Review Article

Theme: Pharmacokinetic/Pharmacodynamic Modeling and Simulation in Drug Discovery and Translational Research

Guest Editors: Cheryl Li, Pratap Singh, and Anjaneya Chimalakonda

Modeling, Simulation, and Translation Framework for the Preclinical Development of Monoclonal Antibodies

Kenneth T. Luu,^{1,3} Eugenia Kraynov,² Bing Kuang,² Paolo Vicini,² and Wei-Zhu Zhong²

Received 22 January 2012; accepted 6 February 2013; published online 14 February 2013

Abstract. The industry-wide biopharmaceutical (*i.e.*, biologic, biotherapeutic) pipeline has been growing at an astonishing rate over the last decade with the proportion of approved new biological entities to new chemical entities on the rise. As biopharmaceuticals appear to be growing in complexity in terms of their structure and mechanism of action, so are interpretation, analysis, and prediction of their quantitative pharmacology. We present here a modeling and simulation (M&S) framework for the successful preclinical development of monoclonal antibodies (as an illustrative example of biopharmaceuticals) and discuss M&S strategies for its implementation. Critical activities during early discovery, lead optimization, and the selection of starting doses for the first-in-human study are discussed in the context of pharmacokinetic–pharmacodynamic (PKPD) and M&S. It was shown that these stages of preclinical development are and should be reliant on M&S activities including systems biology (SB), systems pharmacology (SP), and translational pharmacology (TP). SB, SP, and TP provide an integrated and rationalized framework for decision making during the preclinical development phase. In addition, they provide increased target and systems understanding, describe and interpret data generated *in vitro* and *in vivo*, predict human PKPD, and provide a rationalized approach to designing the first-in-human study.

KEY WORDS: biologics; drug discovery; modeling and simulations; pharmacodynamics; pharmacokinetics.

INTRODUCTION

The growth of biopharmaceuticals (BPs) over the last 20 years has indeed been nothing short of remarkable. In late-stage development, by 2006, there were 111 unique BPs for 190 indications in 38 disease categories (1). In 2009, four monoclonal antibodies (mAbs) gained FDA approval, the highest annual number in over a decade (2). In 2010, of the 21 molecular entities that gained approval, six were biologics (3). By the same year, a total of more than 20 therapeutic antibodies were approved and more than 200 were in development (4). The rise in the proportion of biologics to small-molecule approvals may well be attributed to the advent of technologies that have enabled the engineering of a wide range of targeted biological modalities. In addition to mAbs, antisense oligonucleotides, therapeutic genes, recombinant and DNA vaccines, and antibody–drug conjugates are expanding the industry-wide BP pipeline (5,6).

As BPs are growing in complexity in terms of their structures and mechanisms of action, so are interpretation, analysis, and prediction of their pharmacokinetic (PK) and pharmacodynamic (PD) properties, collectively, pharmacokinetic–pharmacodynamic (PKPD). Unlike what is typically seen for small-molecule compounds, the PK of BPs can be significantly affected by the PD, *i.e.*, target kinetics, abundance, affinity, and depletion or accumulation, etc. Those confounding variables necessitate mechanistic models to describe their PKPD properties. For example, beyond phenomenological models, systems biology (SB) and systems pharmacology (SP) models may be needed to describe and predict their behavior. Undoubtedly, the use of model-based analysis from early discovery leading to the design of the first-in-human (FIH) study is crucial for rationalized decision making during the drug discovery and development process. Thus, data and mechanistic information collected from various *in vitro* and *in vivo* experiments at all stages of preclinical development can, and perhaps should be, compiled into an integrative and quantitative framework. PKPD and SB/SP, collectively modeling and simulation (M&S), is arguably the best available tool to achieve this goal.

The objective of this manuscript is to present an introductory overview of a model-based framework for the successful preclinical development of mAbs (as an illustrative example of BPs) and discuss M&S strategies for its

¹ Department of Clinical Pharmacology, Pfizer Global Research and Development, 10555 Science Center Drive, San Diego, California 92121, USA.

² Department of Pharmacokinetics, Dynamics, and Metabolism, Pfizer Global Research and Development, La Jolla, San Diego, California, USA.

³ To whom correspondence should be addressed. (e-mail: kenneth.luu@pfizer.com)

implementation. For the purpose of this manuscript, the term “preclinical” includes early discovery stages leading to the design of the FIH study. For simplicity, our use of the term “biopharmaceuticals” may be synonymous with others such as “biologics” and “biotherapeutics.”

A M&S FRAMEWORK FOR PRECLINICAL DEVELOPMENT OF mAbs

Depicted in Fig. 1 is an integrated framework for model-based drug discovery for mAbs. The steps in the diagrams are meant to be taken in a continuum rather than strongly demarcated, since knowledge and model building would naturally progress as new data are collected along the R&D process with time. In early discovery, *bona fide* SB approaches may be used to reconstruct the molecular pathway of the target and aid the understanding of the target biology, in addition to supporting target identification, validation, and selection. This is also a stage at which building a physiologically based PK (PBPK) model could begin in conjunction with target system or pathway models to improve the understanding of mAb distribution, especially if tissue localization of the target is important.

During lead optimization, SP, which, for the purpose of this framework, may include mechanistic PKPD, becomes prominent (7). At this stage, heavy emphasis is placed on the *in vivo* PKPD properties of the lead candidate almost necessarily in an animal model of disease (AMD). When feasible, the systems or PBPK model developed in early discovery should be incorporated into the pharmacology understanding. Next, translational pharmacology becomes

essential at the transitional phase between candidate selection and FIH (8). At this stage, the scaling of the PK and PD from animals to human using a model-based approach with no adverse effect level (NoAEL) and minimally anticipated biological effect level (MABEL) (if needed) considerations is used to guide decisions on the starting as well as escalating dose decisions in the FIH study. Agoram *et al.* in a recent review discusses some modeling examples performed at the translational pharmacology stage (9). The rest of the sections in this review will be devoted to expanding the discussion of this framework and concepts related to mAb development in the preclinical setting.

SYSTEMS BIOLOGY MODELING

Applications of SB to improve decision making in the drug development setting have previously discussed (10,11). At the very early stages of drug discovery, emphasis on selecting and validating the drug's target can be more useful than immediately focusing on the drug's properties simply because a drug with the best PK and safety profiles would not succeed in the clinics if the intended target is irrelevant to modifying the disease state. Thus, SB-assisted target validation is a crucial part of early drug discovery. New technologies, *e.g.*, functional mapping, have been suggested to integrate DNA-level changes or genetic information with PKPD approaches and systems biology (12). SB can be applied which integrates the network connectivity with the system dynamic considerations. As an additional general consideration, computational strategies, such as SB models, allow optimizing the choice of target knockdown

Fig. 1. Summary of the model-based preclinical development framework for biopharmaceuticals. Boxes with dotted lines represent modeling and simulation specific activities ideally implemented during preclinical development

technologies. In particular, they may allow choosing an optimal knockdown location to minimize morbidity and mortality in the experimental animal (13).

A notable example of the use of SB to test pharmacological targets in a biological system can be seen in the work of Wangorsch *et al.* (14). Through experimental data, literature, and database mining, Wangorsch and colleagues built an *in silico* model of cyclic nucleotide signaling and tested its signaling sensitivity. From this example, one can identify several methodological elements of SB model testing relevant to the drug discovery setting: (1) testing a target's sensitivity in terms of concentration (dose) response, (2) testing the effect of various effectors (*i.e.*, inhibitors, activators (antagonists, agonists), or drug combination), and (3) evaluating the target under the conditions of permanent and transient perturbations. As listed in Fig. 1, such testing through a validated SB model would provide deep biology understanding, target validation, and selection and early biomarker identification in the early discovery stage.

PHYSIOLOGICALLY BASED PHARMACOKINETICS

PBPK modeling for mAbs was reported as early as 1986 by Covell *et al.* (15). A recent review of PBPK modeling for macromolecules can be found in Thygesen *et al.* (16). Once the target is selected and validated, the emphasis may then be to optimize the mAb's properties, albeit some of this effort may have already been underway or happening in parallel. During the SB/SP phases (Fig. 1), beyond the basic assessment of PK, time may be afforded to build a PBPK model to gain a better understanding of the mAb's tissue distribution characteristics (16–18). Such a model could assist in determining whether the mAb is adequately exposed to the intended tissue or site of action. In addition, such a model could help evaluate the compound's safety profile if a certain extent of exposure to a particular tissue is a cause for safety concern. PBPK models have been used to characterize distribution of antibodies in a variety of model systems (19,20). As accounted for in the above references, critical components dictating the clearance of mAbs such as the influence of FcRn binding and target-mediated disposition should be accounted for in order to improve the predictability of the tissue PK data. Conceivably, mAb selection and optimization may be performed to improve its PK properties on the basis of FcRn affinity. The PBPK model developed by Garg and Balthasar (19,20) may be used to run simulations conditional on FcRn affinity for a range of mAbs.

A resonating example of mAb PBPK can be seen in the work of Davda *et al.* who constructed a PBPK model for the CC49 mAb to predict not only its biodistribution in various tissues but also in the tumor compartment which was the intended site of action (21). The model gave insights into the factors affecting mAb uptake and accumulation into the tumor tissue. The rate and extent of tumor CC49 mAb accretion was determined to be a variable affected by the rate of transcapillary transport. In the drug discovery setting, those important results are a starting point of consideration for optimizing compound's physiochemical properties to have the right range of transcapillary transport rates and, thus, favorable tumor uptake profiles. Another benefit of having a PBPK model is that it may be scalable from mouse to human. When such a model accounts

for mAb distribution at the tumor tissue (intended site of action), an initial projection of human tumor uptake may be made with reasonable assumptions.

A consideration with regard to the application of PBPK modeling during early discovery is its integration with PD. The next step following the PBPK model development is, if feasible, to link predicted tissue levels to PD endpoints. PBPK-PD models are indeed attractive as multi-scale models since (at least for drug distribution) the principle governing their scaling among species have been intensely studied. On the other hand, PD considerations are relatively new in the context of these models.

PKPD RELATIONSHIP IN THE ANIMAL MODEL OF DISEASE

Once a certain level of confidence has been established for the target biology as well as an initial assessment of the mAb properties, building a definitive PKPD relationship in the AMD becomes important. This work, which may begin once the target has been validated, becomes increasingly important throughout the lead optimization phase and, therefore, the SP modeling phase. The success of M&S approaches heavily depends on the selection of the appropriate preclinical AMD and quantitative M&S may help select and improve it. In addition to insufficient understanding of the underlying target biology, poorly predictive preclinical animal models are undoubtedly an additional cause of compound attrition during clinical development. At a fundamental level, models used for establishing PKPD relationship for mAbs are similar to those used for the traditional small-molecule drugs.

Important components of an animal model are its selectivity, reproducibility, and translatability to the human disease. For example, in the CNS area, transgenic mouse models of Alzheimer's disease have been successfully used in drug discovery programs (22). However, *in vivo* models for cancer have been poor predictors of human efficacy (23). Possible success criteria appear to be the extent of the similarity to the human disease and validation and integration of appropriate biomarkers into the translation between the animal model and human (24). In the modeling and simulation effort, the integration of a translatable biomarker as part of the PD model is perhaps one of the most fruitful efforts during the stages of translational pharmacology.

Of particular relevance to M&S in the drug discovery setting is the application of a disease progression model for the AMD. This type of model can be seen in Liu *et al.* (25) who developed a combined PKPD and disease progression model to evaluate the effect of anakinra in collagen-induced arthritic rats and to explore the effect of interleukin-1 β in rheumatoid arthritis. Having a combined PKPD and disease progression model in a validated AMD may be an ideal situation as it allows for an integrated understanding of exposure, response, and disease progression in a single system and reduces uncertainty and variability in the translation.

MODELING CONSIDERATIONS FOR SURROGATE mAbs

When the lead mAb is not cross-reactive with the animal target, the AMD may not be appropriately tested. Cross-species variants in the epitope are important reasons for the

lack of recognition between the clinical candidate and the antigen of lower species. Knowledge of cross-species conservation of an epitope, therefore, may be valuable to assist the selection of an AMD. In the preclinical setting, a common way to get around the lack of cross-reactivity is to generate a surrogate mAb which has similar affinity and functional activity for the target in the animal model as the lead mAb has for the human target. The surrogate mAb can be used preclinically to confirm efficacy and establish a PKPD relationship. In addition, it may help with the early assessment of safety (26).

From a methodological standpoint, developing a PKPD model for the surrogate mAb should be similar to that for the clinical candidate (had it been cross-reactive with the animal target). However, the issue which has not been well tackled across the industry is how to translate the PKPD model of the surrogate mAb to the clinical candidate and eventually to human PKPD. Examples of this type of translational pharmacology are not readily found in the literature. Notwithstanding, one common thread between the surrogate and the clinical candidate is the difference or similarity with the surrogate mAb's affinity. This means that a PKPD/SP model incorporating receptor affinity which will later be integrated into the translational scheme is a sound approach.

MODELING NONLINEAR PK PROFILES OF mAbs

Basic PKPD characteristics of mAbs have been extensively reported (27–30). Of important considerations for modeling is the potential nonlinearity of the PK of mAbs attributable to target-mediated drug disposition (TMDD). “TMDD models” describing the nonlinear PK data associated with TMDD have been well described and widely implemented (31–34). In summary, in addition to catabolic clearance, mAbs can be cleared following target binding. As depicted in Fig. 2, the steps for this pathway would typically include: (1) binding and formation of mAb-target complex, (2) internalization of mAb-target complex in endosomes, (3) displacement of mAb-target complex and degradation in lysosomes, and (4) recycling of the target to the cell surface. TMDD occurs more frequently for mAbs bound to cell surface targets although mAbs bound to soluble targets may have PK profiles similar to TMDD as a result of complex formation and complex degradation through macrophage engulfment (27). TMDD may result in nonlinear PK profiles with volume and in clearance decrease with increasing dose (31).

As the above description implies, TMDD is a drug systems phenomenon. Thus, a model describing this process should justifiably be of SP in nature. As listed in Fig. 2, model building under the “full” TMDD model construct involves the integration of several essential SP components: (1) the *in vivo* PK which involves the catabolic clearance (k_{el}) and distributional parameters (k_{12} , k_{21}), (2) target affinity (k_{on} , k_{off}), (3) target abundance or density, and (4) target turnover (k_{syn} , k_{deg}) and target internalization kinetics (k_{int}).

Although simplified TMDD models have been developed including the quasi-steady state, quasi-equilibrium, and Michaelis–Menten models (33,35), those abbreviated models are limited in their power to test for sensitivity or perturbation of certain systems parameters. For example, in the full TMDD, sensitivity analysis can be performed to correlate *in vivo* potency

Fig. 2. General scheme of target-mediated drug disposition (TMDD) assuming the target is localized in the tissue compartment

conditional on changes in *in vitro* parameters such as k_{on} , k_{off} , k_{int} , and k_{syn}/k_{deg} which are often measured (or can be mined from the literature) in the preclinical setting. When efficacy data are linked to a full TMDD model in an integrated PKPD model, such sensitivity analysis could be performed for a range of mAbs differing in *in vitro* characteristics. This approach can be used to aid in compound selection at an early stage. Agoram et. al. (9), for example, performed a sensitivity analysis from a TMDD model for an anti-IgE mAb program and determined that the therapeutic dose of the candidate mAb could be reduced by half when its affinity was increased five to tenfold higher than the competitor already on the market. In addition, it was determined that a further increase in affinity would not result in improved efficacy, thus, avoiding the need for affinity maturation. Such sensitivity analysis would also be feasible for quasi TMDD models on the basis of K_d affinity values but not specifically for k_{on} and k_{off} values. However, sensitivity analyses of this type would not be feasible for empirical models, especially the Michaelis–Menten model, which does not allow straightforward integration of the *in vitro* parameters. A successful implementation of a full TMDD model can be seen in our recent work (36) which showed how experimentally measured values of k_{on} , k_{off} , k_{int} , and k_{deg} could be directly incorporated (fixed) in the TMDD model (37).

INFLUENCE OF TARGET DENSITY

In the preclinical setting, investment in understanding the target density (*i.e.*, target abundance), especially its differences between animals and humans can be invaluable during the translational pharmacology phase. From the construct of the TMDD model, simulations showed that target concentration can significantly influence the PK profile of the mAb. Figure 3 shows the sensitivity analysis of the effect of target concentration on the PK profile of a typical antibody exhibiting TMDD. Clearly, the influence of TMDD on the total clearance of the compound can be significant, with terminal half-lives decreasing with increasing target level. This simulation was carried out using the parameters obtained from our work with anti-ALK1 mAb (37) using a dose of 2 mg/kg and the following model parameters: $V_C = 0.103$ L, $k_{el} = 0.135$ day⁻¹, $k_{12} = 0.467$ day⁻¹, $k_{21} = 0.467$ day⁻¹,

Fig. 3. Sensitivity analysis of the effect of target concentration on the PK profile of a hypothetical antibody exhibiting TMDD. See text for parameter values used in the simulation

$k_{on}=41.4 \text{ nM}^{-1}\text{day}^{-1}$, $k_{off}=99.36 \text{ day}^{-1}$, $k_{int}=4.10 \text{ day}^{-1}$, and $k_{deg}=5.36 \text{ day}^{-1}$. The impact of target density on the PK profile of the therapeutic mAb should lead one to carefully consider dosing regimen in order to ensure adequate safety margin for compounds going into the clinic. Alternatively, knowing the target expression differences between animals and humans allows us to translate this parameter when making human PKPD projection.

UNDERSTANDING IMMUNOGENICITY AND ANTIDRUG ANTIBODIES

Immunogenicity is often observed with mAbs and may have significant impacts on their safety, PK, and PD. Administration of mAbs, especially with repeated doses, could trigger the generation of antidrug antibodies (ADA) and cell-based immune responses (36). Many factors affect the immunogenicity of mAbs. An important determinant is the degree of sequence and structure similarity of the therapeutic mAbs relative to the endogenous human IgGs (38). mAbs of human origin are, in theory, more immunogenic in animals and less immunogenic in human. On the other hand, protein-based therapeutics are normally produced in nonhuman cell lines (*e.g.*, Chinese hamster ovary, CHO, cells) and may have post-translational modifications of animal type instead of human type (39). Other factors include the level, frequency and route of administration, amount of aggregates in the drug product, and host genetic background and conditions (38).

The occurrence of ADA in preclinical studies raises several potential risks in terms of PK, safety, and therapeutic efficacy (40). First, the generated ADA could bind to the active site of the administered mAb and neutralize its intended therapeutic function. Second, the ADA could alter the PK of the compound. It has been shown that the

formation of immune complexes between ADA and the administered mAb can change the biodistribution of mAb and lead to faster clearance (41,42). Lastly, circulating ADA could effectively compete with the binding of mAbs and interfere with analytical assays. Thus, in consideration of the impact of ADAs on the PK and its associated risks to safety and efficacy, evaluation of immunogenicity should be integral to the development of mAbs and its interpretation should be accounted for during the development of a PKPD model. From a modeling standpoint, models which simultaneously capture the therapeutic mAb and ADA concentrations are not readily available in the literature, thus indicating, an area of development for the field. Although we feel that this is an area of open progress, with the current lack knowledge in the translation between preclinical and clinical immunogenicity, some investigators feel that preclinical immunogenicity data should only be used to help interpret preclinical PK data rather to predict human immunogenicity.

ANALYTICAL CONSIDERATIONS

Understanding the PKPD of mAbs requires reliable bioanalytical methods to quantify drug and target levels. As discussed in the previous section, and shown in Fig. 3, target levels can significantly alter the PK of a given mAb. One of the much discussed analytical issues for mAbs is the measurement of free *versus* total analyte and differentiating between the two is certainly required for proper implementation of M&S. In theory, different ligand binding assay (LBA) formats could be constructed to measure free or total analyte concentrations. In practice, however, there are many analytical challenges to accurately measure the free level using LBA (43,44). Knowledge of target localization could be taken into account to assess whether the assay is measuring the free or total mAb concentration. For example, if the

target is cell membrane-bound and there is no soluble extracellular domain of target in circulation, the mAb concentration being measured could be interpreted as free concentration irrespective of assay format. However, many mAb targets are soluble, *e.g.*, growth factors and cytokines, and membrane-bound receptors may shed soluble extracellular domain into circulation (45). In these situations, it is important to develop an assay that uniquely captures the mAb; the development of such an assay should consider interference.

One consideration for determining free *versus* bound mAb is to develop an assay to measure the target level. However, directly measuring the free target levels has greater challenges. The free target levels measured by LBA in the presence of the administered mAb are usually an overestimation. The measurement of total target level could be also affected by the mAb present in the sample and lead to over- or underestimation of target level (46). Therefore, as with PK assays, this interference on the quantitation of target concentration should also be evaluated. To circumvent the analytical challenges of the free target concentration quantitation, many have attempted to use the data from total assays for both mAbs and their targets in a PK/PD system and to infer the free concentrations that are consistent with other observations (47–49). In general, although understating the free mAb concentration is important, total concentration could be equally informative for M&S activities as long as the target level is also assessed in parallel.

TRANSLATIONAL PHARMACOLOGY

For mAbs, in addition to defining the PKPD relationship in the rodent AMD, PK and TK (toxicokinetic) studies are often conducted in nonhuman primates (NHP). Because the PK of mAbs is often translatable from NHP to human, such studies should be carefully designed to extract the most information for M&S as well as animal-to-human translation. It is important to consider, if feasible, simultaneously collecting PD readouts or potential biomarkers in NHP to build a complete PKPD package from the higher species since it has greater potential for translation to humans.

Although scaling PD biomarkers from NHP to humans might be challenging without prior validation, scaling the PK of mAbs has been reported to be successful. For example, for mAbs exhibiting linear PK, scaling based on an exponent of body weight is often sufficient to predict their clearance and

volume of distribution in human (50–53). However, since many mAbs exhibit nonlinear PK, such direct scaling may be insufficient. As previously mentioned, one of the potential approaches was proposed by us for anti-ALK1 mAb when we built a model based on the construct of a full TMDD model to describe the PK in NHP and then used it to successfully predict the human PK based on scaling of the *in vivo* PK parameters and human-specific *in vitro* receptor kinetic systems parameters (37). Thus, to account for nonlinear PK, the translation of the PK of mAbs needs to be done in a model-based approach rather than a simple scaling of clearance and volume.

MODEL-BASED SELECTION OF A SAFE BUT REASONABLE STARTING DOSE FOR THE FIH STUDY

Many reports have been published on the topic of FIH starting human dose selection for mAbs especially concerning MABEL for high-risk mAbs (54–56). Our approach to MABEL calculation is to apply a model-based approach to the selection of the starting dose, integrating as much mechanistic information as possible from all phases of preclinical discovery and development. Any prior knowledge of clinical information such as PK, biomarker, and target kinetics would be valuable for human PKPD prediction in the translational pharmacology phase. In addition, it is sensible to focus on the pharmacology (*i.e.*, pharmacological mechanism and associated data) rather than toxicological observations alone to determine the starting dose for the clinic. A good example of the PKPD modeling approach to guide the selection of the starting dosing can be found in (56).

The steps for model-based MABEL determination of the starting human dose would include (1) determining the exposure–response relationships or, preferably, building PKPD models for all relevant “biological effect” variables; (2) determining if receptor occupancy (RO) is relevant to efficacy or biological effect and, if so, calculate the RO preferably using the predicted human PKPD model which accounts for target turnover kinetics; and (3) determining the human equivalent (HED) NoAEL (56). The relevance of a biological effect variable should be decided based on the understanding of the pharmacological mechanism.

The proposed “MABEL table” (see Table 1 as an example) is a convenient and highly useful way to capture the range of possible starting human doses derived from quantitative/M&S approaches and may be included in the

Table 1. Example of a MABEL Table Used to Guide the Decision Based on the MABEL Guidance

Efficacy variable	Method of analysis	MABEL	Starting dose (mg/kg)
Primary efficacy endpoint (<i>ex.</i> tumor growth inhibition)	PKPD modeling	10% response	1.0
<i>In vivo</i> biomarker/s	PKPD modeling	10% response	0.10
<i>In vitro</i> mechanistic biomarkers	Modeling or derived from concentration–response plot	10% response or EC10	0.01
Receptor occupancy	PKPD model-based prediction or based on the simple Duff equilibrium equation	10% RO at C_{max}	0.02
		Range of human starting dose	0.01 to 1

PKPD pharmacokinetics–pharmacodynamics, RO receptor occupancy

IND document as a rationale for the starting human dose selection for high-risk mAbs. The MABEL table ideally would list the relevant “biological effects” to be considered, which may include: (1) the primary efficacy endpoint evaluated in the AMD, (2) one or more *in vivo* biomarkers, (3) one or more *in vitro* biomarkers, and (4) the receptor occupancy, if relevant. The translatability of each of these efficacy variables should be carefully evaluated: the higher confidence in the translation the more valid is the rationale based on the MABEL approach.

Once the MABEL table is established, a logical next question has to do with which starting human dose to choose when a full range is listed in the table. For “high-risk biologics” (e.g., biologics that are strong agonists or modulators of the immune system), the regulatory agencies will likely prefer the most conservative (the lowest) dose from the MABEL table. However, the selection of a higher dose within the range can be justified with supporting rationale when the efficacy variable associated with the selected dose is mechanistically most relevant for predicting the “biological effect level.” For mAbs that are not considered high-risk biologics, the MABEL approach is not required; however, it may still be useful to rationally select the starting human dose from a pharmacological standpoint relative to a toxicological standpoint. In this case, the higher end of the dose range can be more easily justified.

CONCLUSION

We present here an integrated, model-based framework for the successful preclinical development of mAbs. Early discovery, lead optimization, and first-in human stages, all are critically reliant on M&S activities including SB, SP, and TP. Modeling efforts provide increased target and systems understanding, describe and interpret data generated *in vitro* and *in vivo*, predict human PKPD, and inform a rationalized approach to designing the phase I study in terms of starting human dose selection. Those activities are essential for addressing the unique systems/PKPD properties of mAbs as they undergo optimization throughout the preclinical phases.

ACKNOWLEDGMENTS

The authors wish to acknowledge Dr. Scott Fountain for reviewing, editing, as well as supporting efforts leading to the completion of this manuscript.

REFERENCES

- Nagle PC, Nicita CA, Gerdes LA, Schmeichel CJ. Characteristics of and trends in the late-stage biopharmaceutical pipeline. *Am J Manag Care*. 2008;14(4):226–9.
- Sheridan C. Fresh from the biologic pipeline-2009. *Nat Biotechnol*. 2010;28(4):307–10.
- Mullard A. 2010 FDA drug approvals. *Nat Rev Drug Discov*. 2011;10(2):82–5.
- Lalonde RL, Honig P. Clinical pharmacology in the era of biotherapeutics. *Clin Pharmacol Ther*. 2008;84(5):533–6.
- Nagle PC, Lugo TF, Nicita CA. Defining and characterizing the late-stage biopharmaceutical pipeline. *Am J Manag Care*. 2003;9(6 Suppl):S124–35.
- Tibbitts J, Cavagnaro JA, Haller CA, Marafino B, Andrews PA, Sullivan JT. Practical approaches to dose selection for first-in-human clinical trials with novel biopharmaceuticals. *Regul Toxicol Pharmacol*. 2010;58(2):243–51.
- Van Der Graaf PH, Gabrielsson J. Pharmacokinetic–pharmacodynamic reasoning in drug discovery and early development. *Future Med Chem*. 2009;1(8):1371–4.
- Gabrielsson J, Fjellstrom O, Ulander J, Rowley M, Van Der Graaf P. Pharmacodynamic–pharmacokinetic integration as a guide to medicinal chemistry. *Curr Top Med Chem*. 2011;11:404–18.
- Agoram BM, Martin SW, van der Graaf PH. The role of mechanism-based pharmacokinetic–pharmacodynamic (PK-PD) modelling in translational research of biologics. *Drug Discov Today*. 2007;12(23–24):1018–24.
- Mujagic H. Systems biology: potential to improve decision making in pharmaceutical development. *Drug News Perspect*. 2006;19(9):575–83.
- Krishna R, Schaefer HG, Bjerrum OJ. Effective integration of systems biology, biomarkers, biosimulation and modelling in streamlining drug development. *Eur J Pharm Sci*. 2007;31(1):62–7.
- Ahn K, Luo J, Berg A, Keefe D, Wu R. Functional mapping of drug response with pharmacodynamic–pharmacokinetic principles. *Trends Pharmacol Sci*. 2010;31(7):306–11.
- Benson JD, Chen Y-NP, Cornell-Kennon SA, Dorsch M, Kim S, Leszczyniecka M, *et al*. Validating cancer drug targets. *Nature*. 2006;441(7092):451–6.
- Wangorsch G, Butt E, Mark R, Hubertus K, Geiger J, Dandekar T, *et al*. Time-resolved in silico modeling of fine-tuned cAMP signaling in platelets: feedback loops, titrated phosphorylations and pharmacological modulation. *BMC Syst Biol*. 2011;5:178.
- Covell DG, Barbet J, Holton OD, Black CD, Parker RJ, Weinstein JN. Pharmacokinetics of monoclonal immunoglobulin G1, F(ab')₂, and Fab' in mice. *Cancer Res*. 1986;46(8):3969–78.
- Thygesen P, Macheras P, Van Peer A. Physiologically based PK/PD modelling of therapeutic macromolecules. *Pharm Res*. 2009;26(12):2543–50.
- Baxter LT, Zhu H, Mackensen DG, Butler WF, Jain RK. Biodistribution of monoclonal antibodies: scale-up from mouse to human using a physiologically based pharmacokinetic model. *Cancer Res*. 1995;55(20):4611–22.
- Baxter LT, Zhu H, Mackensen DG, Jain RK. Physiologically based pharmacokinetic model for specific and nonspecific monoclonal antibodies and fragments in normal tissues and human tumor xenografts in nude mice. *Cancer Res*. 1994;54(6):1517–28.
- Garg A, Balthasar J. Physiologically based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. *J Pharmacokinet Pharmacodyn*. 2007;34(5):687–709.
- Urva SR, Yang VC, Balthasar JP. Physiologically based pharmacokinetic model for T84.66: a monoclonal anti-CEA antibody. *J Pharm Sci*. 2010;99(3):1582–600.
- Davda JP, Jain M, Batra SK, Gwilt PR, Robinson DH. A physiologically based pharmacokinetic (PBPK) model to characterize and predict the disposition of monoclonal antibody CC49 and its single chain Fv constructs. *Int Immunopharmacol*. 2008;8(3):401–13.
- Hussain I. APP transgenic mouse models and their use in drug discovery to evaluate amyloid-lowering therapeutics. *CNS Neurol Disord Drug Targets*. 2010;9(4):395–402.
- Firestone B. The challenge of selecting the ‘right’ *in vivo* oncology pharmacology model. *Curr Opin Pharmacol*. 2010;10(4):391–6.
- Wendler A, Wehling M. The translatability of animal models for clinical development: biomarkers and disease models. *Curr Opin Pharmacol*. 2010;10(5):601–6.
- Liu D, Lon HK, Dubois DC, Almon RR, Jusko WJ. Population pharmacokinetic–pharmacodynamic-disease progression model for effects of anakinra in Lewis rats with collagen-induced arthritis. *J Pharmacokinet Pharmacodyn*. 2011;38(6):769–86.
- Clarke J, Leach W, Pippig S, Joshi A, Wu B, House R, *et al*. Evaluation of a surrogate antibody for preclinical safety testing

- of an anti-CD11a monoclonal antibody. *Regul Toxicol Pharmacol*. 2004;40(3):219–26.
27. Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. *J Pharm Sci*. 2004;93(11):2645–68.
 28. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 2008;84(5):548–58.
 29. Roskos LK, Davis CG, Schwab GM. The clinical pharmacology of therapeutic monoclonal antibodies. *Drug Dev Res*. 2004;61:108–20.
 30. Mahmood I, Green MD. Pharmacokinetic and pharmacodynamic considerations in the development of therapeutic proteins. *Clin Pharmacokinet*. 2005;44(4):331–47.
 31. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn*. 2001;28(6):507–32.
 32. Mager DE, Neuteboom B, Efthymiopoulos C, Munafo A, Jusko WJ. Receptor-mediated pharmacokinetics and pharmacodynamics of interferon-beta1a in monkeys. *J Pharmacol Exp Ther*. 2003;306(1):262–70.
 33. Mager DE, Krzyzanski W. Quasi-equilibrium pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *Pharm Res*. 2005;22(10):1589–96.
 34. Ng CM, Stefanich E, Anand BS, Fielder PJ, Vaickus L. Pharmacokinetics/pharmacodynamics of nondepleting anti-CD4 monoclonal antibody (TRX1) in healthy human volunteers. *Pharm Res*. 2006;23(1):95–103.
 35. Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*. 2008;35(5):573–91.
 36. Shankar G, Shores E, Wagner C, Mire-Sluis A. Scientific and regulatory considerations on the immunogenicity of biologics. *Trends Biotechnol*. 2006;24(6):274–80.
 37. Luu KT, Bergqvist S, Chen E, Hu-Lowe D, Kraynov E. A model-based approach to predicting the human pharmacokinetics of a monoclonal antibody exhibiting target-mediated drug disposition. *J Pharmacol Exp Ther*. 2012;341(3):702–8.
 38. Ponce R, Abad L, Amaravadi L, Gelzleichter T, Gore E, Green J, *et al.* Immunogenicity of biologically-derived therapeutics: assessment and interpretation of nonclinical safety studies. *Regul Toxicol Pharmacol*. 2009;54(2):164–82.
 39. Walsh G. Post-translational modifications of protein biopharmaceuticals. *Drug Discov Today*. 2010;15(17–18):773–80.
 40. Shankar G, Devanarayan V, Amaravadi L, Barrett YC, Bowsher R, Finco-Kent D, *et al.* Recommendations for the validation of immunoassays used for detection of host antibodies against biotechnology products. *J Pharm Biomed Anal*. 2008;48(5):1267–81.
 41. Johansson A, Erlandsson A, Eriksson D, Ullén A, Holm P, Sundström BE, *et al.* Idiotype-anti-idiotypic complexes and their *in vivo* metabolism. *Cancer*. 2002;94(S4):1306–13.
 42. Rojas JR, Taylor RP, Cunningham MR, Rutkoski TJ, Vennarini J, Jang H, *et al.* Formation, distribution, and elimination of infliximab and anti-infliximab immune complexes in cynomolgus monkeys. *J Pharmacol Exp Ther*. 2005;313(2):578–85.
 43. Kuang B, King L, Wang HF. Therapeutic monoclonal antibody concentration monitoring: free or total? *Bioanalysis*. 2010;2(6):1125–40.
 44. Lee JW, Kelley M, King LE, Yang J, Salimi-Moosavi H, Tang MT, *et al.* Bioanalytical approaches to quantify “total” and “free” therapeutic antibodies and their targets: technical challenges and PK/PD applications over the course of drug development. *AAPS J*. 2011;13(1):99–110.
 45. Zhang Y, Pastan I. High shed antigen levels within tumors: an additional barrier to immunoconjugate therapy. *Clin Cancer Res*. 2008;14(24):7981–6.
 46. Salimi-Moosavi H, Lee J, DeSilva B, Doellgast G. Novel approaches using alkaline or acid/guanidine treatment to eliminate therapeutic antibody interference in the measurement of total target ligand. *J Pharm Biomed Anal*. 2010;51(5):1128–33.
 47. Lachmann HJ, Lowe P, Felix SD, Rordorf C, Leslie K, Madhoo S, *et al.* *In vivo* regulation of interleukin 1[beta] in patients with cryopyrin-associated periodic syndromes. *J Exp Med*. 2009;206(5):1029–36.
 48. Albitar M, Do K-A, Johnson MM, Giles FJ, Jilani I, O’Brien S, *et al.* Free circulating soluble CD52 as a tumor marker in chronic lymphocytic leukemia and its implication in therapy with anti-CD52 antibodies. *Cancer*. 2004;101(5):999–1008.
 49. Vugmeyster Y, Tian X, Szklut P, Kasaian M, Xu X. Pharmacokinetic and pharmacodynamic modeling of a humanized anti-IL-13 antibody in naive and *Ascaris*-challenged cynomolgus monkeys. *Pharm Res*. 2009;26(2):306–15.
 50. Wang W, Prueksaritanont T. Prediction of human clearance of therapeutic proteins: simple allometric scaling method revisited. *Biopharm Drug Dispos*. 2010;31(4):253–63. Epub 2010/05/04.
 51. Mordenti J, Chen SA, Moore JA, Ferraiolo BL, Green JD. Interspecies scaling of clearance and volume of distribution data for five therapeutic proteins. *Pharm Res*. 1991;8(11):1351–9.
 52. Mahmood I. Pharmacokinetic allometric scaling of antibodies: application to the first-in-human dose estimation. *J Pharm Sci*. 2009;98(10):3850–61.
 53. Deng R, Iyer S, Theil FP, Mortensen DL, Fielder PJ, Prabhu S. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned? *MAbs*. 2011;3(1):61–6.
 54. Muller PY, Milton M, Lloyd P, Sims J, Brennan FR. The minimum anticipated biological effect level (MABEL) for selection of first human dose in clinical trials with monoclonal antibodies. *Curr Opin Biotechnol*. 2009;20(6):722–9.
 55. Mahmood I, Green MD, Fisher JE. Selection of the first-time dose in humans: comparison of different approaches based on interspecies scaling of clearance. *J Clin Pharmacol*. 2003;43(7):692–7.
 56. Agoram BM. Use of pharmacokinetic/pharmacodynamic modeling for starting dose selection in first-in-human trials of high-risk biologics. *Br J Clin Pharmacol*. 2009;67(2):153–60.