# The role of mechanism-based pharmacokinetic–pharmacodynamic (PK–PD) modelling in translational research of biologics

**Balaji M. Agoram[1], Steven W. Martin[2] and Piet H. van der Graaf[1]**

[1] Pfizer, Department of Pharmacokinetics, Dynamics, and Metabolism (PDM), Sandwich CT13 NJ, UK
[2] Pfizer, Department of Clinical Pharmacology, Sandwich CT13 NJ, UK

**Lack of predictability of clinical efficacy and safety is an important problem facing pharmaceutical research today. Translational PK–PD has the ability to integrate data generated from diverse test platforms during discovery and development in a mechanistic framework. Therefore, successful implementation of translational PK–PD modelling and simulation early in the development cycle could have a substantial impact on overall efficiency and success of pharmaceutical research. Three case studies are presented, which outline successful implementation of the translational PK–PD methodology in the rational development of biotherapeutics across various stages of discovery and development. Emerging developments within the field are also discussed.**

During the last two decades, pharmacokinetic–pharmacodynamic (PK–PD) modelling and simulation has become a widely used methodology to improve the efficiency and quality of decision-making in later stage clinical drug development [1–3]. In more recent years, it has been suggested that PK–PD modelling and simulation can also play a significant role in early (Phase 1) clinical development [4] and in preclinical drug discovery and development [5,6]. An integrated PK–PD approach, linking the exposure of a drug (or combination of drugs) and the modulation of pharmacological targets, physiological pathways and ultimately disease systems, can be used to develop a unified understanding of the data collected during different stages of drug discovery and, as such, can provide a quantitative framework for translational research [7,8] (Figure 1). PK–PD for translational research (or 'Translational PK–PD') is a relatively new area in drug discovery and, to date, has mainly been developed in academic research. However, our proposition is that successful implementation of PK–PD modelling and simulation in early drug discovery could have a substantial impact on overall efficiency and success of pharmaceutical research, since it is now widely believed that attrition in Phase 2, because of apparent lack of translation of efficacy and safety from preclinical models to human physiology, is one of the most serious challenges facing the successful development of new, innovative medicines [9–13] (also see the Food and Drug Administration's Critical Path Initiative document: http://www.fda.gov/oc/initiatives/criticalpath/initiative.html).

Thus, a key aim of translational PK–PD is to support predictions about probable drug activity across species, especially at the preclinical–clinical interface [8,14]. Conventional PK–PD approaches, on the basis of empirical, descriptive models, have limited predictive capabilities and, therefore, a more mechanism-based approach is required to improve methods for predicting PD in humans from preclinical models. As far as we are aware, the term 'mechanism-based' PK–PD was first proposed by Levy [15] and has now been adopted widely in the literature [5,16–21]. A key feature of mechanism-based PK–PD models is the incorporation of specific expressions to characterise processes on the causal path between drug administration and effect [17] and also an explicit distinction between 'drug-specific' and 'system-specific' parameters [21]. System-specific PK–PD parameters typically include organ/tissue blood flow rates (e.g. in physiologically based PK modelling), target/biomarker abundance and turnover rates, cell life-spans, and homoeostatic feedback mechanisms. Ideally, these parameters should be available from the literature or from prior experiments. Drug-specific parameters typically include PK parameters, such as intrinsic clearance and volume of distribution and pharmacologic parameters, such as *in vivo* target affinity and intrinsic efficacy of compounds, and are usually estimated from PK–PD data gathered for the drug.

*Corresponding author:* van der Graaf, P.H. (Piet.van.der.Graaf@pfizer.com)


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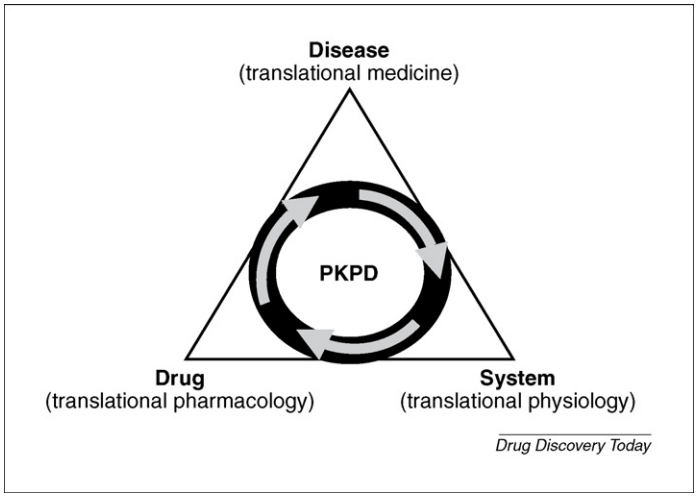


**FIGURE 1**

Role of mechanism-based PK–PD in translational research. Translational research in drug discovery and development could be considered to be divided into three broad disciplines – translational physiology, pharmacology and pathology. Mechanism-based PK–PD modelling, by quantitatively combining system and drug-specific physiological, pharmacological and pathological properties, has the potential to facilitate translational research.

A mechanism-based PK–PD approach is particularly attractive in the area of biologics (referring to therapeutics produced using biological organisms), since these therapeutic agents have certain tractable PK–PD properties which make them amenable to translation across the preclinical–clinical interface. Indeed, for some biologics, such as monoclonal antibodies, it is becoming widely recognised that rational selection of safe first-in-human doses, on the basis of PK–PD modelling, is essential (See: http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_063117). A new parameter, minimum anticipated biological effect level (MABEL), which involves extrapolation of observed preclinical PK–PD data to clinical predictions on the basis of a PK–PD modelling approach, has been suggested for consideration in addition to the no adverse event level (NOAEL) in designing first-in-human dose levels of high-risk therapeutics in the recent European regulatory guidance document (http://www.emea.europa.eu/pdfs/human/swp/2836707enfin.pdf). Thus, PK–PD modelling is being increasingly recognised as an important tool for safety characterisation of biologics, especially during early clinical development.

In this article, we present a brief outline of the PK–PD characteristics of biologics with reference to their ability to translate across species (for a more in-depth review of the PK–PD of biologics and therapeutic monoclonal antibodies in general, please refer to Lobo *et al.* [22] and Tang *et al.* [23]). We then present three case studies with biologics which outline how mechanism-based PK–PD modelling can be used to guide various aspects of translational research during drug development – (a) early clinical development on the basis of preclinical data, (b) translation from healthy subjects to patients and (c) setting discovery objectives on the basis of previous clinical experience. A summary of the outputs is discussed, followed by an assessment of the current state of this methodology along with emerging developments in this field.

## PK–PD characteristics of biologics

The most important physicochemical difference between the majority of biologics and small molecules is in their respective sizes. The molecular weight of biologics typically ranges from a few kDa for recombinant proteins up to 1000 kDa for some immunoglobulin-M (IgM) antibodies, whereas that of small molecules is typically less than 1 kDa. A summary of the PK–PD differences between small molecules and biologics, specifically with respect to their translatability across species is presented in Table 1.

Because of their size, biologics are typically not well-absorbed after oral administration [24]. This is primarily because of digestion by stomach enzymes and lack of permeability across the intestinal epithelial barrier. Therefore, they are typically delivered intravenously, but parenteral administration routes (subcutaneous – SC – and intramuscular – IM) are also common. Absorption from SC and IM sites of administration is believed to occur through both the vasculature and the lymphatic system [25,26]. Thus, unlike orally administered small molecules, the absorption process is free from complex influx–efflux interactions with active transporters at the epithelial barrier. The contribution of the lymphatic route to the overall absorption increases with the size of the biologic [25,26]. Thus, it is conceivable that a vast majority of large biologics, such as monoclonal antibodies, are absorbed almost exclusively through the lymphatic system. The slow

**TABLE 1**

**Comparison of the PK–PD characteristics of small molecules and biologics and the translatability of the PK–PD characteristics**

| Characteristic | Small molecules | Biologics |
|---|---|---|
| **Absorption** | Usually rapid after oral administration. May be subject to influx–efflux interactions at epithelial surface. Bioavailability highly variable | Slow after SC administration. Limited active transport interactions. Amenable to translation across species. Bioavailability typically 30–100% |
| **Distribution** | Widely variable because of plasma protein/tissue binding. Allometric scaling accounting for plasma protein/tissue binding may be predictive | Typically restricted to vascular and interstitial space. Allometric scaling typically predicts human volume of distribution |
| **Metabolism** | Oxidative clearance through P450 enzymes and renal/pulmonary elimination. Variable predictive capability of allometry because of species-specific enzymes | Proteolytic and target-specific elimination. Non-specific clearance could be predicted by allometry. Target-mediated clearance may be mechanistically extrapolated |
| **Pharmacodynamics** | Intra and extra-cellular targets<br>Poly-pharmacology may be seen<br>Off-target toxic effects may be observed | Typically only extracellular targets<br>Selectively bind to target. Limited poly-pharmacology<br>Toxicity usually because of exaggerated pharmacology and immunogenicity |

lymphatic drainage into blood, results in a delayed time to maximum systemic concentrations ($T_{max}$, >1 day) for most biologics. Also, for biologics of a similar size, the absorption rate is approximately the same. This is reflected in the observed $T_{max}$ values after SC administration of three erythropoietin receptor agonists (ERA), epoetin alfa (30 kDa), darbepoetin alfa (38 kDa) and AMG 114 (45 kDa), which are all between 24 and 72 h (1–3 days). Similarly for most IgG1 antibodies, the $T_{max}$ ranges between 3 and 8 days after SC administration [23]. Also, the bioavailability of most macromolecules after SC administration is between 30 and 100% and increases slightly with increasing dose.

Many macromolecules, because of their size, are restricted in their initial distribution to the vasculature. Slow diffusion into the extra-vascular space leads to a larger steady-state volume of distribution and a biphasic PK profile. Thus, the volume of distribution of many protein therapeutics has been reported to be similar to, or slightly higher than, plasma volume (30–200 mL/kg) [23]. However, the reported volumes should be interpreted with caution [22] because they are usually obtained through standard compartmental and non-compartmental PK analyses which assume elimination from a compartment in rapid equilibrium with the central compartment, whereas many biologics, especially monoclonal antibodies, slowly diffuse into target tissues and are subsequently eliminated through receptors in the target tissue. Also, capacity-limited tissue target binding can lead to dose-dependant apparent distribution volumes. In general, large distribution volumes arising from plasma protein binding and tissue partition, seen for small molecules, are not observed for macromolecules and at high doses, the distribution volume approximates that of extravascular and interstitial space.

Substantial elimination of many macromolecules has been shown to occur through the target receptor, hence nonlinear PK is evidenced in many cases – for example omalizumab [20], pegfilgrastim [27,28] and interferon-β [29,30]. This is in contrast to small molecules, which are typically eliminated through renal filtration and/or oxidative enzymes in the liver, gut, and other organs. Because of dose-dependant elimination, PK parameters, such as clearance and half-life, vary with administered dose and route and, hence, direct comparisons of these parameters across different compounds may not be appropriate. It should also be noted that for some proteins (e.g. darbepoetin alfa, epoetin alfa, pegfilgrastim, interferon-β), slow absorption after parenteral administration can result in 'flip-flop' pharmacokinetics where the absorption rate is slower than the elimination rate and hence the observed terminal half-life is more representative of the absorption rate. Other non-target-specific routes of elimination include blood proteolysis for proteins and the reticuloendothelial system for antibodies [31].

From a translation point of view, empirical allometric scaling of animal PK parameters, such as clearance and volume of distribution, to predict clinical PK is generally more accurate in the case of therapeutic proteins than for small molecules [32]. Possible reasons for this include the limited non-specific distribution of macromolecules to various tissues and the absence of the inter-species clearance variation because of differences in the expression and activity of oxidative hepatic enzymes typically responsible for small molecule elimination. However, because target-mediated clearance is an important clearance pathway for many biologics, scaling of clearance across different species should take into account target abundance and dynamics, binding affinity, and nature of interaction (e.g. binding followed by degradation, or binding followed by competing recycling and internalisation [33]), and dose-dependencies of estimated PK parameters. Recent reports [34] have indicated that, independent scaling of non-specific and target-specific clearances estimated in preclinical species using allometric and mechanistic principles respectively, could more accurately predict human PK parameters than allometry alone.

From a PD point of view, macromolecules are, in general, very specific in their action and have limited off-target side effects. In many cases, toxicity is usually because of exaggerated pharmacological effects, for example the 'cytokine storm' seen with TGN1412 [35,36]. In such cases, a single pharmacological biomarker (and an associated PK–PD model) can serve as a measure of both efficacy and safety (e.g. haemoglobin levels with erythropoietin receptor agonists). Also, because the target presents an important clearance pathway for biologics, modulation of the target either by the compound or other factors – disease progression and concomitant treatments – can result in transient changes in the PK and subsequently, the PD effects of the compound. A conventional approach, therefore, which consists of an empirical PK model describing the systemic drug concentrations, which is then used as a forcing function to describe PD, could have difficulties in accurately describing simultaneous changes in PK and PD. A single model accounting for the drug PK, target dynamics and their interaction is often essential in describing the PK–PD of these compounds.

One such interdependent PK–PD model structure has been described by Mager *et al.* [37]. This model explicitly accounts for specific and non-specific distribution and elimination of the drug molecule, as well as providing the flexibility to account for target dynamics. This basic model structure has been applied to describe the PK of recombinant proteins [29] and antibodies [20]. In cases where drug target levels are measurable in blood and could serve as PD biomarkers [20,34,38], this model structure can provide a direct link between dose, exposure and response. Also, differences in target abundance, turnover and target–ligand interaction between preclinical species and human can be quantitatively accounted for during preclinical–clinical translation [34]. Other, more empirical descriptions of the impact of PD on the PK have also been reported for anti-CD11a antibody [39] and for granulocyte-colony stimulating factor [28]. However, these models are conceivably less conducive to accurate preclinical–clinical translation. For macromolecules where PD changes do not directly impact PK, standard mammillary PK models have been linked to semi-physiological PD models through serum drug levels. Such models have been reported for epoetin alfa [40], darbepoetin alfa [41,42], insulin [43] and keliximab [44]. The portability of these models across species and across different molecules with the same mechanism of action will depend on an understanding of the physiological details captured in the PK–PD model in different test species.

## Case study 1. Accelerated early development of a backup erythropoiesis stimulating agent using translational PK–PD

Translational PK–PD was used to predict the clinical PK–PD profile of AMG 114, a hyperglycosylated, longer-acting version of

previously available ERAs, recombinant human erythropoietin (rHuEPO) and darbepoetin alfa, using available clinical and preclinical PK–PD data on darbepoetin alfa and preclinical AMG 114 data. The resulting PK–PD model-based simulations were used to design and execute an accelerated early clinical development program for the treatment of chemotherapy-induced anaemia (CIA). Both empirical and mechanism-based preclinical–clinical scaling of physiological and pharmacological PK–PD parameters was employed to obtain clinical PK–PD parameters. Previous experience of the influence of disease and concurrent therapy was used to predict clinical haemoglobin response to the new therapeutic.

Semi-physiological PK–PD models, on the basis of the indirect effect models, have been used to describe the PK–PD of rHuEPO [40] and darbepoetin alfa [41] (Figure 2(a)). In brief, serum concentrations from a standard mammillary PK model are linked to an increase in the production of red blood cells (and hence an increase in haemoglobin) through an $E_{max}$ type equation. The PD models contain delay parameters which represent the life span of various erythropoietic cell intermediates. The influence of

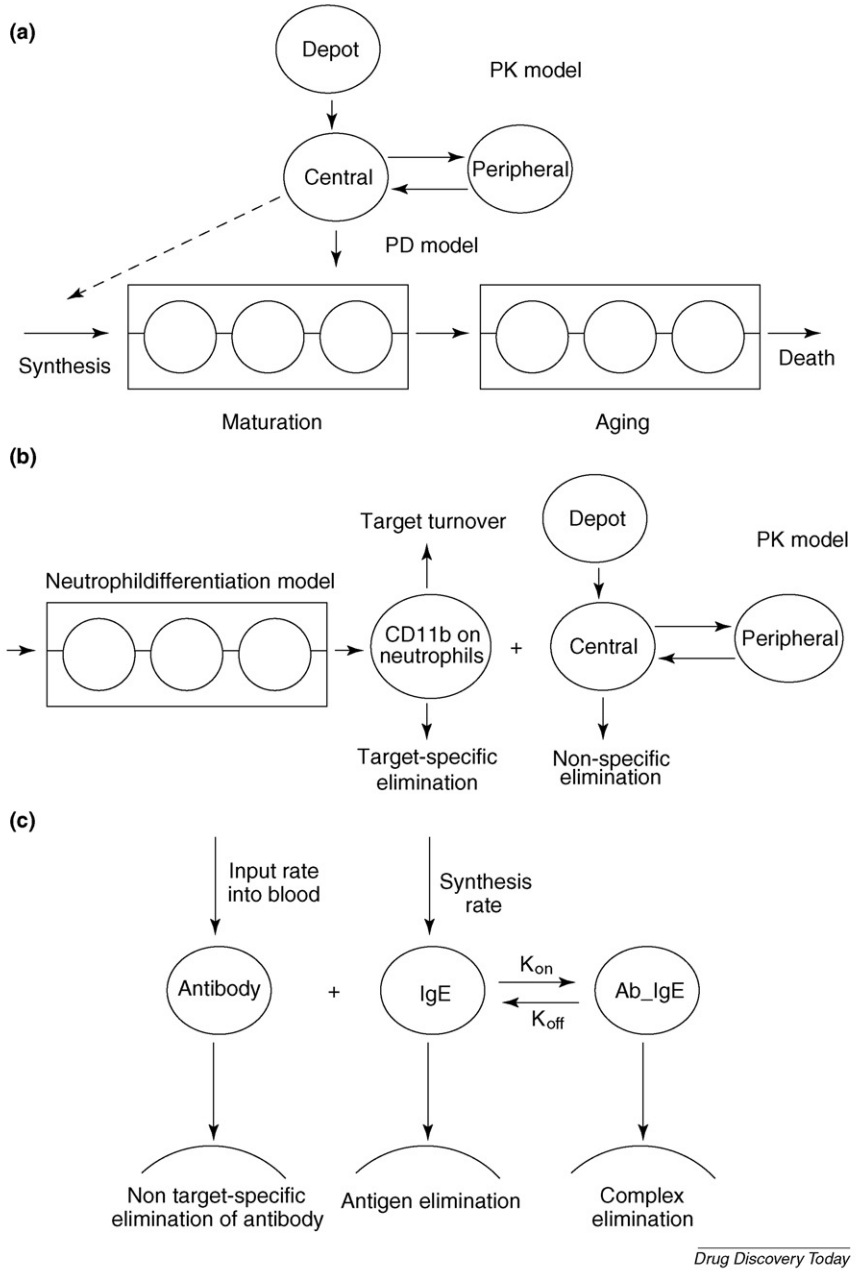


**FIGURE 2**

PK–PD model schematics for the three case studies **(a)** case study 1: ERA-backup. An empirical mammillary PK model is linked to a PD model capturing physiological delay parameters (shown as circles inside a rectangle box) corresponding to different cell intermediate life spans [41]. **(b)** Case study 2: mechanism-based PK–PD model for anti-CD11b antibody capturing neutrophil count, and CD11b count per neutrophil [19] **(c)** case study 3: A mechanism-based PK–PD model for omalizumab [20]. The model explicitly accounts for antigen, antibody, and antigen-antibody complex kinetics.

baseline covariates, such as body weight, age, and so on, on the PK–PD response has been evaluated. Chemotherapy has been known to reduce the clearance, decrease the mature red blood cell lifespan and reduce the efficacy of darbepoetin alfa [41,45]. For AMG 114, empirical scaling was used to obtain the drug-specific PK–PD parameters. Preclinical PK parameters of AMG 114 were allometrically scaled to yield clinical PK parameters. Previously observed PK-covariate relationships for darbepoetin alfa [41,42] were combined with allometric PK predictions to obtain AMG 114 PK in a healthy human population. The clinical *in vivo* potency of AMG 114 was empirically scaled; the observed *in vivo* potency ratio between darbepoetin alfa and AMG 114 in mouse was calculated and was assumed to be the same in humans. Maximum increase in haemoglobin in the clinical setting was assumed to be a system-specific parameter and was assumed to remain constant for darbepoetin alfa and AMG 114. The delay parameters corresponding to cell intermediates' lifespan were obtained from literature. The effect of chemotherapy on PK–PD was assumed to be 'system-specific' and therefore similar between darbepoetin alfa and AMG 114. Other factors assumed, on the basis of clinical experience with darbepoetin alfa, included between subject variability in PK and PD parameters and circadian and measurement-related haemoglobin variability.

Stochastic simulations, using the scaled AMG 114 PK–PD model, were used to guide the design and conduct of an adaptive phase I/II clinical trial in CIA patients [46]. A comparison of the predicted and observed haemoglobin change after 6 weeks of AMG114 treatment (two doses of 200 μg each 3 weeks apart) showed good agreement. Thus, a mechanism-based PK–PD model was used to quantitatively integrate available physiological, pharmacological, and pathological information. The resulting simulation-based early clinical development resulted in substantial cost and time savings.

## Case study 2. Anti-CD11b antagonist recombinant protein

By taking into account disease dependent differences in the pharmacokinetics and pharmacodynamic response, mechanism-based PK–PD models can provide an effective bridge between healthy volunteers and patients or between different disease populations. In many instances, disease dependent differences have already been characterised and quantified in the literature and are often represented as fixed parameters in the model. A successful application of this approach was reported by Marshall *et al.* [19] during the development of UK-276,279 a recombinant glycoprotein (275 amino acids, 41 KDa) that is a selective antagonist to CD11b.

A mechanism-based PK–PD model was used to bridge between healthy volunteers and patients. Binding of UK-276,279 to CD11b blocks infiltration of activated neutrophils to sites of inflammation. Preclinical studies with UK-276,279 suggested the involvement of two clearance mechanisms, neutrophilic and non-neutrophilic CD11b pathways. Using this prior knowledge, a mechanistic PK–PD model based upon CD11b expression was developed [19] to describe the PK and PD in healthy volunteers and patients (Figure 2(b)). The model accounted for the differences between healthy volunteers and patients in target CD11b abundance and time-dependent changes in CD11b cell numbers (number and residence time of neutrophil cells).

The ability to predict the PD in patients from healthy volunteers was an important aspect of the development programme as any future clinical pharmacology studies in healthy volunteers (drug interaction, comparability testing, special populations) could be extrapolated to patients [18]. While the development of an empirical model allowed prediction of single dose administration, multiple dose studies would require a mechanistic PK–PD model to define dose levels and dose frequencies to achieve a targeted level of receptor occupancy and, therefore, potential therapeutic effects in patients in the presence of changing levels of CD11b levels.

## Case study 3. Evaluation of the relationship between *in vitro* affinity and *in vivo* potency: application to the design of a follow-up anti-IgE antibody

An interdependent PK–PD model (Figure 2(c)), which explicitly accounts for the target dynamics and target-mediated binding and clearance of the antibody, has been applied to antibodies against targets, such as immunoglobulin-E [20] and CD4 [38]. The model accounts for non-specific clearance of the antibody, synthesis and elimination rates of the antigen, binding of the antibody to the antigen and elimination of both through the degradation of the complex. The parameters of the PK–PD model are fitted using measured data on both the antibody and the antigen. Because the model describes the distribution and elimination of the antibody through the antigen, it automatically accounts for the capacity-limited distribution and elimination of the antibody. Thus, this model provides a convenient tool to evaluate the role of the individual system and drug components on the overall PK–PD response.

We attempted to characterise the relationship between the antigen-antibody affinity and the overall response using literature-reported PK–PD model parameters. For the anti-IgE antibody omalizumab, free antigen levels were used as a biomarker of efficacy. Literature PK–PD values of omalizumab after intravenous and subcutaneous administration were gathered [20,47] and simulations were performed to characterise the relationship between dose and the associated maximum reduction in free IgE levels at different affinity levels. Mean antibody concentration–time profiles and the free antigen concentration–time profiles after multiple administration of omalizumab were generated. Similar simulations were performed for various antigen-antibody affinity values. The sensitivity analysis revealed that similar maximum reduction in free IgE levels could be achieved with approximately half the dose if the antibody affinity to IgE was 5–10-fold higher than omalizumab (Figure 3). Further increase in affinity did not result in increased *in vivo* efficacy, because the increased affinity was offset by the turnover rate of the IgE–IgG complex. Therefore, expensive affinity maturation steps in the candidate selection stage may be avoided in this case. Simulations also indicated that changes in the non-specific clearance and increased on-rate to the IgE may have additional impact on the overall efficacy profile at the range of affinities being studied [48].

Other, more empirical, descriptions of the IgE–anti-IgE system have also been reported in the literature [49,50]. However, the mechanism-based model, described above, provides more flexibility by directly accounting for the different interactions in the system including on–off rates from the antigen and capacity-limited distribution and elimination of the antibody. Also, this

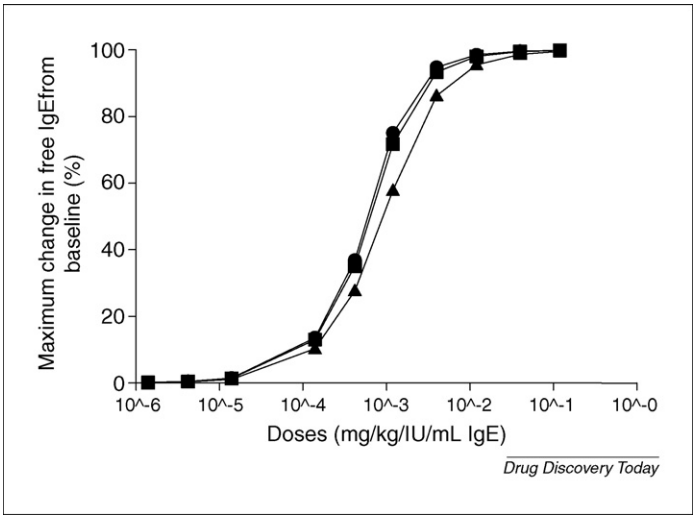


**FIGURE 3**

Simulated maximum IgE reduction vs. dose after a single subcutaneous dose for omalizumab (▲) and 2 theoretical antibodies with five-fold (■) and 10-fold (●) higher affinity than omalizumab. The plot indicates that increases in affinity greater than 10-fold over omalizumab are unlikely to result in any further increase in *in vivo* potency.

model is easily adaptable for a follow-on compound and for different disease states resulting in different antigen capacities and time-dependant antigen dynamics.

## Discussion

The above examples illustrate how mechanism-based PK–PD modelling can be used as the basis for translational research in the area of biologics by incorporating data and information gathered during different stages of drug discovery and development into quantitative, predictive models which can guide future planning and decision making. We believe that implementation of this approach forms an essential component of translational strategies in innovative drug research and, indeed, the FDA has recently highlighted the application of mathematics, statistics and computational analysis to biological information as one of the six main opportunities in its Critical Path Initiative (See http://www.fda.gov/oc/initiatives/criticalpath/reports/opp_list.pdf).

The need for PK–PD modelling to evolve from an empirical to a mechanism-based discipline is increasingly being recognised [1,5,15,17,51]. Theoretically, a fully physiologic/mechanistic PD description is ideal for translational PK–PD since all the parameters used can be obtained from an understanding of the mechanism details. With the generation of vast amounts of data from basic biomedical research, even more granular modelling approaches on the basis of systems biology [52] are being explored. The role of such approaches in early target identification and biomarker selection is a distinct possibility in the near future. In the meanwhile, a necessary area of exploration in this field is the development of methods for cross-species scaling of PD parameters. This area is still in its infancy, however some recent examples have suggested that allometric scaling may be applicable to predict not only pharmacokinetics but also pharmacodynamic responses in humans from data obtained in preclinical models [53–55].

Apart from scientific challenges, significant operational barriers exist in the implementation of translational research in general [8,14]. Further hurdles, specific to PK–PD, include lack of individuals trained and experienced in both biological and quantitative sciences [56], lack of robust computational tools that can handle diverse sets of data, and the lack of an integrated approach to the creation and maintenance of models as a framework for data, information and knowledge retention within pharmaceutical research. In spite of these hurdles, an increasing number of reports are indicating that mechanism-based PK–PD modelling applied to translatable biomarkers can help characterise the efficacy/safety profile of candidate therapeutics early in the development cycle and thus can have a profound impact on increasing the productivity in pharmaceutical research and development.

Overall, we believe that mechanism-based PK–PD, in combination with novel modelling approaches being developed in the areas of physiologically based pharmacokinetics [57], systems biology [52] and quantitative structure-PK–PD relationships [58,59], will become a cornerstone of quantitative drug discovery and development during the next decade.

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