ABSTRACT: Biologics, specifically monoclonal antibody (mAb) drugs, have unique pharmacokinetic (PK) and pharmacodynamic (PD) characteristics as opposed to small molecules. Under the paradigm of model-based drug development, PK–PD/clinical response models offer critical insight in guiding biologics development at various stages. On the basis of the molecular structure and corresponding properties of biologics, typical mechanism-based [target-mediated drug disposition (TMDD)], physiologically based PK, PK–PD, and dose–response meta-analysis models are summarized. Examples of using TMDD, PK–PD, and meta-analysis in helping starting dose determination in first-in-human studies and dosing regimen optimization in phase II/III trials are discussed. Instead of covering the entirety of model-based biologics development, this review focuses on the guiding principles and the core mathematical descriptions underlying the PK or PK–PD models most used. © 2012 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 101:4367–4382, 2012

Keywords: ADME; pharmacokinetics; pharmacodynamics; pharmacokinetic/pharmacodynamic models; physiological model

INTRODUCTION

Biologics drug development has become the center stage for modern drug development because of its promise and potential. With numerous mergers and acquisitions, many big pharmaceutical companies have acquired their own biologic development platforms. Biologic drug and chemical drug differ in their size, where the molecular weight (MW) of small molecules is typically less than 1 kDa and the MW of biologics varies from a few kDa for recombinant proteins to 1000 kDa for some immunoglobulin (Ig) M antibodies. Compared with small molecules, biologics of greater MW such as monoclonal antibodies (mAbs) tend to have a slower absorption rate, confined distribution, and different mechanism of elimination resulting in long half-life ($t_{1/2}$). Most of these compounds are delivered parenterally and are generally designed for a specific target.

On the basis of the United States Public Health Services Act 42 U.S.C. §262(i), biologics are defined as “a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product, or arsphenamine, or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment or cure of a disease or condition of human beings.” Most of the biologics are large complex molecules/mixtures that are not easily identified or characterized. They are often generated from bacteria, yeast, insects, plants, or mammalian cells engineered with the gene of interest, or can be purified from natural sources. In this article, we are focusing on the biologics for therapeutic applications. Therefore, the term “biologics” is more restricted to those products produced by cutting-edge biotechnology. Therapeutic biologic products in this category are mainly mAbs, cytokines, and growth factors. This list of these products will no doubt rapidly expand with ever evolving biotechnology.
This review first provides an overview of the pharmacokinetics (PK) of biologics and first-in-human (FIH) dose selection to lay the foundation for the main purpose of this article: summarizing and discussing modeling and simulation approaches, along with their advantages and limitations, for biologic drug development.

PK OF BIOLOGICS

Monoclonal antibodies represent the majority of the therapeutic biologic products. They are characterized by their long serum half-life, high potency, and limited off-target toxicity. In addition, mAbs may be arguably the most complicated molecule to characterize as they are the largest molecules currently available (MW ~150 kDa) with complex secondary and tertiary structures. Therefore, the overview of PK characteristics of therapeutic biologic products is mainly based on the knowledge gained from mAbs research and development.

Absorption

Because of the mAbs’ size, polarity, and gastrointestinal (GI) degradation, their oral bioavailability is negligible. Therefore, mAbs are administered via a parenteral route such as intravenous (i.v.), subcutaneous (s.c.), or intramuscular (i.m.). Although i.v. is the most common route for delivering the biologics, s.c. or i.m. is a much more desirable alternative route of injection because of the ease of use in the clinical setting. Besides the conventional extravascular route, pulmonary delivery of biologics for systemic efficacy is of great interest as the lungs have a very large surface area and high perfusion rate. Inhaled insulin is a great example of delivering proteins via pulmonary inhalation. Even for mAb, attempts have been made to deliver via nebulizer. mAb can be administered intravitreally (e.g., ranibizumab) or intraperitoneally (e.g., catumaxomab) to promote regional/local effects.

The two primary pathways for systemic drug absorption are the convective transport through lymphatic vessels and diffusion across blood vessels. The exact mechanism of absorption following s.c. or i.m. administration of mAb is unknown, although the absorption is believed to occur mainly via lymphatic drainage. The absorption process via lymphatic flow is relatively slow compared with that via diffusion across blood vessels as for small molecule drugs, partly because of the limited lymph flow rate (/i.e., 1–2 mL/kg h) in the thoracic duct. On the basis of a recent internal survey of Biologics License Application (BLA) packages for 33 approved mAbs, the time to maximum serum concentration ($T_{max}$) for mAbs ranges from 2 to 14 days. MW also influences the rate of absorption following s.c. injection (more so for proteins with smaller MW). Again, this may well be due to the positive correlation between lymphatic uptake and MW. It should be noted that mAb are absorbed more slowly after s.c. or i.m. administration than other kind of biologics. In case of epoetin alpha, a 165-amino acid erythropoiesis-stimulating glycoprotein with a MW of approximately 30,400 Da, the $T_{max}$ is reported to be 5–24 h following after s.c. administration.

Following extravascular administration, therapeutic biologics undergo presystemic clearance (CL) (catabolism), which impacts the bioavailability. As of March 2011, the bioavailability of United States Food and Drug Administration (US FDA)-approved mAbs for therapeutic use following s.c. administration ranged from 52% to 80% based on our internal survey on their application packages (unpublished data). There are a number of potential influencing factors affecting the presystemic CL, such as extracellular degradation (e.g., via proteolysis), rate of endocytosis (e.g., receptor-mediated, fluid phase), and rates of recycling through interaction with the neonatal Fc-receptor (FcRn, also known as Brambell receptor). The underlying mechanisms of these influencing factors are not yet fully explored. Dose and concentration of the biologic products may also influence the bioavailability of the therapeutic biologics. Higher dose delivered at the injection site can saturate presystemic proteolytic degradation and may lead to increase in bioavailability. This sounds very appealing in further improving the delivery efficiency of biologics to the body. However, it is not feasible in reality owing to the limited solubility of IgG (~100 mg/mL) and the limited volume of each injection via s.c. or i.m. (2.5–5 mL). In case of omalizumab (150 mg/1.2 mL after reconstitution), more than one injection is needed to deliver a dose greater than 225 mg.

Distribution

Because of their size, hydrophilicity, and polarity, mAbs have a very limited and very slow distribution from blood to peripheral tissue by diffusion. Therapeutic biologics, especially mAb, distribute into peripheral tissues from blood by paracellular or transcellular movement.

Paracellular movement refers to the entry of antibody into the tissue interstitium via convective transport through paracellular pores in the vascular endothelium. This is thought to be the main route for the mAbs moving from vascular space to the interstitial space. It remains unknown to what percentage paracellular or transcellular contributes to the overall extravasation due to the lack of experimental data. The rate of distribution by convection is determined by the rate of fluid movement from blood to tissue, the size and morphology of the paracellular pores in...
the vascular endothelium (sieving effect) and the size, shape, and charge of the antibody.

The transcellular movement of mAb is mainly via endocytosis. The transcellular movement may occur in the vascular or interstitial spaces depending on which process is involved. The movement consists of three different types of processes: (a) receptor-mediated endocytosis, (b) phagocytosis, (c) fluid-phase pinocytosis (i.e., cells taking up proteins from the surrounding fluid space). Receptor-mediated endocytosis may occur either through the Fcγ receptor or through binding to cell surface antigens resulting in internalization. The fluid-phase pinocytosis/endocytosis occurs virtually in all cells. The fluid-phase pinocytosis is thought to be an important route for mAb entering into the endothelial cells. Once the mAbs are inside the cells, they undergo FcRn recycling pathway, which either transport mAbs to the interstitial spaces or back to the vascular space. This recycling pathway is also called FcRn-mediated transcytosis. In vitro data suggest that FcRn-mediated transcytosis may occur in vascular endothelial cells and the transport runs in a bidirectional manner.8–10

After penetration into the tissue, antibody distribution is mainly determined by convection and cell binding, although diffusion plays some roles as well. Because the diameter of lymphatic vessels is much larger than the diameter of paracellular pores, the rate of lymphatic drainage of mAb is greater than the rate of penetration via paracellular movement. Consequently, antibodies entering into the tissue are quickly drained away via lymphatic convection and the antibody concentrations in the interstitial tissue are lower than those in the blood.11–13

Interaction between the mAb and the target will also affect the distribution of the drug. Higher density of binding target in peripheral tissues and tighter binding to the target cell restrict mAb penetration deeper into tissues, subsequently resulting in limited distribution (i.e., binding-site barrier).14 Because of those processes, the distribution of mAb is somewhat nonhomogeneous. In contrast, the distribution of antibody fragments is less limited than that of the intact mAbs. For example, Fab fragments can better overcome the blood–tissue and binding-site barriers and penetrate deeper into tissues. Taken together, mAb distribution is confined mainly to the blood and interstitial spaces.

Molecular weight also affects the distribution of biologics. Smaller proteins have faster and more extensive distribution into tissues compared with mAbs. For instance, the steady-state volume of distribution ($V_{ss}$) of adalimumab (Humira; MW $\sim$148 kDa, Abbott Laboratories, Abbott Park, IL, USA) and abatacept (Orencia; MW $\sim$92 kDa, Bristol Myers Squibb, New York City, NY, USA) are 4.7–6.0 and approximately 6.3 L, respectively.15,16 In contrast, the $V_{ss}$ value of anakinra (MW 17 kDa) is approximately 10.1 L.17

It is noteworthy that $V_{ss}$ of mAbs derived from a noncompartmental analysis or mammillary compartmental analysis should be interpreted with caution. One key underlying assumption for the aforementioned analysis methods is that the concentration of the studied drug at the peripheral site of elimination is in rapid equilibrium with its concentration in plasma, thus the steady-state $V_{ss}$ is independent of the rate of elimination. It is likely that mAbs have significant elimination in peripheral tissues and their tissue/plasma concentrations may not be in rapid equilibrium because of the size and high affinity of target binding. This assumption violation may lead to erroneous underestimation of $V_{ss}$, where the underestimation may be more than 10-fold for a mAb with high binding affinity, high tissue-binding capacity, and target-mediated elimination pathways.1 To accurately estimate $V_{ss}$ of a mAb, the quantification of both tissue and plasma concentrations via a reliable bioanalytical assay is necessary.1 However, it would be unethical to obtain tissue/organ samples from humans. Hence, to accurately estimate $V_{ss}$ in human is challenging.

To characterize the PK profile of therapeutic biologics, population PK analysis is often employed. From a recent survey of published population PK analyses of mAbs, Dirks and Meibohm18 reported that the two-compartment model was the most commonly used PK model (24 out of 27 mAbs). For some mAbs administered s.c., a one-compartment model was used instead because the distribution phase of those mAbs was masked by their slow absorption processes.

**Metabolism and Elimination**

Unlike small molecule drugs, which are cleared primarily through hepatic metabolism and renal/biliary excretion, IgG elimination mainly occurs via intracellular catabolism (e.g., proteolytic degradation). In contrast, IgA antibodies are mainly eliminated by biliary secretion. On the basis of study results using physiologically based PK (PBPK) models, the contributions of various organs to the elimination of endogenous IgG were estimated to be 33%, 24%, 16%, and 12% for skin, muscle, liver, and gut tissue, respectively.19 Antibodies often exhibit two distinct catabolic pathways: (1) the Fc-receptor-mediated CL and (2) the target-mediated CL pathway.

**Fc-Receptor-Mediated CL**

This pathway is nonspecific and linear (first order). It is called nonspecific because Fc-mediated elimination is a common pathway for both endogenous IgG and exogenous therapeutic IgG mAb with a functional human Fc domain. Unlike target-mediated elimination, CL through this pathway is not affected by the
interaction between mAb and its pharmacological target. There are mainly two types of receptors involved in this CL pathway: FcRn and Fcγ receptors.

The impact of FcRn upon CL is relatively well understood. FcRn receptors play a protective role in IgG elimination. IgG entering into the endosome via fluid-phase pinocytosis binds to FcRn receptor and becomes shielded from lysosomal degradation. When the concentrations of IgG rise to a level that saturates available FcRn receptors, the elimination rate of IgG will increase because of a higher fraction of IgGs that will be transported to and degraded in lysosome. Indeed, differences in binding affinities between IgGs to FcRn result in differences in the terminal $t_{1/2}$ of IgG mAbs. For example, IgG1, IgG2, and IgG4 have similar $t_{1/2}$ of approximately 21 days. In contrast, IgG3 has a shorter $t_{1/2}$ of approximately 7 days. IgGs engineered from difference species have different affinities to human FcRn. As a result, rituximab, a murine IgG mAbs, has a $t_{1/2}$ of approximately 1 day in patients, dramatically different from normal human IgG $t_{1/2}$. Generally, the $t_{1/2}$ of IgG-based mAbs reported in humans increase with the degree of “humanization”, “fully rodent” (e.g., tositumomab, $t_{1/2}$ 2.7–2.8 days) < rodent/human chimeric (e.g., cetuximab, $t_{1/2}$ ~4.8 days) < complementarity-determining region (CDR)-grafted human (e.g., alemtuzumab, $t_{1/2}$ ~12 days) < “fully human” (e.g., adalimumab, $t_{1/2}$ 14.7–19.3 days). The chimeric mAbs may have the same elimination $t_{1/2}$ as humanized and human mAbs if they have the same human Fc framework, as FcRn is one of the critical components in regulating the serum $t_{1/2}$ of IgG antibodies.

Although saturation of the FcRn may occur resulting in capacity limited elimination, the doses of commonly prescribed therapeutic mAbs (most in hundreds of mg) are not likely to cause significant increases in human endogenous serum IgG concentrations (~5 g/L, 50–100 g in total) to the levels saturating the FcRn capacity. Therefore, the therapeutic mAb CL through FcRn recycling pathway is generally linear.

Another type of receptor bound to Fc region of IgG is Fcγ receptor. There are three subtypes of Fcγ receptors: FcγRI, II, and III. These subtypes of Fcγ receptors have varying cellular distributions, specificities, and affinities for the different IgG subclasses. For example, IgG1 affinity to FcγRI, II, and III are $1 \times 10^6$, $2 \times 10^6$, and $2 \times 10^6$ M$^{-1}$, respectively. Fcγ receptors are thought to play a role in CL of soluble mAb–antigen immune complexes or cells opsonized by the mAb. The significance and exact mechanism of Fcγ receptor-mediated CL are currently not well understood.

Target-Mediated CL Pathway

This mechanism of CL involves the interaction between a mAb and its pharmacological target. An example of target-mediated CL is receptor-mediated endocytosis. The binding of the mAb to a cell-surface receptor (e.g., Fcγ) triggers internalization and subsequent lysosomal degradation of the mAb–receptor complex. Target-mediated CL may also happen without involving cell-surface receptors. Formation of large immune complexes, a result of soluble substance binding with two or more antibodies, can lead to phagocytosis and rapid elimination of mAbs.

Target-mediated CL is saturable (i.e., capacity limited) because of the finite number of targets expressed on the cell surface. The nonlinear CL seen with many mAbs is thought to be due to the saturation of this pathway. Receptor concentration and distribution and the rate of receptor internalization and turnover determine the degree of target-mediated CL. Because this pathway is saturable, it is probably more important than Fc-receptor-mediated CL.

Changes in the number of targets as a result of a designed effect of mAbs inevitably will alter the CL of mAb going through target-mediated elimination, which supports the notion that the PK of biologics may be time dependent. Patients with higher CD19-positive cell counts or larger measurable tumor lesions at pretreatment had a higher CL of rituximab, a chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen, and lower rituximab serum concentrations. Similarly, patients with higher baseline shed antigen levels were more likely to have lower serum trough concentrations of trastuzumab. Furthermore, two multiple-dose studies reported that the $t_{1/2}$ of rituximab increased (i.e., decreased CL) with increased number of infusions, presumably because of the decreased number of CD20+ B cell following rituximab treatment. With such observations, the population PK model of rituximab was set as a two-compartment model with two CL components, a constant CL and a CL linearly decreasing over time [i.e., pharmacodynamics (PD)-mediated drug disposition]. In addition, a covariate analysis has identified that patients with higher CD19 counts at baseline had faster initial time-varying CL.

Generally, target-mediated drug disposition (TMDD) models have been commonly used in characterizing the PK and PK–PD relationships of given mAbs. Typical models consist of a series of equations for the concentrations of the free drug, the target, and the drug–target complex. The theoretical components of modeling the target-mediated CL (TMDD model) are further discussed in the latter part of this review.
Impact of Immunogenicity and Antidrug Antibody on the CL

Depending on the number of sites on the therapeutic mAb that the endogenous anti-mAb antibodies are directed against, changes in elimination rate due to immunogenicity may be either enhanced or reduced. Formation of neutralizing antibodies and immune complexes that trigger proteolytic elimination in reticuloendothelial system (RES) will cause an increase in CL. As reported, infliximab, a chimeric IgG1 mAb (composed of human constant and murine variable regions) specific for human tumor necrosis factor alpha (TNF-α), was cleared more rapidly in patients when human antichimeric antibodies (HACAs) were formed. Responders to infliximab treatment of ankylosing spondylitis had higher trough concentrations and lower incidence of HACAs (8%), whereas nonresponders had lower trough concentrations and higher incidence of HACAs (36%). A similar trend was observed in rheumatoid arthritis (RA) patients. Decreasing trough concentration with increasing of immunogenicity was also seen with golimumab, a human IgG1 mAb specific for human TNF-α. Patients with RA, psoriatic arthritis, and ankylosing spondylitis treated with golimumab 50 mg and methotrexate (MTX) had approximately 52%, 36%, and 21% higher mean steady-state trough concentrations of golimumab, respectively, compared with those treated without MTX on board. The presence of MTX reduced antigolimumab antibody incidence from 7% to 2%. In contrast, an immune complex that does not trigger RES may become a depot for the therapeutic proteins and subsequently result in increased/prolonged systemic exposure. This was observed more often in cytokines and hormones.

The degree of humanization of mAbs determines the incidence of immunogenicity because the immunogenicity is associated with the percentage of foreign sequence in the mAbs. In chimeric antibodies, approximately 67% of the primary sequence of the antibody was reported to be derived from human, and 33% derived from rodent sequence. In CDR-grafted antibodies, the primary sequences derived from human and rodent were reported to be approximately 95% and approximately 5%, respectively. In general, the influence on the immune response is inversely dependent on the grade of humanization of the antibody. In the case of tositumomab, the incidence of conversion to human antimouse antibody (HAMA) seropositivity was 70% in 76 previously untreated patients with low-grade nonHodgkin’s lymphoma who received the tositumomab therapeutic regimen. Chimeric, humanized, and fully humanized antibodies were reported to have incidence of immunogenicity from <1% to approximately 10%. Note, human and fully human sequence-derived antibody molecules still could carry high degree of immunological risk. Immunogenicity rates ranging from 5% to 89%, which varied depending on the disease and the therapy, were reported by administrating adalimumab to a subset of patients.

Other factors that affect the incidence of immunogenicity are duration of therapy, dose, and route of administration. The incidence increases with longer duration of therapy, and sometimes, following reintroduction of the treatment. Of the 230 chemotherapy-relapsed or refractory patients in the clinical studies, the cumulative incidences of HAMA seropositivity of tositumomab at 6, 12, and 18 months were 6%, 17%, and 21%, respectively. In the case of infliximab, a higher incidence of antibodies to infliximab was observed in Crohn’s disease patients receiving treatment after drug-free intervals >16 weeks. Contrary to conventional thinking, clinical data suggest that immunogenicity decreases with increase of dose administered. However, this phenomenon may be exaggerated by assay interference where the presence of higher quantities of drug in the sample affects the ability of the assay to detect antidrug antibodies. Higher immunogenicity is possible following administration of therapeutic biologics by the s.c. and i.m. routes than by the i.v. route, as phagocytes and NK cells are found under skins and in mucosal epithelia where they are responsible for the initial innate immune responses. However, clinical data do not firmly support this hypothesis in human.

Renal Elimination

Limited data are available to examine renal elimination on the disposition of therapeutic proteins. In principle, intact immunoglobulin is not filtered by the glomerulus owing to its large MW. Smaller proteins, for example, Fab and Fv, are filtered. However, most of the filter Fabs/ Fvs are reabsorbed and/or metabolized by proximal tubular cells of the nephron.

Renal impairment study of kineret, a nonglycosylated form of the human interleukin (IL)-1 receptor antagonist with a MW of 17 kDa, revealed that plasma CL was reduced by 16%, 50%, and 70% in mild, moderate, and severe renal impairment patients, respectively. Consequently, dose modification is required in severe renal impairment patients. Renal impairment study of peginterferon alfa-2b with a MW of 31 kDa, found that its CL decreased by 17% and 44% in moderate and severe renal impairment patient, respectively, and thus dose reduction was recommended. In contrast, population PK analysis on ranibizumab, a recombinant humanized IgG1x isotype mAb fragment with a MW of 48 kDa, showed no notable change in PK in renal impaired patients. For mAbs, the current consensus is that studies to evaluate the effect of renal impairment...
are not required. However, for therapeutic proteins with MW less than 69 kDa, renal elimination becomes important, thus a renal impairment study is generally warranted.

**CL Models**

Many efforts have been made to model the disposition of mAb because the model can be subsequently used to predict clinical response as well as to estimate key PK parameters such as CL. Compartmental PK models with linear, nonlinear, or parallel linear and nonlinear CL pathways have been well explored. When enough data are available, a TMDD model is also researched. A two-compartment model usually fits the mAb PK data well, although a one-compartmental model has been applied to efalizumab and ustekinumab. From published population PK analyses on 27 therapeutic mAb,18 the most frequently used PK model is a two-compartment model with linear CL, which is inconsistent with the mechanism of mAb elimination. Linear CL is possible when the target-mediated CL pathway is saturated with a high dose of mAb. Consequently, the nonsaturable linear Fc-mediated CL becomes the major determinant. Alternatively, nonlinear or TMDD models have been commonly employed to describe mAb CL. For example, population modeling work for sibrotuzumab, matuzumab, and efalizumab have employed TMDD models.18 The structure model for these mAbs is a two-compartment model incorporated both linear and nonlinear CL terms.

**STARTING DOSE SELECTION FOR FIH STUDIES**

The initial dose selected for a FIH study should result in no pharmacological or toxicological effect. A safe starting dose may be better estimated by predicting human PK profiles by PK parameters post interspecies scaling on parameters obtained from relevant animal models. Allometric scaling, (semi-) mechanistic-based PK, and PBPK modeling are some examples of the methods used in interspecies scaling to predict human PK.

The application of allometric scaling to mAb drugs has been extensively reviewed by Mahmood. In general, the allometric approach can provide reliable prediction if the compound is a small protein (<40 kDa), excreted primarily through renal CL, or a mAb against a soluble target (e.g., mAb against soluble target IL-13). Often times, three different species are needed for a reliable prediction. However, for mAbs against a membrane bound target, this approach may become challenging and unreliable. This is because the assumptions underlying allometric scaling include the absence of nonlinear PK and species-specific CL. The CL of a mAb is affected by the interspecies difference in FcRn (affinity to the receptor, expression of FcRn, and baseline IgG level), target-mediated disposition (target expression, target antibody affinity, target turnover, and Fcγ-receptor binding and activity), and renal CL differences for fragments. Interspecies differences in volume of distribution in central and peripheral compartments, the fraction of uptake, and mAb binding to tissue sites all affect the accurate estimation of the volume distribution of a mAb. Thus, for therapeutic proteins that target cell-surface receptors, a more comprehensive approach such as mechanistic PK modeling may be employed.

Physiologically based PK models can address the concerns of effects of saturable processes (e.g., target-mediated binding, species differences in FcRn) upon PK as well as the influence of a variety of factors (e.g., antigen expression, antibody affinity) on the tissue selectivity of mAb elimination. However, PBPK models are not only mathematically difficult, but also time consuming to construct. The biggest barrier for establishing a PBPK model is the lack of tissue concentration data, parameter availability, or parameter identifiability.

An algorithmic approach extrapolating animal data to human is one of the common methods for initial dose determination (Fig. 1). The 2005 US FDA Guidance for Industry on estimating the maximum recommended starting dose (MRSD) of a new molecular entity in healthy adult subjects presents an outline on how to use this approach. The first step of this approach requires a determination of nonobserved adverse effect level (NOAEL) in the most sensitive or most clinically relevant species. Then, a body surface area conversion factor (BSA-CF) is applied to convert NOAEL to a human equivalent dose (HED). Noteworthy, BSA-CF-based dose conversion is required for small molecules but not required for most of the biologies. The MRSD is determined by applying a safety factor specifically to the HED from the most relevant species. The default value for this safety factor is set at 1/10th the HED, although this may be adjusted upward or downward with good justification. Finally, depending on the toxicity profile of the investigational compound, additional information such as pharmacological active dose may be factored in to determine the dose. The 2005 US FDA Guidance did not specify in providing guidance for biologics starting dose selection. However, the rationale provided in the guidance in general is applicable to large molecules like mAb. Of special note, mAbs pose some unique challenges in FIH dose selection and study design, not only because of their MW, but also because of their human-specific nature. Mainly, adequate nonclinical in vivo toxicological testing may be impossible because of the lack of cross-reactivity. Even for cross-reactive mAbs, the NOAEL obtained in test species may not be relevant to human testing.
An alternative guidance for FIH dose selection is using the minimum anticipated biological effect level (MABEL) approach, which incorporated pharmacological effect and was initiated by European Medicines Agency for high risk biologics after the TGN1412 incident. The MABEL dose approach is specifically important when dealing with biologics with cellular receptor targets, for which binding by a therapeutic protein (e.g., mAb) may trigger intracellular pathways through receptor clustering (e.g., cytokine release). Estimation of human MABEL dose depends on exposure–response data from in vitro and/or in vivo studies involving human cells or animal species. Animal–human differences in affinity/potency, exposure, and distribution and the anticipated duration of effects all need to be accounted for when calculate the MABEL dose. For instance, the MABEL dose can be determined to be a dose resulting in a maximum human drug serum concentration less than the concentration corresponding to 20% of the maximal drug bioactivity (IC20, assumed to be 1 μg/mL for illustration) identified from an in vitro experiment. The FIH dose can be a dose that will render a maximum drug concentration (Cmax) of 1 μg/mL. As illustrated in Figure 2, the 0.1 mg/kg every other week dosing regimen can be selected as the FIH dose because its simulated Cmax equals to 1 μg/mL. Noteworthy, it is assumed in this case that the human PK parameters of the drug candidate are known (e.g., from human PK studies conducted outside USA). In addition, the drug PK exhibits TMDD characteristics as revealed by the nonlinear PK exposure across different doses (i.e., 0.1 vs. 15 mg/kg). If human PK data are unavailable, human PK simulation may not be unreliable. Under this circumstance, a dosing regimen resulting in a maximally possible Cmax of 1 μg/mL (e.g., assuming at the absence of TMDD) can be used as the FIH dose with good scientific justifications.

A recent example of using modeling and simulation approach to guide FIH MABEL dose selection is the FIH dose determination of an antibody compound targeting a blood cell surface receptor. The antibody acted as both an antagonist of proliferation and a facilitator of antibody-dependent cellular cytotoxicity, causing depletion of the target blood cell subtype. The MABEL dose was defined by target cell depletion. A mechanistic model for human PK and PD (target cell depletion) including receptor occupancy (RO) and target blood cell depletion was constructed based on monkey and in vitro data. The model was first built and fitted to describe monkey data from a dose-range finding study including study endpoints of PK, RO, and target blood cell depletion over time. The dose ranging study included three single i.v. dose levels with six monkeys in each dose group. The same model structure was subsequently used for human PK–PD model excluding the unidentifiable parameters in human. The model allowed simulation of a worst-case scenario such as target cell depletion. All other model
parameters were adapted to the human cases. For example, binding affinity was scaled reflecting species cross-reactivity; in vitro EC$_{50}$ values generated from monkey cells were replaced with EC$_{50}$ from human cells. Allometric scaling principles, for example, scale by body weight, were also applied to the parameters when appropriate. The final model was used for simulating human PK dose–response for three single i.v. dose. PD responses such as target cell depletion over time were also predicted to guide MABEL dose selection.

MODEL-BASED DRUG DEVELOPMENT FOR BIOLOGICS

Frequently used PK–PD Models

Mechanism-Based PK–PD Models

Mechanistic models provide unique advantage in understanding drug efficacy and safety by mathematically describing the underlying biological and pharmacological processes as realistically as possible. Biologic drug development starts from the selection of a target responsible for disease pathophysiology. With a chosen disease target, various drug candidates can be developed based on the targeting mechanism of action. With this regard, the most frequently used mechanism-based models are to simultaneously describe the dynamics of drug disposition and target suppression.

About half of the mAb drugs on the market exhibit nonlinear PK characteristics when the concentration falls below certain threshold level.$^{52}$ The first issue to address the observed nonlinear PK phenomenon inevitably leads to the study of target capacity in impacting drug CL, the TMDD. From PD perspective, TMDD also serves as the mostly used PK–PD model to describe target suppression by revealing the target concentration–time profile. As the typical empirical TMDD model. It is a challenge to have the right assay and experiment set up in a timely manner given the tight drug development timelines. Using the simplified TMDD models thus has become a practical choice.

By making additional assumptions, simplified TMDD models come with a tradeoff. For example, the QSS model assumes that the drug–target association process is fast enough to overwhelm the other processes including drug dissociation/distribution/elimination and drug–target/target eliminations $[k_{on}C \times R - (K_{int} + k_{off}) \times RC = 0]$. In addition to the QSS assumption, the RB models assume that $K_{int}$ is negligible from the system $[k_{on}C \times R - k_{off} \times RC = 0]$. The Wagner approximation assumes that the total target concentration is a constant $(R + RC = A \text{FixedValue})$ and thus the differential equations associated with the target concentration can be reduced to one. The MM model becomes similar to QSS model if the free drug concentration overwhelms the total target concentration or the drug–target complex is constant under drug binding saturation. As proposed by Gibiansky and Gibiansky,$^{52}$ it cannot be applied to describe the systems when free and total drug concentrations differ significantly.

The leading opinion recommends always using the most parsimonious TMDD model when appropriate assumptions can be made as supported by experimental findings.$^{53}$

\[
V_C \frac{dC}{dt} = \text{Input} - (K_{12} + K_{el}) \times V_C \times C + K_{21} \times X_T - k_{on}C \times R + k_{off}RC
\]

\[
\frac{dX_T}{dt} = K_{12} \times V_C \times C - K_{21} \times X_T
\]

\[
\frac{dR}{dt} = k_{syn} - K_{deg}R - k_{on}C \times R + k_{off} \times RC
\]

\[
\frac{dRC}{dt} = k_{on}C \times R - (K_{int} + k_{off}) \times RC
\]
**PBPK Models**

Biodistribution of drug over time is of critical interest in PK and it is referred to as PBPK models. All of the published models are whole-body models that view the human body as a closed circulatory system composed of interconnecting organs or tissues via blood or lymph flows. In the PBPK models, all of these organs and tissues are compartmentalized and mass balance differential equations are used to characterize the drug transfer against time among these compartments. For each compartment, the mass balance input is the inbound blood flow, whereas the output is the outbound blood and/or lymph flows entering or leaving the corresponding tissue or organ, respectively. There are three underlying guiding principles associated with the whole-body PBPK models. First, the sum of the inbound flow rates equals the sum of outbound flow rates. Second, the sum of the non-portal venous flow rates equals the lung blood flow rate. Third, the portal flow rate equals the arterial flow rates from the GI tract, spleen, and pancreas. Here, the portal vein refers to the hepatic portal vein and the hypophyseal portal system is currently not in consideration in PBPK models. Compartment lumping is a common technique used to simplify the system based on the nature of the problem.

The essence in difference among the various types of PBPK models for mAb or proteins reside in how drug transfer/penetration occurs at the blood and tissue barrier/boundary, referred to as the endothelial or endosomal space in PBPK literatures. The evolving view of mAb transport in these boundaries reflects an advancement of knowledge and slight difference in opinions.

The first PBPK model was developed by Covell et al. in 1986 to describe the whole-body PK of IgG1 mAb and its fragments [i.e., F(ab')2, and Fab'] in mice. The uptake process for mAb or its fragment was mainly described by passive diffusion or convection. The drug elimination rates from various organs for mAb and its fragments were estimated individually and served as the main parameter to account for the PK profile differences. Baxter et al. advocated using the concept of “two-pore formalism” to describe the drug transport at the blood and tissue boundary, via both passive diffusion and convection. The two-pore formalism was originally proposed by Rippe and Haraldsson to quantitatively describe the transcapillary exchange in interested organs. In the filtration mode under the two-pore formalism, macromolecules (i.e., mAb or other therapeutic proteins) or small molecules cross the blood–tissue boundary, the blood vessel or the endothelial space, through large pores (250 Å in diameter), whereas only small molecules cross the boundary through small pores (45 Å in diameter). Under isogravimetric condition (no unidirectional net flow), drug transport from blood to tissue via convection will be viewed as nonexistent by conventional models. However, for the two-pore formalism, a recirculation of fluid can be formed with large pore serving as the transport channel from blood to tissue and small pores as the channel from tissue to blood. This fluid recirculation can still lead to macromolecular extravasation. Fluid recirculation is the major distinction between the two-pore formalism model and the first PBPK model developed by Covell et al.

Following a prototype model that first took FcRn binding into account by Ferl et al., Garg and Balthasar have improved the PBPK model by considering the FcRn binding for all organs/tissues. Although the model proposed by Garg and Balthasar has been conventionally referred to as one-pore model, it does not necessarily mean that the model has less flexibility or efficiency in describing the mAb PK. Overall, the one-pore model is characterized by the following features: First, the convection flow is unidirectional, from blood to tissue. It means a zero convection transport of mAb under the isogravimetric condition. Second, it ignores the active diffusion process given the limited amount that can be transported via this process because of the large size and surface charge associated with mAbs. Third, it takes the process of mAb endocytosis to vascular endothelial cells into account, which has been extensively reviewed in our earlier section. Fourth, the FcRn binding process in the endothelial space is also mathematically described in the one-pore model. That is, the FcRn bound mAb can be recycled back either to the blood/vascular space or to the interstitial space, whereas the unbound mAbs are subject to elimination via intracellular catabolism. The third and fourth features represent the major distinctions between the one-pore model and the two-pore model. In the authors’ opinion, the fourth feature of the one-pore model implies a bidirectional transport of mAb between the vascular and the interstitial spaces. In contrast, the two-pore model structure only allows for a one-directional extravasation process. It is also the authors’ opinion that the disadvantage associated with one-pore model by ignoring the fluid-recirculation-mediated drug transport, which means a zero mAb transport via convection under isogravimetric condition for the one-pore model, can be at least partially compensated by the active endocytosis-mediated drug transport that features this model. The effect of FcRn-mediated protection on mAb PK had been verified in mice either by inhibiting the FcRn with i.v. immunoglobulin treatment in wild mice or comparing mAb between wild and FcRn knockout mice. These findings definitely have given weight to considering FcRn-mediated mAb protection when developing mAb PBPK models.
fact, the latest version of the two-pore model has also taken both the endocytosis process and the FcRn-mediated mAb recycling features into account. However, the new version of two-pore models does not consider FcRn-mediated transport as opposed to one-pore model.

Technically, the set of representative equations associated with the one-pore model is demonstrated as follows for a generic organ.

\[
\frac{dC_v}{dt} = [FR \times R_2 \times (1 - \text{fu}) \times V_E \times C_f] \\
- (R_1 \times C_V \times V_F - [(1 - \sigma_V) \times L \times C_V] \\
- (Q - L) \times C_V \\
\frac{dC_E}{dt} = (R_1 \times C_V \times V_F) - (\text{fu} \times CL \times C_E) \\
- [(1 - \text{fu}) \times R_2 \times V_E \times C_E] + R_1 \times C_1 \times V_1 \\
\frac{dC_I}{dt} = [(1 - \sigma_V) \times L \times C_V] \\
+ [(1 - FR) \times R_2 \times (1 - \text{fu}) \times V_E \times C_E] \\
- [(1 - \sigma_L) \times L \times C_I] - R_1 \times C_1 \times V_1 \\
\]

with

\[
f\text{u} = 1 - \frac{1}{2 \times C_{E}^{\text{Total}}} \times \left[ (K_d + nPt + C_{E}^{\text{Total}}) \\
- \sqrt{(K_d + nPt + C_{E}^{\text{Total}})^2 - 4 \times C_{E}^{\text{Total}} \times nPt} \right] \\
C_{E}^{\text{Total}} = C_{E}^{\text{Endogenous}} + C_{E} \\
\]

where \( C_v \) represents the total mAb drug concentration in vascular space, \( C_E \) the total mAb drug concentration in endothelial space, \( C_I \) the total mAb drug concentration in interstitial space, \( V \) the total organ volume, \( Q \) the plasma flow rate, \( L \) the lymphatic flow rate, \( V_V \) the vascular space volume, \( V_I \) the interstitial volume, \( V_E \) the endothelial volume, FR the recycling fraction of FcRn bound mAb, CL the clearance of antibody from endothelial space, \( R_1 \) the endothelial uptake rate, \( R_2 \) the endothelial return rate, fu the unbound antibody fraction, nPt the FcRn concentration in organ, \( K_d \) the dissociation constant for mAb–FcRn binding, \( \sigma_L \) the lymphatic reflection coefficient, \( \sigma_V \) the vascular reflection coefficient. \( C_{E}^{\text{Endogenous}} \) is the endogenous mAb concentration.

Physiologically based PK models have been used for biologics PK extrapolations and understanding their delivery. For example, because blood flow and body composition varies with sex, age, and race, PBPK modeling is a powerful tool for investigating the influence of physiological conditions and drug-specific parameters on PK. Therefore, PBPK models can assist PK extrapolations from animal to human, from adult to infant, from healthy volunteers to patients by taking the pathophysiological changes associated with the disease into account. In addition, of particular interest is the understanding of biologics distribution at interested organs/tissues based on the presumed mechanism of drug action. Characterization of the relationships between drug exposure and efficacy/adverse response can be better served with the advancement of PBPK methodologies. Relationship between drug exposure on site of actions and its corresponding response gives insight about dynamics of drug efficacy and safety. In the past decades, radio-imaging technologies have greatly helped the quantification of drug exposure in tumor. Such technology advancement can greatly assist further development of the next generation of PBPK models.

Development in Quantitative Methods that can be Applied in TMDD and PBPK Models

In their current status, the conventional TMDD/PBPK models are associated with several limitations. First, for drug concentration as measured from the central compartment, the current PBPK models do not differentiate drug molecules that have visited the site of interest from those which have never visited the site. Second, the conventional models do not recognize drug molecules that follow a particular traveling route (i.e., pass through a series of organs with particular order). Potentially, the traveling route of a drug can be of great importance to predict efficacy. For example, bispecific T cell engager (BiTE) molecules are designed as biologics that will engage T cell to attack tumor cells to exert cytotoxicity. Therefore, it will be of particular interest to evaluate the fraction of BiTE molecules following a route of s.c. injection site → lymphatic system → blood circulation → tumor site.

To counter the model limitations as discussed above, the classically available approaches, such as the ones using continuous-time Markovian models with finite number of states to describe drug kinetic data as developed from statistical or engineering fields, cannot be directly adapted to PBPK models because they are oriented with different purposes. To meet the needs, new methodology advancements have been made recently. In a linear Markovian system, the systemic calculation of probability functions for a drug molecule to travel through a defined route and the probability density functions (PDFs) for a drug molecule to stay in interested compartments with/without certain residence times can be calculated by the Matrix Convolution Expansion approach. This approach provides closed form solutions for transitional probability function, and the PDF of residence time. Matrix Convolution Expansion reveals that the drug time–concentration...
function can be decomposed into the summation of a series of component functions associated with distinct drug molecule traveling routes. The key findings are represented in the following paragraphs.

Theorem 1. In a linear multicompartment system, the probability \( P_{ij}(t) \) for a drug molecule to travel from compartment \( i \) to compartment \( j \) after an elapsed time \( t \), is the element in the \( i \)th row and \( j \)th column of the \( P(t) \) matrix where

\[
P(t) = \sum_{i=1}^{\infty} P^i(t) = \sum_{i=1}^{\infty} [(R(t)K)^i * sR(t)]
\]

Here, \( P^i(t) \) is the probability matrix for a drug molecule to travel from one compartment to another with \( i \) intercompartment transitions after an elapsed time \( t \), where

\[
K' = \begin{bmatrix}
K_{11} & \ldots & K_{1n} \\
\vdots & \ddots & \vdots \\
K_{n1} & \ldots & K_{nn}
\end{bmatrix} - \text{Diag}(K_{11}, \ldots, K_{nn}) = \begin{bmatrix}
0 & \ldots & K_{1n} \\
\vdots & \ddots & \vdots \\
K_{n1} & \ldots & 0
\end{bmatrix}
\]

and \( R(t) = \begin{bmatrix}
P_{11}(t) & \ldots & 0 \\
\vdots & \ddots & \vdots \\
0 & \ldots & P_{nn}(t)
\end{bmatrix} \) with \( P^i_{ij}(t) = e^{-\sum_{k=1}^{n} K_{kk} t} \).

Here, \( i \) represents \( i \) times of intercompartment transitions and \( n \) is the number of total compartments. Matrix convolution refers to convolution product of two matrices. It is performed by switching the multiplication operations to convolution operations in each element of the outcome matrix resulted from conventional matrix multiplication. The definition of convolution "\(*\)" is given by \( f(t) * g(t) = \int_0^t f(t-t)g(t)dt \).

\[
\int_0^t \ldots \int_0^t f(t)dt \times \ldots \times f(t) \text{ is abbreviated as } f(t)^r \text{ and } r \text{ is defined as the convolution power. By definition, } P^k_{ij}(t) \text{ is the element of function matrix } P^k(t) \text{ in its } i \text{th row and } j \text{th column with } k \text{ representing } k \text{ times of intercompartment transitions. It is the probability of a drug molecule that is initiated from the compartment } i \text{ and has traveled to the compartment } j \text{ after an elapsed time } t \text{ with exactly } k \text{ intercompartment transitions in all of its possible traveling routes. Note that, for any arbitrary traveling route, say } 1 \rightarrow i \rightarrow j \rightarrow k \rightarrow 1, \text{ its corresponding transitions coefficients must be } K_{1i}, K_{ij}, K_{jk}, K_{kj} \text{ and its corresponding convolution operations must be } P'_{11}(t) * P'_{12}(t) * P'_{2j}(t) * P'_{jk}(t) * P'_{kj}(t). \text{ The same procedures can be repeated to obtain the probability functions associated with other route of interest.}

The PDF, for joint residence times associated with certain traveling route in a multicompartment system, can also be conveniently calculated by using the matrix convolution operations. A standard procedure to calculate residence times in a linear compartment system can be found in previous publication.

In a nonlinear system, the matrix convolution process can still be utilized for probability function and PDF calculations. However, all these calculations involve multilayer integrals. Usually an \( i \)-layer-integral calculation is needed for a probability function corresponding to \( i \) times of intercompartmental transitions. Therefore, it is a bigger computational challenge than in linear system because the multilayer integrals for linear systems can be simplified by convolution operations whose calculations can be further facilitated with Laplace transformations, whereas no short-cut operation is available in nonlinear systems. With such regard, a new method has been developed to circumvent the challenges presented by multilayer integrals in nonlinear systems,\(^20\) which is named the compartment expansion method.

In general, these new quantitative methodologies can greatly enhance the capabilities of current TMDD/PBPK models by offering new insights about drug mechanistic action by following a particular route among human organs and evaluating the residence time at the action site. An application case of using compartment expansion method to understand antibody absorption process post s.c. or i.m. administration has been recently accepted for publication.\(^21\)

Meta-Analysis to Assist Trial Design and Drug Development for Biologics

Biologics, especially mAbs, are developed against a specific disease antigen, cell-surface receptor, or a soluble ligand. Therefore, mAbs designed to neutralize the same target can lend each other key message and experience in their development. Gobburu and Lesko\(^22\) advocated using quantitative disease-drug-trial models as a powerful solution to improve pharmaceutical R&D productivity.\(^22\) In their opinion, the disease and trial models are independent of the drug or drug candidate, but the drug models are not. Highly important to industry, the commercial viability for a drug candidate depends very much on its competitive edge over other drugs regarding treatment effect size, time-to-event characteristics, safety profile, and eventually the benefit–risk ratio.

The meta-analyses of approved drug dose (exposure)–response have served as perfect examples on how to use available clinical information of approved mAbs to assist the development of new mAbs with the same target or with the same mechanism of action. Model-based parametric models can be built across all relevant trials to study disease progression under placebo treatment, biomarker response, efficacy, and safety responses following the active treatments. It can offer a head-to-head comparison of drug...
potencies, guide on finding the optimized treatment regimen, evaluate the existence and relationship between biomarker and clinical endpoints, and give insight in designing better trials. Prominent examples of meta-analysis for small molecules include modeling the effects of age, dosage, and duration of parathyroid hormone treatment on bone mineral density changes (15 trials),\(^73\) evaluating potential correlations of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B levels with the risk of cardiovascular events among patients treated with statin therapy (eight trials),\(^74\) and modeling anticoagulants effect for venous thromboembolism prevention after hip/knee replacement (89 trials).\(^75\) Typically, the published data sources provide only study-level data can be found in the published trial results. The technical challenges to assemble high-quality data for meta-analyses include publication bias, incomplete description of trial design and methods, potential autocorrelation among response data within each study, and the appropriate incorporation of patient-level data if available.\(^76\)

Latest meta-analysis performed for biologics against RA was based on the percentage of patients attaining American College of Rheumatology (ACR) 20, 50, and 70 responses. In this case, data were extracted from 50 randomized controlled trials representing 21,500 patients for nine biologics with five mechanisms of action. The analysis revealed that all TNF inhibitors (anti-TNFs) (i.e., golimumab, infliximab, adalimumab, etanercept, and certolizumab) would have similar dose–response relationship for ACR 20/50/70 if difference in potency were accounted. However, dissimilar dose–response relationships were found between anti-TNFs and other biologics, which may indicate their differences in efficacy that require different strategy for dose titration.\(^76–79\)

Similar analyses have been conducted for anti-TNFs (i.e., infliximab, adalimumab, and etanercept) along with the IL-1 inhibitor anakinra for the treatment of RA. A mixed effects logistic regression model that adjusted the log odds ratio for study-level prognostic factors was used to compare both biologics efficacy and safety.\(^76–79\) The analysis stated that the anti-TNFs as a class were not different from each other in treatment effects and the apparent differences in the randomized trials among TNF-\(\alpha\) antagonists came as a result of differences in prognostic factors. A network meta-analysis of randomized controlled trials of biologics (i.e., abatacept, adalimumab, anakinra, etanercept, infliximab, and rituximab) for RA based on Cochrane reviews was also conducted and an indirect comparison of the treatment effects among these biologics was made based on mixed-effects logistic regression.\(^76–79\) This analysis found that anakinra was less effective than adalimumab and etanercept, and etanercept was safer than adalimumab, anakinra, and infliximab. Because of the differences in study population characteristics among the trials, caveat was given that the findings must be interpreted with caution and longer comparative studies to provide data about the relative and absolute benefit and safety of biologics during various stages of RA (early, established, and late) are still needed to draw the definite conclusion.

The common considerations used to develop meta-data parametric models are the differences in patient demographics, baseline disease status/biomarker quantity, study-level covariates, comediations, trial characteristics, and variability structures. Logistic-\(E_{\text{max}}\) model is viewed as the most used one which can be illustrated as follows for a binary clinical outcome.

The probability of a patient achieving clinical response in a treatment arm \(j\) of a trial \(i\), \(P(\text{event})_{ij}\), can be modeled as a function of a placebo response in that trial \(E_{0j}\) and a dose–response relationship for the treatment effect \(g(x)\) that includes covariates \(X_{ij}\) and trial-specific model parameters \(\theta_{i}\) as follows:

\[
P(\text{event})_{ij} = f\left[ E_{0, i} + g(Dose_{ij}, X_{ij}, \theta_{i}) \right]
\]

Here, \(f\) assumes values of 0–1 and is the inverse logit transformation. The placebo level contains the inter-trial variability as described by:

\[
E_{0, i} = E_0 + \eta_i
\]

Here, \(E_0\) is a fixed effect for each trial and \(\eta_i\) is a trial-specific random effect. The dose–response relationship for randomized treatments can be characterized as follows:

\[
g(Dose_{ij}) = \frac{E_{\text{max}, i} \times Dose_{ij}}{Dose_{ij} + ED_{50, \text{Drug}, i}}
\]

Here, \(E_{\text{max}, i}\) is the maximal drug effect. A different \(E_{\text{max}}\) should be used if a different mechanism of action is to be modeled. A similar \(E_{\text{max}}\) can be assumed for drugs with the same target or with the same mechanism of action. \(ED_{50}\) is the dose required to achieve 50% of \(E_{\text{max}}\) and is drug specific. Linear models can be used on a case-by-case basis. Appropriate layers of error structures should be added if more than one clinical endpoints are considered for the same drug.\(^1,54\)

**Empirical and Semi-Mechanistic Models**

Empirical exposure–response models have received their popularity mainly because of practical conveniences. This is mainly because many of the downstream actions after drug binding to its target remain unknown. In this regard, empirical exposure–response models used for small molecule can be
Figure 3. A PK–PD/clinical response modeling and simulation cycle
directly adapted to characterize the drug effects of biologics.

Pharmacokinetic and pharmacodynamic models can be used in optimizing dosing regimen selection and trial design via simulations. As depicted in Figure 3, a PK–PD/clinical response modeling and simulation cycle is an iterative approach to reaching a high-quality decision in designing phases I–III trials. In a sense, models to describe disease progression can be partially considered as empirical. For example, tumor growth rate has been assumed to be exponential at the beginning and linear at a later stage in disease progression models. This is purely because of the limited understanding of tumor physiology and the biological transitions associated with its growth. Many modeling assumptions, supported by observations instead of mechanistic understanding, have been made to model disease progression in various therapeutic areas and for both large and small molecules. The review of these models can be found in a vast of literature and is out of the scope of this paper. The regulatory agencies like US FDA encourages the drug developers to discuss with regulators on using these types of models in the clinical development at the End of Phase 2A meetings.

CONCLUSION
Biologics possess unique and complex PK characteristics when compared to small molecules, mainly due to their relatively larger size and biological/biophysical characteristics such as target binding and FcRn-mediated recycling for mAbs. These characteristics have been mathematically described by two types of quantitative models, the mechanism-based TMDD models and the PBPK models. TMDD and PBPK models have not only been used to predict PK characteristics of biologics, but also shed light on the time course of target suppression and action site concentration of a biologic. Although PBPK models are used more for exploratory purpose, TMDD models have been used to facilitate and optimize study designs in different stages of clinical development, such as FIH and phase II/III studies. For biologics with the same molecular structure and mechanism of action, for example, mAbs neutralizing the same target, meta-analysis allows establishing drug-independent dose/exposure–response relationships for head-to-head comparisons, providing valuable reference measures. Empirical or semi-mechanistic models used in evaluating benefit/risk profiles for small molecules can also be adapted in guiding biologics development given their practicality and less dependence on mechanistic information. Overall, PK, PK–PD, meta-analysis, and exposure–response models are powerful tools to facilitate the development of biologic drugs. With the advancement of various types of models for biologics, drug developers, and researchers can gain powerful advantage and exploratory insight to design the most effective therapeutic regimens.

REFERENCES


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