal data for 18 anticancer drugs, and concluded that the MTD expressed as mg/m2 in animals accurately predicted the MTD dose in human. Although Pinkel and Freireich suggested BSA-based dosing be used to determine the MTD, neither publication recommended BSA-based dosing in dose escalation in Phase I studies. Without solid scientific investigation, BSA-based dosing was then adopted in adults Phase I trials, and then carried through Phase II and III studies, and ultimately used in the approved labeling for most anticancer drugs.

Body surface area is difficult to measure directly; therefore it needs to be estimated using formulas that incorporate body weight and height in the calculation. The original formula to calculate BSA was first developed by DuBois and DuBois in 1916 from a study that enrolled only nine subjects[199]: BSA=0.20247 x Height (m) $^{0.725}$ x Weight (kg). $^{0.425}$ The nine subjects weighed 25 to 90 kg. A mold was made of their body, and was cut into small flat pieces, and then the surface area was calculated. The study included only one child, so the prediction of pediatric BSA was beyond the range of this formula. One commonly used formula was published by Mosteller.[200] The major formulas to calculate BSA are summarized in Table 4-1. In 1970, Gehan and George derived the formula BSA=0.02350 x Height (cm) $^{0.422246}$ x Weight (kg) $^{0.51456}$ which works well both in adults and children. Gehan and George also validated the original Dubois formula in more than 401 subjects, and the Dubois formula was reported to overestimate the BSA by more than 15% in about one fifth of the people, while underestimating only 1% of the people.[201] This finding indicated the lack of accuracy of the DuBois formula to determine the BSA of cancer patients and to further individualize dose for cancer patients. This finding however, surprisingly did not result in the Gehan and George BSA formulas to replace the Dubois furmula as the medical standard. It was not until 1987, when Mosteller has modified and simplified the original formula, was it commonly used by medical professionals: BSA=√ ([Height (cm) x Weight (kg)]/3600).[200] Mosteller's formula has been extensively used in oncology to calculate dosage for many chemotherapy drugs, and it has been considered as the "gold standard" for dosing anticancer agents. However, the use of BSA formula in obese patients is still uncertain. In the current clinical use, many patients are assigned a BSA

of 2 m^2 when patients have actual BSA larger than this value.[202] Though we have listed several formulas, the correlations among the formulas were reported high (r> 0.97) indicating very small differences.[203] However, significant differences of BSA values was observed for overweight and obese adults between the DuBois formula and other formulas.[203] This study compared different formulas, and reported that for overweight adults, the DuBois formula underestimated the BSA by 3% for male and 5% for female when compared to Mosteller's formula. Nowadays, a 3D scan can be used to determine BSA using high technology tools.[204]

In 1958, Pinkel proposed that BSA correlates to the pharmacokinetics of the anticancer drugs better than body weight.[7] BSA is believed to provide better individualized medication in daily practice, but many other factors can affect systemic exposure of anticancer drug concentration in patients. These factors includes the patients' characteristics (e.g. gender, race, age, weight, height, menopausal status, pregnancy), genetic differences (e.g. polymorphisms in metabolizing enzymes and transports), disease related characteristics (e.g. tumor type, cancer stages, surgery, liver function, renal function, albumin and alpha -1- acid glycoprotein levels), comedications (e.g. antibiotics, herbal supplements, over the counter medications), and patient life style (e.g. adherence to medications, food, alcohol, smoking, coffee, exercise, stress). Body size (body weight or BSA) is only one of those factors that affects the interindividual variability from patient to patient, and simply just linearly adjusting dose accordingly to BSA may lead to reduced, unchanged, or even increased intersubject variability in cancer patients. For anticancer cytotoxic drugs, after the BSA dose adjustment, the intersubject variability, if expressed as coefficient of variation

(standard deviation divided by the mean and multiply by 100), is often still in the range of 25% to 70% if not more.[205]

As early as 1990, Crochow et al. has questioned the dose adjustment by body surface area.[198] Baker et al. reported in a retrospective study that for the 33 investigational anticancer agents, BSA-based dosing significantly reduced the interpatient variability in clearance for only 5 drugs, such as docosahexaenoic acid-paclitaxel, 5-fluorouracil/eniluracil, paclitaxel, temozolomide, and troxacitabine. It was reported that for some anticancer agents, BSA-based dosing reduced intersubject variability between the ranges of 15% to 35%; as a result, BSA can only explain up to one-third of the total interindividual variability.

The objectives of this study are1) for the first time utilize population pharmacokinetics approach to systemically evaluate intersubject variability for anticancer drugs, 2) provide a model based analysis method on dosing strategies for small oncology drugs under development, and 3) recommend a dosing strategy for clinical trials conducted in adults at different stages of the development of anticancer drugs.

Methods

Data Collection

Data used in the current simulation were collected from the population PK/PD studies of anticancer drugs published. The selection criteria included the availability of population PK models for adult patients and assessment of the body size effect on the PK parameters.

Population PK Models

The population PK and/or PD models of the selected anticancer drug (see Table 4-1) were obtained from published journal articles. General properties of these population PK models and the body size effect, such as BW or BSA, on the PK parameters are summarized in Table 4-2. Mixed-effect models were used to describe the PK of all the selected small oncology drugs. The jth observation for the ith individual was given by

$$Y_{ij} = f(\theta_i, t_{ij})(1 + \varepsilon_{1ij}) + \varepsilon_{2ij}$$

where θ_i is a set of PK parameters for the ith individual, and ε_{1ij} and ε_{2ij} are the residual errors following normal distributions with a mean of zero and variance of σ_1^2 and σ_2^2, respectively. θ_i can be further described by

$$\theta_i = g(z_i, \theta) + \eta_{ij}$$

where z_i is a set of fixed effects on the PK parameters, θ is a set of typical population values of PK parameters, and η_i is the intersubject variability following a normal distribution with a mean of zero and variance of Ω^2. Simulation analysis was investigated using NONMEM (version VI; GloboMax, Hanover, Maryland).

PK Simulation

Population performance. Simulations to evaluate population performance of two dosing approaches were investigated the same way as previously described.[56] Briefly, Monte Carlo simulation was conducted using the final PK model reported for each anticancer agent to generate the concentration-time profiles following both fixed dosing and body size-based dosing approaches. The dose used for simulation was one of the doses recommended in the labeling for marketed products. The median value of body

size (BW or BSA) was used as the assumed standard for dose determination so that the dose used in the fixed-dosing dataset is the same as the dose for the participants with median (typical) body size in the body size-based dosing dataset. For all simulation studies, 1000 subjects were simulated for each dosing approach. The sampling points were chosen based on the PK properties of the anticancer drugs, often the reported sampling points in the selected PK model article is used. The exact same sampling schedule was used for both fixed and body size-based dosing approaches.

For each simulation study, values of the covariates were randomly generated using S-PLUS 8.0 (TIBCO, Palo Alto, California) assuming normal, lognormal or binomial distribution. The values of parameters used for generating these covariates were selected by trial and error, with a goal of reproducing the patient population by matching the median, standard deviation, and/or the range of covariates to those reported in the corresponding population PK/PD study.

Individual performance. To evaluate the individual performance, the PK profiles were simulated for the participants with typical, low extreme, and high extreme body size. The typical, low extreme, and high extreme BW/BSA used in this study were 75.7 kg/1.8 m^2, 40 kg/1.3 m^2, and 140 kg/2.3 m^2, respectively. For covariates other than BW/BSA, typical values were used. The intersubject variability and residual errors were all set to zero for the simulations conducted for both dosing approaches. The reason for fixing other covariates values to be the same, and inter- and intra- subject variabilities to be zero, is that the exposure difference among the typical, low extreme and high extreme body size patients is only attributed to the difference of dosing approaches.

Calculation of α Values

A simple way to assess whether fixed dosing or body size-based dosing may be better in reducing intersubject variability in AUC is to evaluate the α value (the power function of the equation CL=TVCL x (individual BW/median BW)$^{\alpha}$ of the body size effect on CL. However, the covariate models used to characterize the effect of body size on CL for the selected anticancer drugs are not all in the form of this equation (Table 4-2). Therefore, a translation was made to obtain the α values for all anticancer drugs evaluated. For those whose α values were not reported, the following process were used to obtain the α value for each molecule: (1) calculate a series of CL values over the range of BW or BSA reported based on the reported original paper with PK model reported and (2) fit the generated CL versus body size data using equation CL=TVCL x (individual BW/median BW)$^{\alpha}$ to obtain the α value using WinNonlin 5.2 (Pharsight, Mountain View, California).

AUC calculation. The AUC for each subject was calculated as dose/CL if the molecule presented linear PK. When the molecule presented nonlinear PK, the AUC was calculated by integration of the concentration-time curve by the trapezoidal rule using S-PLUS 8.0 (TIBCO, Palo Alto, California).

PK C_{max} determination. The maximum concentration (C_{max}) for each individual was calculated as the maximal concentration from the simulated concentration-time profile of the subject.

Performance Evaluation

The performance of the two approaches in terms of reducing intersubject variability in AUC was assessed by evaluating the α value of the CL versus body size relationship based on the following criteria:

α < 0.5—fixed dose is better.
α = 0.5—fixed and body size-based dosing are similar.
α > 0.5—body size-based dosing is better.

These criteria apply to both population and individual performances. To be consistent with chapter 2 and to confirm the predictive performance of the α value, the comparison of simulation studies of the 2 dosing approaches were presented as described below.

Population performance was evaluated by comparing the intersubject variability (expressed as % coefficient of variation [CV %]) in the exposure (AUC and C_{max}) of 1000 subjects simulated following both fixed and body size-based dosing approaches. Coefficient of variation of the 1000 subjects for each anticancer drug is calculated by ratio of the mean of the 1000 subjects and the standard deviation of the 1000 subjects. A good dosing approach should provide consistent exposure for the whole patients' population. The dosing approach that produced less intersubject variability should be a better dosing approach for the patient population.

Individual performance was evaluated by comparing the percentage difference in the C_{max} or AUC between subjects with extreme low/high body size and typical body size following the 2 dosing approaches. The dosing approach that provides a smaller percentage difference in PK exposure between individuals with extreme body size and those with typical body size has a better individual performance.

Contribution of Body Size Effect to Overall Intersubject Variability of Relevant PK Parameters

A simulated PK data set of 100 participants was generated using the published "final" PK models, including all influential covariates following a fixed dose. The relevant covariate values were randomly generated as described above. This simulated data set

was then fitted using both the “final” model and the “reduced” model, which excluded body size as covariate(s) for any PK parameters. The percentage change in the intersubject variability of relevant PK parameters by the “final” model in comparison to the “reduced” model was calculated to determine the contribution of body size effect to the overall intersubject variability of the relevant PK parameters.

Comparison of BW and BSA-based Dosing at Population Level

Once we confirmed that body size-based dosing is suitable for a particular anticancer drug, how do we decide which body size to be used for dosing calculation? An example simulation is given to compare body weight and body surface area-based dosing, since these two are the most common dosing approaches for anticancer drugs. Monte Carlo simulation was conducted using the final PK model reported for each anticancer agent to generate the concentration-time profiles following both body weight-based dosing and body surface area-based dosing approaches. The dose used for simulation was one of the doses recommended in the labeling for marketed products. Each simulation is done with one dataset. Body weight-based dosing and body surface area-based dosing methods have separate datasets. The only difference between the two datasets is the dosing information. The median value body weight subject in the body weight data set is assumed to be given the same dose as the median value body surface area in the body surface area dataset. For all simulation studies, 1000 subjects were simulated for each dosing approach. The sampling points were chosen based on the PK properties of the anticancer drugs, often the reported sampling points in the selected PK model article is used. The exact same sampling schedule was used for both fixed and body size-based dosing approaches.

For each simulation study, values of the covariates were randomly generated using S-PLUS 8.0 (TIBCO, Palo Alto, California) assuming normal, lognormal or binomial distribution as described in the population performance section. If there are two covariates related to each other, such as body weight or creatinine clearance, both of the covariates are ranked from low to high.

Individual simulation for BW and BSA is done the same way as described above for fixed dosing and body size-based dosing approaches.

Performance evaluation of BW and BSA-based dosing. Cisplatin was chosen as an example to demonstrate the comparison of BW and BSA-based dosing. BW and BSA population data set were both divided in to four groups according to the BW or BSA value (≤25%, >25% and ≤ 50%, 50% > and ≤ 75%, and ≥75%). Take BW for example, if the BW range is 40-140kg, then BW could be divided into four groups: ≤50kg, >50kg and ≤ 75kg, 75kg > and ≤ 100, and ≥100kg. In order to compare BW and BSA-based dosing, it was assumed that the person with median BSA and the person with median BW receive the same amount of total dose from the two datasets. The cut off values for each group depends on the range and distribution of the body weight. For each group, 5^{th} and 95^{th} quartile of each group were plotted for both BW and BSA. Visual comparison of the two profiles can be made for BW and BSA-based dosing.

The similar analysis at population level and individual level as mentioned above for all the selected drugs are also made to compare BW and BSA-based dosing.

Results and Discussion

Data Collection

A total of 28 anticancer drugs were selected based on the data collection criteria specified in the Methods section (Tables 4-2). The effect of body size on various PK

parameters, including CL, intercompartment clearance (Q), volume of the central compartment (V or V1), and volume of the peripheral compartment (V2), is summarized in Table 4-2. Body size has been found to be covariate(s) of 1 or more of the PK parameters for 20 anticancer drugs (Table 4-3).

It should also be noted that for ifosfamide, although body size had been found not to be covariates of its PK parameters, the population PK models were developed based on data from only 24 patients (Table 4-3). One should be cautious with the interpretation of the results.

Among these 28 selected anticancer drugs, nineteen are administered based on body size in adult patients (Table 4-2). Interestingly, for some products that are administered using body weight-based dosing, such as cladribine, cyclophosphamide, and Thiotepa (Table 4-2), body size measures (BW or BSA) had not been shown to be a covariate of their PK parameters (Table 4-3). Similarly, etoposide, gemcitabine, ifosfamide, and melphalan are given per BSA, body size was not found significant to be a covariate for their PK models as well.

Dosing Approach Performance

Performance evaluation based on AUC

As discussed in the chapter 2, the performance of AUC for the two dosing approaches can be simply assessed by the α values, the exponent of the power function as defined in Equation (2-1), with α value of 0.5 as the cutoff point. The exponent of power function α values that describe the body size effect on CL were obtained for all the 28 selected anticancer drugs and listed in Table 4-3. The α values were directly recorded from the published models if they are available or obtained in such a way as described in the Methods “Calculation of α Values” section. For

anticancer drugs where body size was not found to be significant covariate of CL, a zero value was assigned to α. As shown in Table 4-3, 15 of 28 molecules had α values less than 0.5, and 13 molecules had α values greater than 0.5. These results suggest that fixed dosing would perform better for 14 molecules (α < 0.5), body size-based dosing would perform better for 14 molecules (α > 0.5). The only exception is Melphalan. Overall, the two dosing approaches would perform not too differently across all the molecules.

The results of the simulation studies for comparing the performance of two dosing approaches at the population level are presented in Figure 4-1A. Consistent with the prediction based on the α values, 14 therapeutic biologics with α > 0.5 presented less intersubject variability in AUC when body size-based dosing was adopted, whereas the other 14 biologics with α < 0.5 exhibited less variability in AUC when fixed dosing was used, with only one exception, melphalan. For melphalan, etoposide, and methotrexate, body size was not, but creatinine clearance was a covariate of CL or V. For melphalan, etoposide, creatinine CL was a covariate for CL, and for methotrexate, creatinine CL was a covariate for V. Both etoposid and methotrexate, the population AUC variability is less when fixed dosing was used, which is consistent with when α < 0.5, fixed dosing presents less variability. However for melphalan, body size-based dosing presents less variability AUC at population level. The reason might be that creatinine CL is highly related to the body weight of in the melphalan study. For the BSA simulation dataset, both BSA and creatinine CL were ranked from low to high for all the subjects. The study did not mention the relation between BSA and creatinine CL. If there is high relation between the two, then BSA is likely to provide less interindividual variability to the AUC

across the population. In the other hand, for etoposid and methotrexate, body size is likely not highly related to creatinine CL in these two study; thus fixed dosing provides less interindividual variability for AUC.

Similar results were also obtained for individual performance (Figure 4-2A). For most of the anticancer drugs investigated, the dosing approach that had better population performance also had better individual performance. The only exception is melphalan. The difference between population and individual AUC for melphalan might be because of the creatinine CL values. In the population dataset, creatinine CL ranges from 30 to 195 ml/min. However, for the individual dataset, creatinine CL was randomly assigned in order for low extreme, high extreme and typical body size patients, and the value range of creatinine CL is not as wide as the body size range. This might be the reason for melphalan to have different population and individual variability results. It should be noted that the zero difference in AUC between patients with extreme body size and typical body size following a fixed dose for capecitabine, cladribine, cyclophosphamide, dexamethasone, erlotinib, etoposide, everolimus, gemcitabine, ifosfamide, imatinib, irinotecan, methotrexate, pemetrexed, and Thiotepa is a result of the lack of BW/BSA effect on their CL (Figure 2-2A).

The consistent conclusions obtained based on the α values and from the simulation studies further reconciled the recommendation of using the α value to select the optimal dosing approach if AUC is the exposure parameter of the main concern. However, when other body size related measurements are the covariates for CL,such as creatinine CL, one should be more cautious.

Performance evaluation based on C_{max}

The population and individual performances of the two dosing approaches based on C_{max} were evaluated by simulation studies and shown in Figures 4-1B and 4-2B, respectively. At the population level, body size-based dosing resulted in less intersubject variability in C_{max} for 14 of 28 anticancer drugs, whereas fixed dosing produced less variability in C_{max} for the other 14 compounds (Figure 4-1B). At the individual level, body size-based dosing produced a smaller percentage difference in C_{max} between participants with extreme and typical body sizes for 13 of 28 anticancer drugs, whereas fixed dosing produced a smaller percentage difference for the other 15 compounds (Figure 4-2B). The results from both population and individual level evaluations are again very consistent with the only exception of capecitabine, for which fixed-based dosing was shown to have better individual performance but a slightly worse population performance. The difference between the population and individual CV% for C_{max} of capecitabine is very little, less than one percent. BSA α value is 0.812 on V_3 (volume of distribution of the deep peripheral compartment). The reason for this inconsistent result might be because that the body size effect on volume of distribution of the deep peripheral compartment is diluted, so the effect is not as obvious as for the central volume of distribution. As shown for the population performance, there is almost no difference between fixed dosing and body size-based dosing.

It was noted that body size-based dosing tends to overdose patients with large body size and underdose patients with small body size. The opposite is true for fixed dosing, that is, overdose patients with small body size but underdose patients with large body size (Figure 4-2A, B).

Contribution of Body Size Effect to Overall Intersubject Variability in PK Parameters

The contribution of the effect of body size to the overall intersubject variability of relevant PK parameters was evaluated for 19 anticancer drugs with body size as a covariate, and the results are summarized in Table 4-4. It was observed that the effect of body size had a small and, in some cases, moderate contribution, in a few cases, bigger contribution to the overall intersubject variability of major PK parameters, ranging from 3.32% to 60.9% for CL and from 0.55% to 75.59% for V/V1 (Table 4-4). It was observed that BSA or body weight can explain a relatively bigger portion of the intersubject variability for busulfan, cisplatin and thalidomide. BSA/BW contributes to 39.18%, 59.55%, and 60.90% intersubject variability of CL for busulfan, cisplatin and thalidomide, respectively. The contributions to volume of distribution for these three compounds are 75.59%, 45.24% and 48.44. BSA/BW also explains 38.28% and 35.67% intersubject variability of CL for imatinib and paclitaxel. For these compounds, body size seems to be a major source for intersubject variability, body size-based dosing may provide a clinical benefit when supported by other factors, such as a narrow therapeutic window. When body size only explains a very small percentage of the intersubject variability—for example, in the case of 5-Fluorouracil, doxorubicin, and oxaliplatin— adjusting the dose based on body size would lead to a minimal reduction in the variability in AUC

Performance of BW and BSA-based dosing

After body size-based dosing is confirmed to be better than fixed dosing, the next step is to find out whether body weight or BSA is appropriate for dosing adjustment. The evaluation method to compare BW and BSA-based dosing was introduced in Methods

section. Figure 4-3 shows the example of cisplatin, the 5th and 95th percentile of the concentration-time profiles were plotted for four groups according to the four quartiles of BW or BSA value (≤25%, >25% and ≤ 50%, 50% > and ≤ 75%, and ≥75%). It is very obvious that the middle two quartiles, there is tiny difference between the profiles after BSA-based dosing and BW-based dosing (Figure 4-3 B and C). For the fourth quartile, BSA-based dosing seems slightly underdose the patients compared to BW-based dosing (Figure 4-3 D). In the other hand, there is a little larger difference between the two dosing approaches in the first quartile body size group, but the different is not dramatic either (Figure 4-3 A)..

A comparison of CV% of AUC and C_{max} at population level between BW and BSA-based dosing is shown in Figure 4-4. BW based dosing showed less CV% for both AUC and C_{max} at population level (Figure 4-4A). The similar observation was found at individual level, BW showed less % difference for both AUC and C_{max}(Figure 4-4B).

In summary, the result shows little difference between BW and BSA-based dosing when visually comparing the 5th and 95th concentration-time profiles. BW-based dosing was showing to have less intersubject variability at both population and individual level than BSA-based dosing.

Relationship between the Class of Anticancer Drugs and Body Size Effect on Pharmacokinetics

The 28 anticancer drugs selected in this study fall in a variety of drug classes. There are 8 alkylating antineoplastic agents, 4 topoisomerase inhibitors, 3 antimcrotubule agents, 2 tyrosine kinase inhibitors, 2 mTOR (mammalian target of rapamycin) inhibitors, 1 nucleoside analog, 1 DNA crossliker. The rest of the anticancer agents are either inhibitors of certain enzymatic pathway or involving in multiple

pathways. There is no apparent correlation between the drug class and the α values of body size effect on CL or V. There is also no apparent correlation between the drug class and the performance of AUC and C_{max} at either population level or individual level. Among the drugs that body size contributes to relatively larger percentage of intersubject variability, there is no trend observed in terms of drug classes. Overall, there is no observed correlation between the drug class of an anticancer drug and the body size effect on the pharmacokinetic parameters.

Discussion and Summary

Baker et al. has conducted analysis evaluating the role of body surface area in dosing anticancer drugs.[206] They defined the criteria as 1) a linear regression coefficient between BSA and CL (R) ≥.50; 2) P<.01; and 3) a relative reduction in the variability of clearance ≥.15%. They have concluded that body surface area-based dosing statistically significantly reduced interpatient variability in drug clearance for only 5 of the 33 agents: docosahexaenoic, acid (DHA)-paclitaxel, 5-fluorouracil / eniluracil, paclitaxel, temozolomide, and troxacitabine. Our results presents a lower intersubject variability in AUC at both population and individual levels for 5-fluorouracil for BSA-based dosing. Our result of paclitaxel and temozolomide is also in consistent with Baker's conclusion that paclitaxel and temozolomide showed less intersubject variability for AUC and C_{max} at both population and individual levels for BSA-based dosing. Interestingly, temozolomide was approved with a fixed dosing on its labeling, and more than one study have shown that CL increased with BSA for both gender, and BSA should be used for dosing temozolomide.[207, 208] Surprisingly, in our study, body size is only showed to be able to explain 2.24% intersubject variability of temozolomide CL. Our results show that BSA contributes to 35.67% intersubject variability of paclitaxel CL.

BSA normalized dose showed benefits for paclitaxel. It was reported that the distribution of paclitaxel in the blood strongly depends on its formulation vehicle (Cremophor EL-dehydrated ethanol USP; Bristol-Myers Squibb, Wallingford, CT),[209] due to the fact that paclitaxel has strong affinity to Cremophor EL in the blood. Blood volume has long been demonstrated to correlate with BSA in 1986.[210] Sparreboom evaluated the disposition of Cremophor EL and reported that Cremophor EL has a volume of distribution that is similar to the blood volume and body surface area is a significant covariate for Cremophor EL clearance.[211] Therefore, BSA effect on PK parameters of paclitaxel is likely related to the affinity of paclitaxel to its vehicle Cremophor EL,[212] and the distribution of paclitaxel depends on the distribution of Cremophor EL which is linked to blood volume.

Previous studies showed that there is no correlation between BSA and busulfan CL when busulfan is given by i.v. administration,[213] but BSA has significant influence on busulfan CL when busulfan is given orally.[214] Our result of the simulation shows that after busulfan administration, body weight-based dosing provides less intersubject variability for AUC and C_{max} at both population and individual level. The PK model for busulfan contains body weight as a covariate for both V and CL. Body weight contributes to 39.18% of intersubject variability of CL and 75.59% intersubject variability of V. Overall, our results supports body size-based dosing for busulfan.

Cisplatin was found to have lower intersubject variability for AUC and C_{max} in our study at population level, but difference is minimized. In our study cisplatin was also found to decrease intersubject variability for AUC and C_{max} at individual level. Additionally, for cisplatin, BSA contributes to 59.55% of intersubject variability of CL and

49.25% intersubject variability of V. A previous study by de Jongh concluded that body surface area-based dosing does not increase accuracy of cisplatin exposure.[215]

It is debatable for docetaxel whether BSA has a clinically meaningful effect on its clearance. Baker's regression for docetaxel CL and BSA has a p-value smaller than 0.001, and our results show that less intersubject variability for AUC and Cmax at both population and individual level with BSA-based dosing.[206] However, the intersuject variability that attributes to BSA among patients is only 3.5%[206], and the impact of transaminases and alkaline phosphatase levels on CL has been shown to be more clinically relevant.[216]

Our finding for capecitabine aligns with previous study that BSA has no influence on CL of capecitabine.[217] Both our finding and another study supports the conclusion for cyclophosphamide that neither BSA nor body weight has correlation with the clearance of the cyclophosphamide.[218]

A study has shown that BSA has no correlation with CL for methotrexate,[219] which is in agreement with our results. The impact of body size on irinotecan clearance has been studied by Mathijssen.[220] This study examined 82 patients, and BSA normalized clearance exhibited higher intersubject variability. The metabolite of irinotecan was also studied, and BSA normalized clearance for the metabolite also showed higher intersubject variability. Mathijssen recommended that alternative dosing strategies should be studied for irinotecan. Our result for irinotecan indicates that fixed dosing provides less intersubject variability for AUC and C_{max} at both population and individual levels.

In our study, besides temozolomide, other three anticancer drugs (mitomycin, temsirolimus, thalidomide) that are approved for fixed dosing administration present less intersubject variability for AUC and C_{max} when body size-based dosing is used in simulation. Especially for thalidomide, body weight was tested to contribute to 60.90% and 48.44% intersubject variability in CL and V, respectively. As a result, for these drugs, further analysis and evaluation needs to be done to find a better dosing strategy.

Overall, finding a good dosing strategy is challenging for anticancer drugs. Some lessons were reported in the literature: drugs with approved body size-based dosing shows no correlation of BSA with their PK parameters, and drugs with approved fixed dosing exhibits a correlation of body size with their PK parameters. The reason for this situation might be a lack of assessment of body size effect on PK or PD of these anticancer drugs.

At the end, we recommend fixed dosing to be used for first in human studies for anticancer drugs under development. Once data is available, body size effect should be evaluated on PK and PD of anticancer drugs. Since most of the small oncology drugs are cytotoxic agents with narrow therapeutic windows, often times, adjustment of dosage is made according to the body size. However, a large intersubject variability can still exist. This could lead to failure of the treatment or harmful toxicity in the patient population. The goal is to detect any possible factors that could significantly impact the PK and PD of the drugs, and further dosing strategies should be made based on these factors but not restricted only to body size. The analysis of covariates that affect PK and PD is extremely important information for the Phase III dose selection. Fortunately, the challenge of BSA-based dosing for anticancer drugs started two decades ago, and

nowadays the importance of the analysis has been accepted by more and more professionals.

Table 4-1. BSA formulas

Year	Authors	Number of Subjects	Formula
1916	DuBois, DuBois	9 (1 Child)	$BSA\ (m^2) = 0.20247 \times height\ (m)^{0.725} \times weight\ (kg)^{0.425}$ or $BSA\ (m^2) = 0.007184 \times height\ (cm)^{0.725} \times weight\ (kg)^{0.425}$
1935	Boyd	231	$BSA\ (m^2) = 0.0003207 \times weight(g)^{0.7285 - 0.0188 \log(Weight(g))} \times height\ (cm)^{0.3}$
1970	Gehan, George	401	$BSA\ (m^2) = 0.0235 \times height\ (cm)^{0.42246} \times weight(kg)^{0.51456}$
1978	Haycock et al	81	$BSA\ (m^2) = 0.024265 \times height\ (cm)^{0.3964} \times weight(kg)^{0.5378}$
1987	Mosteller	Unknown	$BSA = \sqrt{([Height\ (cm) \times Weight\ (kg)]/3600)}$ or $BSA = \sqrt{([Height\ (in) \times Weight\ (lbs)]/3600)}$

Table 4-2. Selected anticaner drugs and their dosing approaches for adult patients

Generic Name	Brand Names	Dosing	Drug Class
5-Fluorouracil	Adrucil®, Efudex®, Fluoroplex®, Carac®	mg/kg, mg/m ^{2}	Thymidylate synthase inhibitor
Busulfan	Busulfex®, Myleran®	mg/kg	Alkylating antineoplastic agent
Capecitabine	xeloda®	mg/m^2	Thymidylate synthase inhibitor
Cisplatin	Platinol®, Platinol®AQ	mg/m^2	Alkylating antineoplastic agent
Cladribine	Leustatin®	mg/kg	Adenosine deaminase inhibitor
Cyclophosphamide	Cytoxan®, Neosar®	mg/kg	Alkylating antineoplastic agent
Dexamethasone	Decadron®, Dexasone®, Diodex®, Hexadrol®, Maxidex®	mg	Anti-inflammatory
Docetaxel	Taxotere®	mg/m^2	Antimicrotubule agent
Doxorubicin	Adriamycin PFS, Adriamycin RDF, Rubex®,Doxil®	mg/m^2	Topoisomerase II inhibitor
Erlotinib	Tarceva®	mg	Tyrosine kinase inhibitor
Etoposide	Etopophos®, Toposar®, VePesid®	mg/m²	Topoisomerase II inhibitor
Everolimus	Afinitor®	mg	mTOR inhibitor
Gemcitabine	Gemzar®	mg/m^2	Nucleoside analog
Ifosfamide	Ifex®	mg/m^2	Alkylating antineoplastic agent
Imatinib	Gleevec®	mg	Tyrosine kinase inhibitor
Irinotecan	Camptosar®	mg/m^2	Topoisomerase I inhibitor
Melphalan	Alkeran®	mg/m^2	Alkylating antineoplastic agent
Methotrexate	Amethopterin®, Rheumatrex®, Trexall®	mg	Dihydrofolate reductase inhibitor
Mitomycin	Mutamycin®	mg	DNA crosslinker
Oxaliplatin	Eloxatin®	mg/m^2	Alkylating antineoplastic agent
Paclitaxel	Onxal®, Taxol®	mg/m^2	Antimicrotubule agent
Pemetrexed	Alimta®	mg/m^2	Thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide formyltransferase inhitor
Temozolomide	Temodar®	mg	Alkylating antineoplastic agent
Temsirolimus	Torisel®	mg	mTOR inhibitor
Thalidomide	Thalidomid®	mg	Multiple pathways
Thiotepa	Thioplex®	mg/kg	Alkylating antineoplastic agent
Topotecan	Hycamtin®	mg/m^2	Topoisomerase I inhibitor
Vinorelbine	Navelbine®	mg/m^2	Antimicrotubule agent

* mTOR :mammalian target of rapamycin.

Table 4-3. Population pharmacokinetics/pharmacodynamics (PK/PD) models for the selected anticancer drugs

Genetic Name	$\alpha_{(CL)}$	$\alpha_{(V)}$	Covariate models	Ref	N
5-Fluorouracil	1	1	CL=TVCL*BW V=TVV*BW	[221]	44
Busulfan	0.83	0.89	CL=TVCL*(BW/60)^0.833 V=TVV*(BW/60)^0.889	[222]	30
Capecitabine	0	0.81	V3=TVV3*(BSA/1.8)^0.812	[223]	481
Cisplatin	1.85	1.38	CL=TVCL*(BSA/1.74)^1.85 V=TVV*(BSA/1.74)^1.38	[224]	32
Cladribine	0	0	BSA was not found significant to be a covariate	[225]	161
Cyclophosphamide	0	0	BSA was not found significant to be a covariate	[226]	46
Dexamethasone	0	0.63	V1=TVV1*(WT/57.5)^0.626	[227]	897
Docetaxel	1.11	0	CL=TVCL*(BSA/1.53)^1.11*(ALB/3.7)^0.251*(97/AAG)^0.776	[228]	200
Doxorubicin	1.4	0	CL=TVCL*(BSA/1.8)^1.4)*(AST/21)^-0.24*(AGE/56)^-0.54	[226]	46
Erlotinib	0	0.73	V=TVV*(BW/74)^0.73	[229]	42
Etoposide	0	0	BSA was not found significant to be a covariate,but CRCL is on CL	[230]	52
Everolimus	0.4	0.32	CL=CL0+CL1*(WT-71)+CL2*(AGE-44))*1.2^RACE, V=V0+V1*(WT-71)	[231]	673
Gemcitabine	0	0	BSA was not found significant to be a covariate	[232]	94
Ifosfamide	0	0	BSA was not found significant to be a covariate	[233]	24
Imatinib	0.30	0.41	CL=TVCL*(WT/80)^0.301*(HB/13)^0.897*(WBC/16)^-0.105, V=TVV*(WT/80)^0.405*(HB/13)^0.676*(WBC/16)^-0.070	[234]	371
Irinotecan	0	0.2	V=TVV*(1+0.004*(WT-80))	[235]	78
Melphalan	0	0	BSA was not found significant to be a covariate, but CRCL is on CL	[236]	64
Methotrexate	0	0	BSA was not found significant to be a covariate,but CRCL is on V	[237]	51
Mitomycin	1.63	0	CL=TVCL*(BSA/1.53)^1.63	[238]	47
Oxaliplatin	1.1	1.29	CL=TVCL*(WT/71)^1.1*(CRCL/87)^-0.57*(0.6*GEN(F)),V1=TVV1*(WT/71)^1.29,Q=TVQ*(WT/71)^1.01	[239]	56
Paclitaxel	Non-linear	1.17	V3=TVV3*(BSA/1.8)^1.17, VMT=VMT0*1.2^GEN*(BSA/1.8)^0.911	[240]	45
Pemetrexed	0	1.32	V=TVV*(BSA)^1.32	[241]	287
Temozolomide	1.05	0	CL=TVCL*(BSA)^1.32	[208]	445
Temsirolimus	1.28	0	CL=TVCL*(BSA)^1.28	[242]	50
Thalidomide		1	V=TVV*WT, ke was modeled instead of CL	[243]	65
Thiotepa	0	0	BSA was not found significant to be a covariate	[244]	65
Topotecan	0.75	1	CL=TVCL*(WT/70)^0.75,V=TVV*(WT/70) Q=TVQ*(WT/70)^0.75,V2=TVV2*(WT/70)	[245]	245
Vinorelbine	1.25	0	CL=TVCL*(BSA/1.61)^1.25	[246]	30

*Ref: Reference number in the reference list; N is the number of patients enrolled in the study.

Table 4-4. Percentage contribution of body size measurements to the overall intersubject variability of pharmacokinetics (PK) parameters in anticancer drugs

Anticancer drugs	% contribution of BW/BSA to the intersubject variability	
	CL	V1
5-Fluorouracil	3.32	0.55
Busulfan	39.18	75.59
Capecitabine	14.48	17.08
Cisplatin	59.55	45.24
Dexamethasone	9.60	NA
Docetaxel	11.20	NA
Doxorubicin	5.61	NA
Erlotinib	NA	23.81
Everolimus	9.69	14.49
Imatinib	38.28	NA
Irinotecan	NA	10.85
Mitomycin	19.82	NA
Oxaliplatin	4.58	6.75
Paclitaxel	35.67	NA
Pemetrexed	NA	17.02
Temozolomide	2.24	NA
Thalidomide	60.90	48.44
Topotecan	12.50	NA
Vinorelbine	11.54	NA

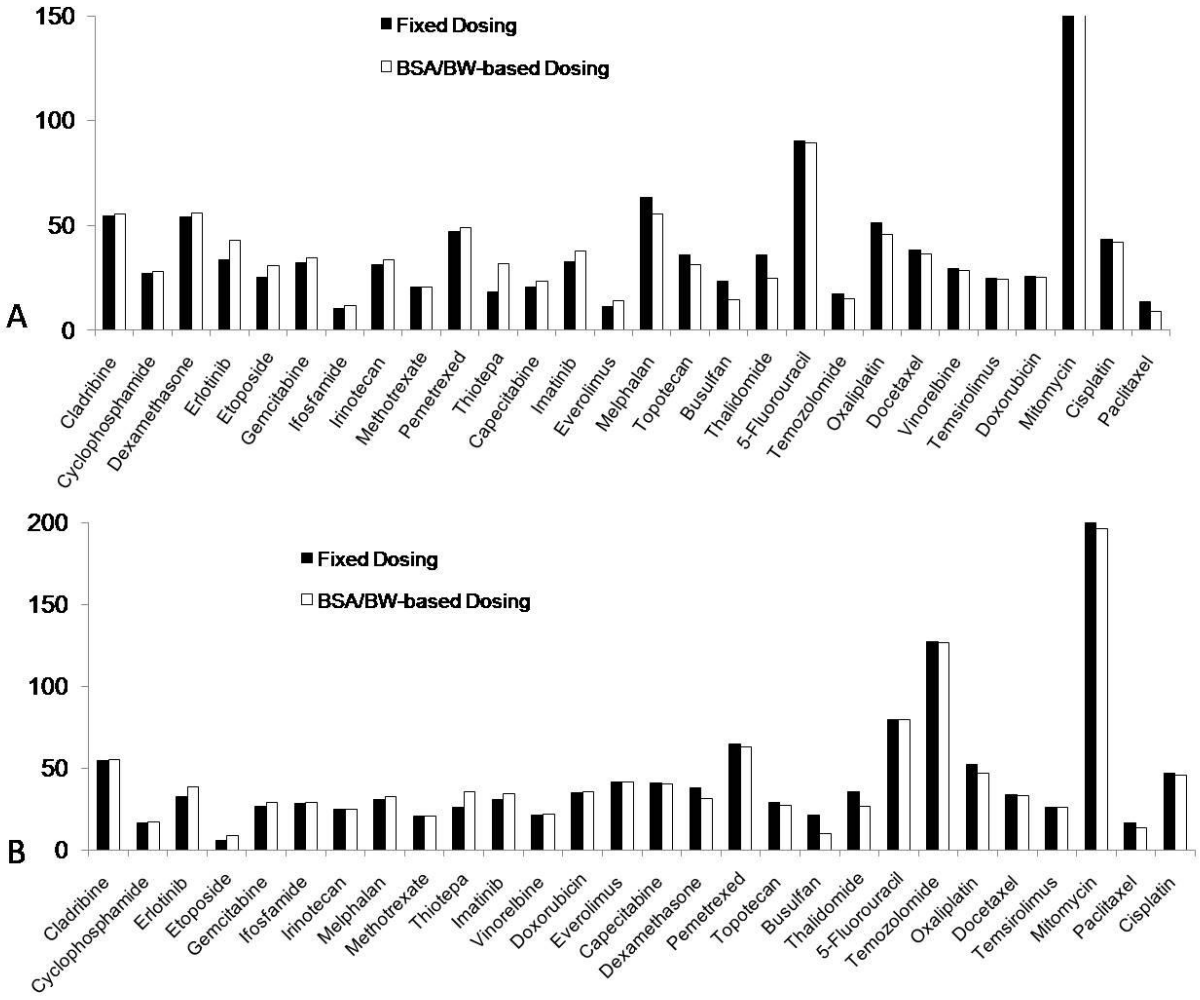

Figure 4-1. Comparison of the inter-subject variability of simulated AUC (A) and C_{max} (B) of 1000 subjects after receiving a single fixed (solid bar) dose or a body size (BW/BSA)–based dose(open bar) for selected anticancer drugs

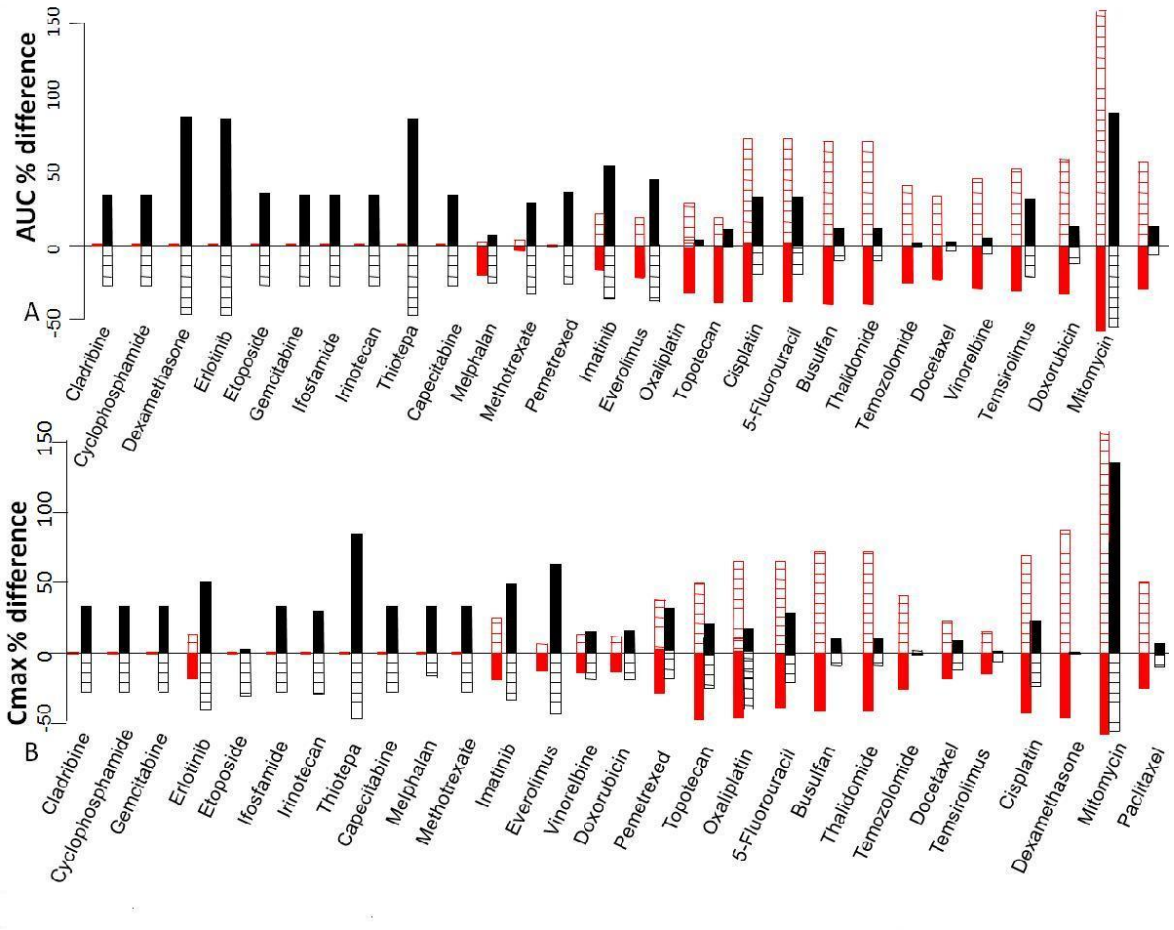

Figure 4-2. Comparison of the deviation (% difference) of AUC (A) and C_{max} (B) for subjects with low (open bar) and high (solid bar) extreme body size (BW/BSA) measurements from the typical values (AUC and C_{max} for subjects with median body size measurements after a fixed dose (red) or a body size (BW/BSA)–based dose (black)

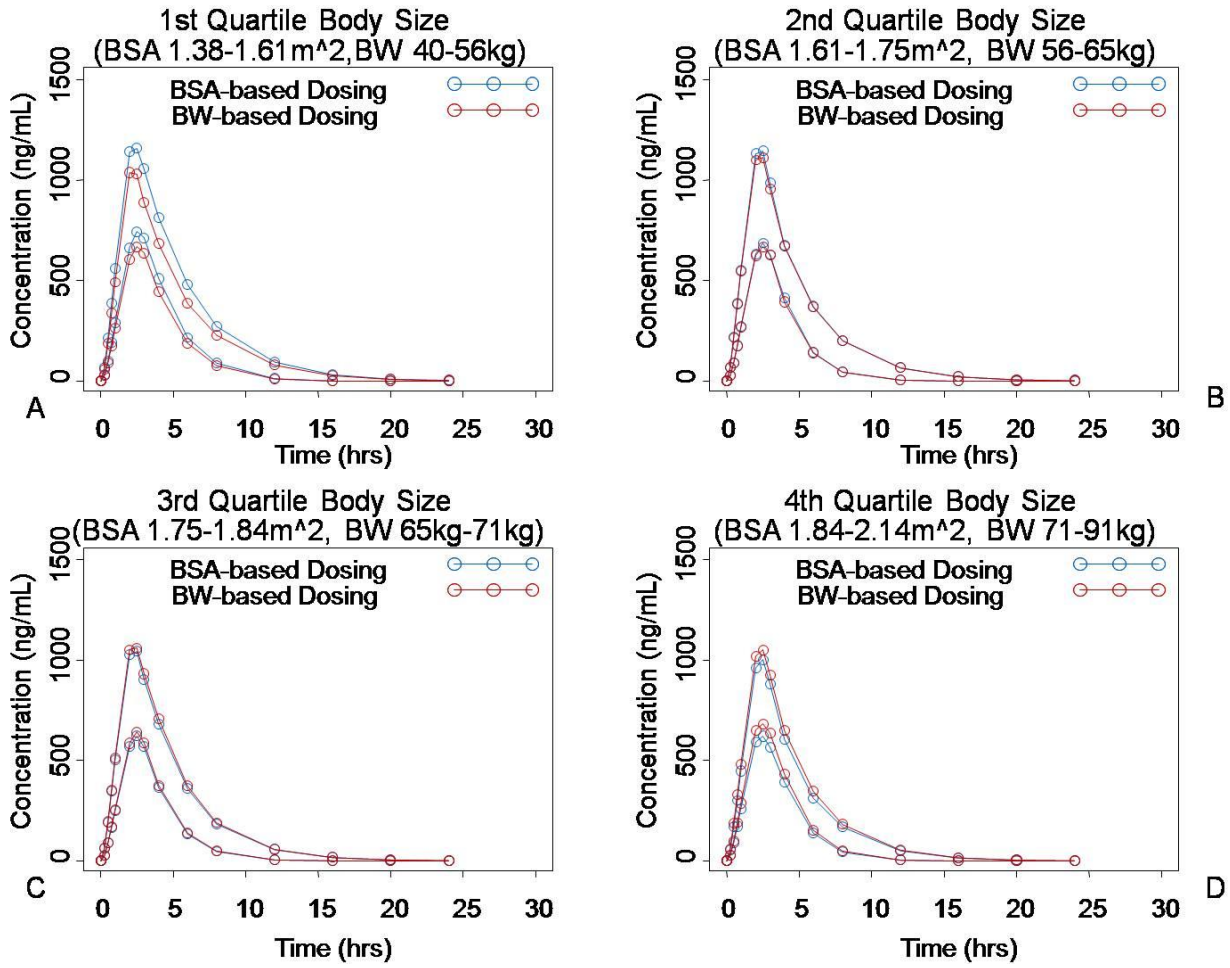

Figure 4-3. Visual comparison of the 5th and 95th percentile of cisplatin concentration-time profiles after a BSA-based dose and a BW-based dose for four BW or BSA value quartiles groups (A. ≤25%, B.>25% and ≤ 50%, C.50% > and ≤ 75%, and D. ≥75%)

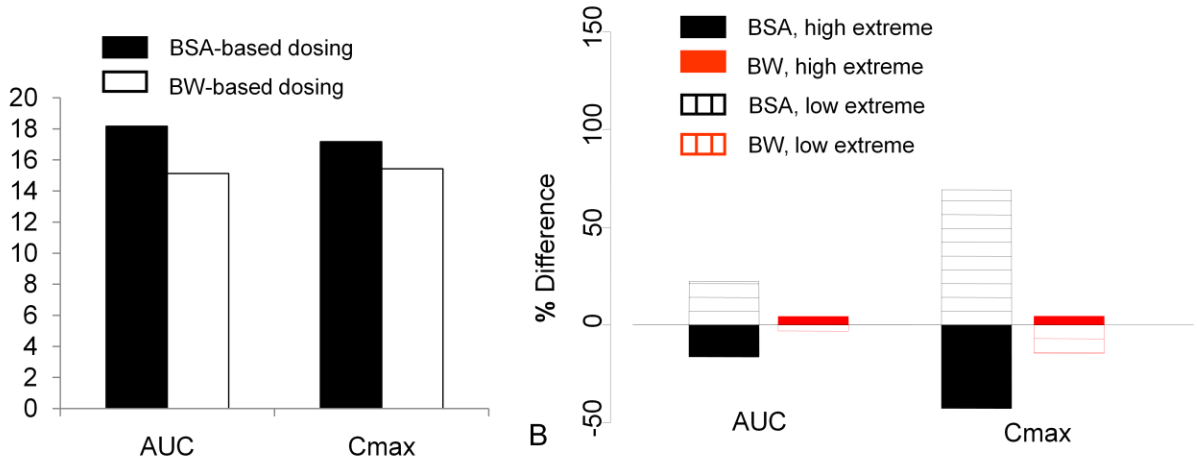

Figure 4-4. Comparison of BSA-based dosing and BW-based dosing at population and individual levels. A. Comparison of the inter-subject variability of simulated AUC and C_{max} of 1000 subjects after receiving a single BSA-based (solid bar) dose or BW–based dose(open bar) for cisplatin. B. Comparison of the deviation (% difference) of AUC and C_{max} for subjects with low (open bar) and high (solid bar) extreme body size (BW/BSA) measurements from the typical values AUC and C_{max} for subjects with median body size measurements after a BW-based dose (red) or BSA-based dose (black)

CHAPTER 5
CONCLUSION

Small molecule drugs, besides anticancer agents, are usually administered using a flat fixed dosing for the target patient population, while most small oncology drugs and biotherapeutic proteins and peptides are administered per body size, which was and may be still believed to provide less interindividual variability and optimized risk/benefit ratio. A previous study has evaluated body size-based dosing and fixed dosing were evaluated for 12 mAbs in terms of their population and individual performances in reducing intersubject PK and/or PD variability in adult patients.[56] This dissertation systemically evaluated therapeutic proteins and peptides besides mAbs as well as anticancer drugs via population PK/PD simulation studies in terms of interindividual PK and or/PD variability in adults. The objectives are: 1) systemically evaluate the performance of fixed dosing and body size-based dosing for therapeutic peptides and proteins in adults using population pharmacokinetics approach; 2) for the first time, utilize population pharmacokinetics approach to systemically evaluate intersubject variability for anticancer drugs; 3) provide a model based analysis method on dosing strategies for biotherapeutic large molecules and oncology drugs under development 4) recommend a dosing strategy for clinical trials conducted in adults at different stages of the development of therapeutic biologics and anticancer drugs.

The simulation analysis results demonstrated that body size-based dosing did not always result in less intersubject variability in drug exposure, and fixed dosing does not always presents higher intersubject variability than body size-based dosing. In fact, fixed dosing showed better performance for 12 of 18 evaluated biologics based on both AUC and C_{max} assessments. Similarly, fixed dosing showed better performance for half

of the evaluated anticancer drugs based on both AUC and C_{max} assessments. Therefore, the recommendations for adult FIH studies, fixed dosing is recommended because it offers advantages in ease of dosing preparation, reduced cost, and reduced chance of dosing errors. When sufficient data become available, a full assessment of body size effect on PK and/or PD should be conducted. The final dosing approach for Phase III trials in adults should be selected based on the established body size effect on the PK and PD, the therapeutic window of the therapeutic products, and other imprant factors that may affect the clinical outcomes.

Body size-based dosing of biologics is also discussed in pediatrics. Most of the studies in the current study showed that body weight or BSA dose adjustment produced comparable exposure for proteins and peptides in pediatrics and adults. However, not all pharmacokinetic studies result in promoting dosing adjustment. For basiliximab, a fixed dose of two 10 mg doses for patients less than 35 kg and a fixed dose of two 20 mg dose for patients more than 35 kg was recommended for pediatrics.[112] Some studies suggested dividing children into different groups as a dosing strategy. Children should not be treated as “small adults”. Changes in clearance of proteins and peptides in pediatric patients cannot always be explained by changes in body size. Simply adjusting dose linearly according to the body weight/BSA does not necessarily provide desirable exposure in pediatrics.

Overall, individualized dosing is not equivalent to body size-based dosing. Dose optimization using population PK/PD modeling and simulation can help to identify factors that contribute to the overall intersubject variability. A good dosing approach

should be made based on those factors and provide consistent exposure to the patient population and overall beneficial clinical outcomes in the target patient groups.

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BIOGRAPHICAL SKETCH

Rong Shi was born in October 1981, in P.R. China. In 2004, she received her bachelor's degree in Pharmaceutical Engineering from Zhejiang University of Technology, Hangzhou, P. R. China. The same year, she joined the graduate program at University of Missouri–Rolla (now Missouri University of Science and Technology), and received her Master of Science degree in Chemistry two years later. In 2006, Rong Shi enrolled in the graduate program in Pharmaceutics at University of Florida, under the supervision of Dr. Hartmut Derendorf to work on her Doctor of Philosophy. Rong has finished two internships during her Ph.D. study in the department of Clinical Pharmacology at Pfizer La Jolla, CA an Pfizer Groton, CT. Rong completed her Ph.D. in May 2011.