Discussion

Preclinical Pharmacokinetic/Pharmacodynamic Modeling and Simulation in the Pharmaceutical Industry: An IQ Consortium Survey Examining the Current Landscape

Edgar Schuck,^{1,19} Tonika Bohnert,² Arijit Chakravarty,³ Valeriu Damian-Iordache,⁴ Christopher Gibson,⁵ Cheng-Pang Hsu,⁶ Tycho Heimbach,⁷ Anu Shilpa Krishnatry,⁴ Bianca M Liederer,⁸ Jing Lin,⁹ Tristan Maurer,¹⁰ Jerome T Mettetal,¹¹ Daniel R Mudra,¹² Marjoleen JMA Nijssen,¹³ Joseph Raybon,¹⁴ Patricia Schroeder,¹⁵ Virna Schuck,^{11,18} Satyendra Suryawanshi,¹⁴ Yaming Su,¹⁶ Patrick Trapa,¹⁰ Alice Tsai,¹⁷ Majid Vakilynejad,³ Shining Wang,¹⁶ and Harvey Wong^{8,19}

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Abstract. The application of modeling and simulation techniques is increasingly common in preclinical stages of the drug discovery and development process. A survey focusing on preclinical pharmacokinetic/pharmacodynamics (PK/PD) analysis was conducted across pharmaceutical companies that are members of the International Consortium for Quality and Innovation in Pharmaceutical Development. Based on survey responses, ~68% of companies use preclinical PK/PD analysis in all therapeutic areas indicating its broad application. An important goal of preclinical PK/PD analysis in all pharmaceutical companies is for the selection/optimization of doses and/or dose regimens, including prediction of human efficacious doses. Oncology was the therapeutic area with the most PK/PD analysis support and where it showed the most impact. Consistent use of more complex systems pharmacology models and hybrid physiologically based pharmacokinetic models with PK/PD components was less common compared to traditional PK/PD models. Preclinical PK/PD analysis is increasingly being included in regulatory submissions with ~73% of companies including these data to some degree. Most companies (~86%) have seen impact of preclinical PK/PD analyses in drug development. Finally, ~59% of pharmaceutical companies have plans to expand their PK/PD modeling groups over the next 2 years indicating continued growth. The growth of preclinical PK/PD modeling groups in pharmaceutical industry is necessary to establish required resources and skills to further expand use of preclinical PK/PD modeling in a meaningful and impactful manner.

KEY WORDS: pharmaceutical industry; preclinical pharmacokinetic/pharmacodynamic modeling; simulation.

INTRODUCTION

Drug discovery and development has been plagued by clinical attrition rates exceeding 90%, where the primary cause was identified by Kola and Landis (6) as lack of efficacy and unexpected safety findings. The authors highlighted that, while poor pharmacokinetics was identified as a main cause for drug attrition in the early 1990s, this was no longer a leading cause for attrition 10 years later. Advances in preclinical *in vitro* (9, 5, 10) and *in vivo* methodologies (13, 14, 5, 10) for predicting human pharmacokinetics served to reduce the drug failure rate due to poor pharmacokinetics such that, by 2000, lack of efficacy became the main cause of drug attrition. In an updated look at causes for drug failures in phase II (between 2008 and 2010; (1)) and phase III and drug submission (between 2007 and 2010; (2)), lack of efficacy remained the primary cause of attrition contributing to 51% and 66% of drug failures, respectively.

The International Consortium for Innovation and Quality in Pharmaceutical Development (IQ Consortium) is an organization of pharmaceutical and biotechnology companies with the mission of advancing science-based and

¹ Modeling and Simulation, Eisai Inc., 155 Tice Blvd, Woodcliff Lake, NJ 07677, USA.

² Biogen-Idec, Cambridge, MA, USA.

³ Takeda, Deerfield, IL, USA.

⁴ GlaxoSmithKline, Upper Merion, PA, USA.

⁵ PPD, Merck Research Laboratories, West Point, PA, USA.

⁶ PKDM, Amgen Inc., Thousand Oaks, CA, USA.

⁷ Novartis Institutes for Biomedical Research, East Hanover, NJ, USA.

⁸ Drug Metabolism and Pharmacokinetics, Genentech Inc., 1 DNA Way, MS 412a, South San Francisco, CA 94080, USA.

⁹ Sunovion, Marlborough, MA, USA.

¹⁰ Pfizer Inc., Cambridge, MA, USA.

¹¹ Drug Safety and Metabolism, Astra-Zeneca, Waltham, MA, USA.

¹² Eli Lilly and Company, Indianapolis, IN, USA.

¹³ Abbvie, North Chicago, IL, USA.

¹⁴ Bristol-Myers Squibb, Princeton, NJ, USA.

¹⁵ EMD Serono, Billerica, MA, USA.

¹⁶ Sanofi, Bridgewater, NJ, USA.

¹⁷ Vertex Pharmaceuticals Incorporated, Boston, MA, USA.

¹⁸ Present Address: Novartis, East Hanover, NJ, USA.

¹⁹ To whom correspondence should be addressed. (e-mail: Edgar_Schuck@eisai.com; wong.harvey@gene.com)

scientifically driven standards and regulations for pharmaceutical and biotechnology products worldwide. The need to improve an understanding of the drivers of efficacy was recently highlighted at the 2013 IQ Consortium Drug Metabolism Leadership Group managers meeting. In a survey conducted at the meeting, >90% of the attendees agreed that an “in-depth understanding of drivers of efficacy, including biomarkers and translational sciences” would lead to the greatest advances in drug discovery and development over the next 15 years. Pharmacokinetic/pharmacodynamic (PK/PD) modeling and simulation is an important tool that can provide a better understanding of drug efficacy at an earlier stage in the drug discovery and development process.

PK/PD analysis involves the use of mathematical functions to quantitatively interrelate drug behavior and its effects on the biological system of interest. This type of analysis is particularly helpful in understanding exposure–response relationships where there are apparent disconnects in drug concentration and effect related to temporal delays in drug action. In addition, mechanism-based PK-PD models allow the quantitative assessment of known species differences in factors such as pharmacokinetics or *in vivo* drug potency, and enable a more robust characterization of concentration–pharmacodynamic/effect relationships from frequently variable *in vivo* preclinical efficacy data. More recently, there has been an increase in reports describing the utility of PK/PD analysis to help interpret and translate the results of preclinical studies to human (11, 3, 7, 8, 15–17, 4, 18). Finally, the establishment of PK/PD models enables integration of all available data and allows for leveraging of these data for prospective simulations. Just as an early assessment of preclinical pharmacokinetics helped to reduce drug failures due to poor human pharmacokinetics in the 1990s, a better understanding of drug effect using preclinical pharmacokinetic/pharmacodynamic analysis offers an important tool to potentially reduce drug attrition due to a lack of efficacy.

The IQ PK/PD Discussion Group (PK/PDDG), consisting of representatives from 17 pharmaceutical companies, was formed by the IQ Consortium Drug Metabolism Leadership Group as a means to promote innovation through sharing of best practices involved with preclinical PK/PD analysis. The PK/PDDG identified a clear need to better understand the landscape of preclinical PK/PD analysis in pharmaceutical industry. Therefore, a survey focusing on preclinical PK/PD analysis was conducted across IQ member companies. This communication presents the survey results and attempts to provide insights on the current state of preclinical PK/PD analysis in pharmaceutical industry including barriers that may impede its broad use in an impactful manner.

METHODS

The results presented in this communication were obtained by conducting an industry wide survey of pharmaceutical companies that are members of the IQ Consortium. Survey questions were provided and edited to their final form by members of the IQ Consortium PK/PDDG. The types of questions included single/multiple choice, dichotomous (e.g.,

yes/no), rank questions, and open-ended or free text. The final survey consisted of 49 questions aimed to gather information in five different areas: demographics, organizational structure, operating logistics, applications, and impact/perspectives. In some instances, certain questions had a small degree of overlapping information but were collated in the area that provided the best context to the question. “Demographics” questions provided information about the general characteristics of the pharmaceutical companies and the composition of the groups responsible for preclinical PK/PD modeling. “Organizational structure” questions focused on gathering information regarding how preclinical PK/PD groups fit within the organizational structure of various pharmaceutical companies. “Operating logistics” questions provided information on practical operational aspects of preclinical PK/PD modeling groups. “Application” questions gathered information on how preclinical PK/PD modeling is being utilized in each company and in which therapeutic areas. Finally, “impact/perspectives” questions assessed how preclinical PK/PD modeling is perceived within each company, its place in the company’s decision-making processes, its impact on project progression, and the challenges for implementation of preclinical PK/PD modeling throughout the drug discovery and development process.

The survey was conducted using an online questionnaire and survey software (SurveyMonkey; www.surveymonkey.com) and sent to representatives of IQ Consortium member companies that agreed to participate in the survey. Each representative was responsible for providing responses that were reflective of the company as a whole since only one response was collected from each company. The collection of responses occurred over an approximately 1-month period (October 17, 2013 to November 15, 2013). All responses to the questionnaire were kept anonymous. Data analysis and graphs were generated using Microsoft Excel v10 (Microsoft Corporation, Redmond, WA, USA). In some cases, data analysis was performed to see if company size impacted survey responses. Data analyses that considered company size compared pharmaceutical companies with ≤10,000 employees (designated as small to mid-sized companies) to pharmaceutical companies with >10,000 employees (designated as large companies). This division of companies into two groups was due to the lower number of companies with <10,000 employees participating in the survey (7 of 22). Finally, the authors reviewed survey responses as a group and provided potential reasons as to why certain trends were observed. These thoughts have been included in the manuscript and may result in a certain level of bias in the discussion of survey results. However, the authoring group is a reasonable representation of individuals involved in preclinical PK/PD analysis in pharmaceutical industry so these opinions serve to provide context to survey results.

RESULTS AND DISCUSSION

Despite the perceived importance of PK/PD in the discovery and development of new medicines, there have been a limited number of surveys assessing the current state of PK/PD modeling in pharmaceutical industry. A recent survey by Vlasakakis *et al.* (12) surveyed the landscape of drug and disease modeling and simulation in both academia and industry. However, the focus of that survey was to gather

information to develop a framework of competencies to guide future training of PK/PD scientists in both academia and industry. To our knowledge, the survey described in this manuscript serves as the first to specifically examine the state of preclinical PK/PD analysis in pharmaceutical industry. The survey results have been grouped into the following sections: demographics, organizational structure, operating logistics, applications, and impact/perspectives.

Demographics

Survey results were gathered over an approximate 1 month period during which responses were received from 22 pharmaceutical companies. The breakdown of the size of the pharmaceutical companies that participated in the survey is shown in Fig. 1.

The majority of the survey respondents were from companies with >10,000 employees (~68%). This is reflective of the composition of IQ Consortium membership, which consists largely of major pharmaceutical companies with research units based in the USA.

With the rise in the development of biologics by pharmaceutical companies, we wanted to gather information on whether or not a research focus on traditional small molecules *vs* biologics influenced the use of preclinical PK/PD modeling. Figure 2a shows that currently the majority of the US-based pharmaceutical companies (68%) focus their efforts on both small molecules and biologics, which is reflective of the trend to diversify portfolios especially in large pharmaceutical companies. Based on the large proportion of companies with mixed small molecule and biologics focus, we were unable to examine the effect of research focus on the use of preclinical PK/PD modeling. Of interest, small to mid-sized pharmaceutical companies ($\leq 10,000$ employees) appeared to work primarily on small molecules (71%; Fig. 2b) compared to large pharmaceutical companies (>10,000 employees), which focused on both classes of therapies (86%; Fig. 2c). Such a trend may be related to a smaller amount of resources and expertise in small to mid-sized companies limiting diversification.

The breakdown of clinical and preclinical PK/PD modelers is shown in Fig. 3. Companies appeared to have more clinical modelers compared to preclinical modelers with ~50% of the companies involved in the survey having >10 clinical modelers compared to ~33% of companies having >10 preclinical modelers. No difference in this trend was observed when examining the small to mid-sized *vs* large companies. It is not possible to explain the reason for the difference in the number of preclinical *vs.* clinical modelers based on the responses of the survey. However, the greater

number of clinical modelers may be reflective of an evolution of PK/PD modeling from the clinical to preclinical area similar to what occurred during the implementation of pharmacokinetics in pharmaceutical industry. In addition, the nature of the work in the clinical *vs* the preclinical space is different with analyses of clinical trial data often being more labor intensive and thus requiring more modelers. However, it appears that the majority of companies (~59%) intend to increase the number of preclinical modelers in the next 2 years, highlighting the investment in preclinical modeling by IQ member companies (Fig. 3). The growth appears to be largely in large companies (>10,000 people) with 73% of large companies, indicating an expected increase in the number of modelers *vs* only 29% of small to mid-sized companies indicating an expected increase. Overall, preclinical PK/PD modeling is increasing in demand. Preclinical PK/PD modelers come from a variety of backgrounds (Fig. 3d). By far, the most common background of preclinical PK/PD modelers is pharmacokinetics/pharmaceutics with all companies having preclinical modelers with this background. The background is likely to be linked to the most common training for scientists working in preclinical Drug Metabolism and Pharmacokinetics (DMPK) departments since many modelers are members of DMPK departments and are closer to the projects and the biological issues (see below).

Organizational Structure

The results of survey questions focused on gathering information on how preclinical PK/PD modelers are organized are shown in Figs. 4, 5, 6, and 7. The results indicate that, in general, for the majority of the companies, preclinical PK/PD modelers (91%) are members of a DMPK department/group (Fig. 4). All small to mid-sized companies participating in the survey indicated having PK/PD modelers in DMPK. Surprisingly, two large companies did not report having any preclinical PK/PD modelers in their DMPK groups. In addition to DMPK, a large percentage of pharmaceutical companies indicated having preclinical PK/PD modelers reside in the clinical pharmacology/translational sciences (41%) and modeling and simulation (23%) groups (Fig. 4). The presence of preclinical modelers in clinical modeling groups is not surprising since clinical modeling groups were likely established earlier than their preclinical counterparts. A lower percentage of large companies had preclinical PK/PD modelers in these two groups external of DMPK compared to small to mid-size companies (47% *vs* 84%). In most large companies, preclinical groups (such as DMPK) are likely to be resourced sufficiently such that there is less reliance on groups that traditionally support clinical PK/PD to be involved with the preclinical modeling.

Half of the companies that participated in the survey reported having formal PK/PD or modeling and simulation (M&S) group(s) within their organizations (Fig. 5a). The majority of these companies (92%) having a formal M&S group(s) reported that these formal M&S group(s) report into the DMPK group. A smaller percentage of the companies also indicated that the M&S group(s) reported into clinical pharmacology, translational sciences, and/or quantitative sciences groups (Fig. 5b). For pharmaceutical companies with a formal PK/PD or M&S group, this group is most commonly

Fig. 1. Pie chart showing size of the pharmaceutical companies providing responses to survey

Fig. 2. Pie charts indicating proportion of pharmaceutical companies working on small molecules, biologics, or both small molecules and biologics (mixed). **a** Pie chart for all companies ($n=22$) responding to survey, **b** small to mid-sized companies ($\leq 10,000$ employees; $n=7$), and **c** large companies ($>10,000$ employees; $n=15$)

centralized (~59%) or organized into groups depending on geographic regions (29%) (Fig. 6a). This difference in organization may reflect differences in how the drug discovery organizations are arranged with some companies finding more efficiency in pooling modeling resources into one group (global), whereas others prefer closer contact to the “end users” (local). Furthermore, some companies may only be in one geographic region. An examination of trends between larger vs small to mid-sized companies shows that larger companies seem to have a slight preference for a centralized preclinical PK/PD group (67% for larger companies vs 40% for small to mid-sized companies).

More companies have preclinical PK/PD modelers that are an integral part of the project team (64%) rather than acting as a “service provider” (36%) (Fig. 6b). This partition was independent of company size. This percentage differs from the percentage of companies with formal PK/PD group(s) (Fig. 5a) where one would expect more “service

provider” type project support by formal groups. Direct integration of modelers into project team likely increases their effectiveness. Thus, there is likely some integration into discovery project teams even for companies with formal PK/PD groups.

In general, dedicated preclinical PK/PD modelers are a minority within the companies that responded to the survey (Fig. 7). Only two large companies (9.5%), both with over 10,000 employees, reported that their preclinical PK/PD modelers were fully dedicated to modeling and simulation work, while the other 19 companies reported that their preclinical PK/PD modelers had other responsibilities beyond providing modeling and simulation support. Out of these 19 companies, 11 indicated that their modelers were also DMPK representatives in project teams. Interestingly, the two companies with dedicated preclinical PK/PD modelers did not report having a formal PK/PD or M&S group to support preclinical PK/PD modeling within their organizations.

Fig. 3. Bar graphs indicating relative number of preclinical and clinical PK/PD modelers (a, b), anticipated growth of preclinical PK/PD groups over the next 2 years c, and training background of preclinical PK/PD modelers (d) in pharmaceutical companies responding to the survey. PK/Pharm in Fig. 3d is an abbreviation for pharmacokinetics/pharmaceutics

Overall, these results indicate that, in general, preclinical PK/PD modeling and simulation is not a dedicated activity, but an expected and desired skill for members of the DMPK groups. In most companies (59%), preclinical PK/PD modelers handle three to four projects at one time (Fig. 7). The number of projects assigned to modelers seems to be independent of company size.

Operating Logistics

Timing

The most common response from companies (approximately half) was that preclinical PK/PD modeling and simulation activities were initiated during the “late lead optimization” stage (Table I, question A1). This was true

for both large and small to mid-size companies. The timing reflects the stage of drug development where an adequate amount of information is known about a specific molecule to enable preclinical PK/PD analysis. Typically, any modeling efforts occurring earlier than this stage would only be performed on a “tool” or “benchmark” compound if one was available and suitable to characterize in an *in vivo* PK/PD or efficacy model. However, it is fairly common that such a “tool” or “benchmark” molecule does not exist at stages earlier than late lead optimization especially for novel therapeutic targets. The amount of preclinical modeling that occurs during “post-IND” and “clinical development” is expected to be less since clinical biomarker and pilot efficacy data is often available post-IND from clinical trials, and is of greater relevance. In ~18% of companies, the initiation of preclinical PK/PD modeling is dependent on the disease area

Fig. 4. The group/department where the majority of the preclinical PK/PD modelers reside in for pharmaceutical companies responding to the survey. Responses are expressed in the figure as a percentage of pharmaceutical companies providing a given response. Selection of more than one response was allowed if required

Fig. 5. Bar graphs indicating **a** the percentage of companies having formal PK/PD or modeling and simulation group(s) to support preclinical PK/PD modeling and **b** the function/group that this formal PK/PD group reports into. For **b**, selection of more than one option was allowed if there was more than one group performing preclinical PK/PD modeling and simulation

(Table I, question A1). This may be related to differences in the availability and/or suitability of preclinical *in vivo* efficacy or PK/PD models for various therapeutic areas.

More companies reported that PK/PD modeling was planned ahead of time with input from modelers on study design (64%) rather than without input from modelers (36%) (Table I, question A2). Interestingly, the same percentage of

companies responded that preclinical PK/PD modelers were an integral part of the project team *vs* being “service providers” (Fig. 6b). Based on personal experiences and observations, the authors felt that the responses to these two questions were linked since a consequence of including modelers into the project teams is that they are aware of and assist in the design of preclinical efficacy studies such that the data that are acquired are suitable to build quantitative PK/PD models.

Fig. 6. Pie charts showing the percentage of pharmaceutical companies that participated in survey with **a** formal PK/PD groups that are either centralized, or divided and **b** preclinical PK/PD modelers that are either direct or indirect members of the project teams

Standardization and Information Transfer

A cursory look at preclinical modeling practices suggests that companies in general (>90%) are attempting some form of standardization or overlap of practices. In the majority of companies (58%), there appears to be some overlap in modeling practices by each particular therapeutic area; however, each therapeutic area can develop their own practices (Table I, question B1). Some individuality of preclinical modeling practices may exist as preclinical biology models for each therapeutic area likely differ in terms of experimental design, biomarkers, and relevance to human disease.

An examination of standardization and transfer of knowledge between preclinical and clinical PK/PD modeling groups suggests that most companies (>60%) attempt to ensure that information is transferred as there appears to be either shared databases or transfers/hand offs of information when the drug candidates advance from the preclinical to the clinical space (Table I, question B2). This appears to be an area that requires further development since there is a third of companies (33%) where any type of knowledge transfer

Fig. 7. Bar graphs showing percentage of pharmaceutical companies where preclinical PK/PD modelers have other responsibilities beyond PK/PD modeling, and the number of projects each modeler typically handles at one time

process does not exist (Table I, question B2). Lack of a formal process for knowledge transfer appears to be more prevalent for small to mid-sized companies (50%) compared to large companies (25%).

Data Source

Although both *in vitro* and *in vivo* data are being utilized for preclinical modeling, the primary dataset for preclinical modeling appears to be derived from *in vivo* studies (86%) (Table I, question C1). Only three companies, all of which were small to mid-size companies, responded that their primary dataset for PK/PD modeling was *in vitro*. Since *in vitro* studies are in general less costly than *in vivo* studies, this observation might again be a reflection of a budget-driven decision than a strategic one. Most of the *in vivo* data used for preclinical PK/PD modeling is still generated in-house based on the low percentage of companies responding that data for preclinical PK/PD modeling is mostly generated at CROs (9.1%) (Table I, question C2). There appeared to be less of a reliance on CROs from large pharmaceutical companies with 60% of large companies, indicating that data came mostly from studies performed in-house.

Finally, we looked at differences in how the preclinical and clinical modeling groups utilized outsourcing for PK/PD analyses (Table I, questions C3 and C4). Overall, it appears that more outsourcing was performed by the clinical (~35%) rather than the preclinical modeling groups (~13%). Potentially, there are a number of reasons why this trend exists. First, the nature of modeling clinical data sets may play a role. Modeling of clinical data sets requires more standardization, and often, the analyses are laborious and operate under fixed timelines, and with well-vetted analysis strategies. These characteristics make outsourcing more amenable for clinical PK/PD data analyses. In addition, the establishment of specialized clinical modeling groups likely preceded the establishment of the analogous preclinical modeling groups, leading to a natural establishment of several capable outsource providers. Therefore, the higher amount of outsourcing may be related to how long clinical PK/PD groups have been operating. It may be of interest to see if

this trend remains the same over time. No consistent trend in outsourcing was observed when comparing large companies to small and mid-sized companies.

Software

In order to understand which software is being utilized for preclinical PK/PD modeling, a question was included to survey the prevalence in use of various software packages (Table I, question D1). Phoenix/WinNonlin (100%), SIMCYP (86%) and NONMEM (77%) appear to be the most widely used software packages by scientists in pharmaceutical industry for preclinical PK/PD modeling.

Applications

Responses to the survey indicate that preclinical PK/PD modeling is used by almost all companies involved with IQ and widely used by most companies (~68%) in all therapeutic areas (Table II, question A). Overall, the preclinical PK/PD modelers appear to be quite well integrated with the translational biology/pharmacology groups as preclinical modelers in most companies (~67%) have some influence over the study design on preclinical pharmacology studies. The response is consistent with a similar question (Table I, question A2) described in an earlier section of the survey. However, there is room for improvement as modelers in approximately a third of the companies have little or no influence over study design (i.e., selection of either “rarely” or “never” as responses to question B in Table II).

It appears that preclinical PK/PD modeling support is provided to almost all functions that are involved in the drug discovery setting based on the response to question C in Table II. Preclinical modeling support is mostly provided in the context of a project team (~91%), whereas support provided to all other functions appears to be evenly distributed ranging from 41% (biology) to 68% (clinical pharmacology and *in vivo* pharmacology). Approximately 14% of companies supplied preclinical modeling PK/PD support to other functions that were not specified in the survey response. These functions include medicinal chemistry,

Table I. Operating Logistics

Questions	Answers	Response (%)
A. Timing		
A1. At what stage is preclinical PK/PD modeling normally initiated in your company?	Hit-to-lead	9.1
	Late lead optimization	45.5
	Pre-IND	13.6
	Post-IND	0
	Clinical development	9.1
	Depends on therapeutic area or project	18.2
	My company does not do this	4.5
A2. Regarding the timing in which preclinical modeling is done, please indicate the option that best applies:	Modeling is planned ahead of time, modelers participate in efficacy study design	63.6
	Efficacy studies are planned ahead of time, mostly without modeler's input (modeling is opportunistic)	36.4
B. Standardization and information transfer		
B1. If preclinical PK/PD modeling group is not centralized, are practices the same or different with groups supporting different indications/therapeutic areas?	Practices are standardized to all therapeutic areas	33.3
	There is overlap of some practices, but each therapeutic area can develop their own practices	58.3
	Groups are completely independent; practices can vary significantly from one group to another	8.3
B2. If the group is divided between preclinical and clinical, how are the models shared?	We have a shared database of models and data	5.6
	There is an official hand-off of data/databases, models, and reports, which ends the involvement of the preclinical team	11.1
	There is a gradual hand-off of data/databases, models, and reports, with the preclinical modeler working with the clinical team to keep developing the model for clinical application	50.0
	No formal process to transfer knowledge from preclinical to clinical; this has generally been a missed opportunity within our organization	33.3
C. Data source		
C1. Indicate the PRIMARY dataset used for the modeling projects in your company	<i>In vitro</i>	13.6
	<i>In vivo</i>	86.4
	<i>In silico</i>	0
	Literature	
	Other	0
C2. Where is the data generated most of the time?	Data is generated mostly from in-house studies	45.5
	Data is generated mostly at CROs	9.1
	Data can be generated either in-house or at CRO; depends on the project	45.5
C3. In your company, what percentage of pre-clinical PK/PD modeling is done in-house <i>versus</i> outsourced to modeling CROs?	In-house (%)	90
	Outsourced (%)	13.3
C4. In your company, what percentage of clinical PK/PD modeling is done in-house <i>versus</i> outsourced to modeling CROs?	In-house (%)	65.2
	Outsourced (%)	34.8
D. Software		
D1. What are the software tools used in your company for preclinical PK/PD modeling (check all that apply):	Phoenix/WinNonlin	100
	NONMEM	77.3
	SAAM II	31.8
	ADAPT V	22.7
	MATLAB	50.0
	Berkeley Madonna	40.0
	SIMCYP	86.4
	GastroPlus	59.1
	Statistical packages: R, SAS, Splus, etc.	45.5
	Others ^a (Mathematica; ACSL-TOX; MONOLIX; SCIENTIST)	18.2

^a The written responses supplied by those who selected "Others" are shown in the parentheses

pharmaceutics, and imaging. The primary goal of preclinical PK/PD analysis for all companies (100%) appears to be selection/optimization of doses and/or dose regimens,

including prediction of human efficacious doses. This was followed by "comparison with competitor compound" (64%) and "assess optimal target engagement" (59%) (Table II,

Table II. Applications

Question	Answers	Response (%)
A. How would you describe the use and application of PK/PD modeling across functional areas in your company?	Used and applied in all therapeutic areas	68.2
	Widely applied but not in all therapeutic areas	27.3
	Weakly supported; limited to one or two therapeutic areas	4.5
	Not used	0
B. How often does PK/PD modeling inform preclinical pharmacology study design in your company?	Always	0
	Frequently	66.7
	Rarely	28.8
	Never	4.8
C. In your company, to what function do the modelers provide preclinical PK/PD support to. Please select all that apply.	Biology	40.9
	<i>In vivo</i> pharmacology	68.2
	Toxicology	54.5
	Translational medicine	59.1
	Clinical pharmacology	68.2
	Project teams directly	90.9
	Others (medicinal chemistry; pharmaceuticals; imaging)	13.6
D. Please indicate the primary goal of the PK/PD modeling in your company (check all that apply).	Description of the data with a mechanistic/semi-mechanistic model	68.2
	Target validation	18.2
	Triage compounds for advancement	45.5
	Comparison with competitor compound	63.6
	Assess optimal target engagement	59.1
	Selection/optimization of doses and/or dose regimens, including prediction of human doses	100.0
	Optimal sampling times	50.0
	Other ^a : (medicinal chemistry design; aid <i>in vivo</i> study design)	18.2
	Oncology	40.9
	Neuroscience	13.6
E. In what therapeutic areas does preclinical PK/PD modeling provide the most support in your organization?	Autoimmune disorders	0
	Infectious diseases	4.5
	Cardiovascular	0
	Metabolic disorders	13.6
	Other ^a (similar across multiple therapeutic areas; biologics)	27.3
	Oncology	10.0
	Neuroscience	35.0
F. In what therapeutic areas does preclinical PK/PD modeling provide the least support in your organization?	Autoimmune disorders	20.0
	Infectious diseases	10.0
	Cardiovascular	0
	Metabolic disorders	5.0
	Other ^a (renal)	20.0
	Oncology	38.1
	Neuroscience	14.3
G. What therapeutic area has the implementation of preclinical PK/PD modeling been the most impactful?	Autoimmune disorders	4.8
	Infectious diseases	9.5
	Cardiovascular	0
	Metabolic disorders	14.3
	Other ^a (all therapeutic areas; biologics)	19.0
	Never	9.1
	Sometimes	86.4
H. Regarding systems pharmacology, to what extent is it being used in your company?	Often/always	4.5
	What is systems pharmacology?	0
	Pharmacology	38.1
I. Which departments are actively involved in the use of systems pharmacology? Please indicate all that apply.	Biology	14.3
	Biomarkers/bioinformatics	28.6
	DMPK	52.4
	Statistics	9.5
	Others ^a (clinical pharmacology; modeling & simulation; computational biology; translational medicine)	38.1
	Never	22.7
	Sometimes	72.7
J. How often is PBPK analysis combined with a PD measurement (PB/PK/PD)?	Often/always	4.5

^a The written responses supplied by those who selected "Others" are shown in the parentheses

question D). These responses are consistent with preclinical PK/PD modeling being used in the context of a project team since these activities provide very important information used to select and advance drug candidates to the clinic, which is the primary goal of drug discovery project teams.

Of the various therapeutic areas supported by preclinical PK/PD modeling, oncology was clearly most supported (~41%; Table II, question E). This was followed by neuroscience and metabolic disorders (both ~14%). Accordingly, the therapeutic area where preclinical PK/PD modeling showed the most impact was in oncology (38%) followed by neuroscience (~14%) and metabolic disorders (~14%) (Table II, question G). Dose and schedule are of critical importance for the development of oncology agents. Therefore, the high use of preclinical PK/PD modeling in oncology is in line with the response from all companies that primary goal of preclinical PK/PD modeling is “selection/optimization of doses and/or dose regimens, including prediction of human doses.” The therapeutic area that was least supported by PK/PD modeling was “neuroscience” at 35% (Table II, question F). Surprisingly, neuroscience was also among the therapeutic areas where modeling was the most supported and most impactful as discussed above. Based on these responses, it appears that some companies perform preclinical PK/PD modeling using neuroscience data where others are of the view that there is little value gained. The results may also be reflective of the specific CNS disease that each company is working on and the degree of translatability to man of the particular preclinical CNS disease models being used.

In contrast to the wider use of preclinical PK/PD modeling, the majority of the survey participants (~86%) indicated systems pharmacology models are only “sometimes” used (Table II, question H). The majority of systems pharmacology users reside in DMPK (52%), which suggests that responses include the use of commercial software such as SIMCYP and GastroPlus, which are physiologically based pharmacokinetic (PBPK) modeling software often included under the broader systems pharmacology umbrella (Table II, question I). The lower frequency of use of systems pharmacology models compared to preclinical PK/PD models may relate to the larger amounts of compound specific information needed to build a systems pharmacology model as well as the relative “infancy” of the discipline in pharmaceutical industry. Large amounts of compound specific information are often not available early on in the drug discovery process. In addition, information around new biological targets is typically incomplete and thus serves to impede the development and implementation of systems pharmacology models.

It appears that use of hybrid PBPK models with PK/PD components (PB/PK/PD) is gaining interest as a large number of companies indicated some use of PB/PK/PD modeling based on the large combined responses of either “sometimes” (72.7%) or “often/always” (4.5%) (Table II, question J). However, the low number of companies selecting “often/always” indicates that this practice of using PBPK modeling in combination with preclinical PK/PD analysis is not commonplace. In addition, 43% of the small to mid-size companies indicated that PBPK is never combined with PD measurements, compared to only 13.3% in larger companies. This can be explained by the fact that PBPK models require a

large amount of data and expertise to develop, which may impede its common use with PD measurements, especially in smaller sized companies. In addition, commercial PBPK software are generally more expensive compared to traditional PK/PD software, so this observation may simply reflect the ability of larger companies to afford PBPK software.

Impact/Perspectives

Generally, it appears that preclinical PK/PD modeling is fairly established and growing in the IQ companies that responded to the survey with all companies viewing preclinical modeling as either “very important” or “somewhat important” (Table III, question A). Larger companies more frequently viewed preclinical modeling as “very important” with approximately double the number of responses from large companies when compared to smaller organizations (53% vs 28%). This slight difference may be due to more resourcing to perform this work in large organizations.

Considering the primary goal of pharmaceutical companies is to discover and develop new medicines, a potential area of growth could be in the application of preclinical PK/PD modeling with a particular emphasis towards influencing the drug development process. Currently, in only approximately a third of the companies (32%), preclinical PK/PD modeling appears to “always” impact the decision-making process in drug development (Table III, question B). Approximately 59% of the companies responded that preclinical modeling sometimes has an impact on decision making and the remaining 9% of the companies view the data as being largely descriptive in nature and rarely has any influence on decision making. Larger pharmaceutical companies appear to value the use of preclinical PK/PD modeling and its impact/influence on decision making more compared to small to mid-sized companies based on a higher percentage of responses indicating that it “always” impacts the decision making process (40% vs 14%). There appears to be no relationship between therapeutic area that preclinical PK/PD modeling is most impactful and its influence on the decision-making process as all companies that replied “always” for question B in Table III found its use to be most impactful across different therapeutic areas (data from responses to question G in Table II). Preclinical PK/PD modeling is on critical path for molecule advancement in more than half of the companies surveyed at ~64% (Table III, question C). However, this is double the percentage of companies that report PK/PD analysis always influencing decision making (Table III, question B). A critical look at how these preclinical PK/PD analyses are used in the decision-making process is warranted in order to improve its effectiveness considering the large number of companies that have this activity on critical path.

An examination of factors impeding the implementation of preclinical PK/PD modeling suggests that multiple factors make implementation difficult (Table III, question D). The factors that half of the companies identified as issues are the inability to “gain support from project/management team” and the lack of “time and resources for continuous training of staff.” As many of the modelers reside in DMPK (Fig. 4), it is possible that the preclinical PK/PD modeling efforts grew out of existing DMPK groups. Typically, only advanced or “tool”

Table III. Impact/Perspectives

Question	Answers	Response (%)
A. What is the general view within your company on the importance of preclinical PK/PD modeling?	Very important	45.5
	Somewhat important	54.5
	Not important	0
B. Does preclinical PK/PD modeling have an impact on drug development decision-making in your company?	Always	31.8
	Sometimes	59.1
	Rarely, it is mostly descriptive	9.1
C. Is preclinical PK/PD on the critical path for molecule advancement in your organization?	Yes	63.6
	No	36.4
D. What do you think are the challenges for PK/PD modeling implementation in your company? Please select all that apply.	Gain support from project/management team	54.5
	Lack of expertise (trained modelers)	36.4
	Lack of time to dedicate to modeling projects	45.5
	Lack of time and resources for continuous training of staff	54.5
	Lack of appropriate tools (software programs)	0
	Not enough data available or shared across groups/teams	45.5
	Lack of communication across different functions (e.g., DMPK, Pharmacology, Clin Pharm, Biostats, etc.) or geographical regions	50.0
	Other ^a (lack of awareness, lack of clear objectives, retention)	18.2
E. Other than human PK prediction or PK DDI liability assessment, how often is preclinical PK/PD modeling included in regulatory submissions such as IND, IB, and briefing documents in your company?	Never	27.3
	Sometimes, it depends on the project	54.5
	It is often included	18.2
F. Regarding regulatory submissions, is there an increasing trend to date, or expected over the coming years?	Certainly, yes	54.5
	Maybe, not sure	45.5
	No	0
G. Is preclinical PK/PD modeling used to inform the phase 2 POC study design in your company?	Always	13.6
	Sometimes, if the models are available	54.5
	Not very often, even when models are available	22.7
	Never	9.1
H. Have you personally seen PK/PD modeling have an impact in drug development?	Yes	86.4
	No	13.6
I. Has your company had interactions with the FDA, EMA, or other regulatory agency regarding preclinical PK/PD, PBPK, and PB/PK/PD models?	Yes	47.6
	No	52.4
J. In what phase of drug development has interaction with regulatory agencies happened using preclinical PK/PD, PBPK, and PB/PK/PD models?	Pre-IND	10.0
	Prior to phase 2	50.0
	End of phase 2 meeting	10.0
	Briefing Document	0
	Other ^a (interactions occurred in more than 1 phase)	30.0

^aThe written responses supplied by those who selected “Others” are shown in the parentheses

compounds have enough existing data to perform modeling analysis. As such, preclinical modeling may not be a regular activity on projects, and therefore, obtaining support from the project team and management to get adequate resource to perform such analysis may be prohibitive.

On the regulatory front, it appears that preclinical PK/PD modeling is increasingly being included in regulatory packages, with approximately 73% of companies including these analyses in regulatory submissions at some point for particular projects (Table III, question E). Inclusion of preclinical PK/PD modeling in regulatory submissions appears more prominent in larger compared to smaller companies, with only 13% of large companies never including these data in regulatory packages compared to 57% for smaller companies. When asked whether inclusion of preclinical PK/PD modeling as a trend would increase in regulatory submissions, companies surveyed were evenly split between answering “yes, certainly” and “maybe, not sure” (Table III,

question F). The use of preclinical PK/PD modeling to inform phase II POC study design appears to be company and likely therapeutic area dependent (Table III, question G). Only 14% of companies use preclinical PK/PD modeling to “always” inform phase II proof of concept (POC) study design. For other companies, its use for phase II appears to be inconsistent and likely dependent on the particular project as the majority of the surveyed companies (~77% combined) responded with “sometimes, if the models are available” or “not very often, even when models are available.” Finally, the majority of companies (86.4%) have seen preclinical PK/PD modeling have an impact in drug development (Table III, question H). Approximately half of the companies surveyed (~48%) have had regulatory interactions with the FDA regarding preclinical modeling of some form (Table III, question I). Most of these interactions occurred prior to phase II likely because preclinical data typically becomes less

informative as more and more clinical data are collected (Table III, question J).

CONCLUSION

Preclinical PK/PD modeling is widely used in pharmaceutical industry with the most common goal of these analyses being to enable the selection/optimization of human doses and/or dose regimens, including prediction of human efficacious doses. However, the consistent use of more complex models including systems pharmacology and hybrid physiologically based pharmacokinetic models with PK/PD components was less common compared to traditional PK/PD models. Preclinical PK/PD analysis is increasingly being included in regulatory submissions with ~73% of companies including these data to some degree. Most companies have seen impact of these preclinical analyses in drug development. The continued growth of preclinical PK/PD modeling groups in pharmaceutical industry is necessary to establish the required resources and skills to further expand the use of preclinical PK/PD modeling in an impactful manner.

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REFERENCES

- Arrowsmith J. Trial watch: phase II failures: 2008–2010. *Nat Rev Drug Discov*. 2011;10:328–9. doi:10.1038/nrd3439.
- Arrowsmith J. Trial watch: phase III and submission failures: 2007–2010. *Nat Rev Drug Discov*. 2011;10:87. doi:10.1038/nrd3375.
- Chang C, Byon W, Lu Y, Jacobsen LK, Badura LL, Sawant-Basak A, *et al*. Quantitative PK-PD model-based translational pharmacology of a novel kappa opioid receptor antagonist between rats and humans. *AAPS J*. 2011;13:565–75. doi:10.1208/s12248-011-9296-3.
- Heimbach T, Gollen R, He H. Practical anticipation of human efficacious doses and pharmacokinetics using preclinical in vitro and in vivo data. In: Wang J, Urban L, editors. *Predictive ADMET: Integrated approaches in drug discovery and development*. Wiley Inc.; 2014. p. 319–352.
- Jones RD, Jones HM, Rowland M, Gibson CR, Yates JW, Chien JY, *et al*. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 2: comparative assessment of prediction methods of human volume of distribution. *J Pharm Sci*. 2011;100:4074–89.
- Kola I, Landis J. Can the pharmaceutical industry reduce attrition rates? *Nat Rev Drug Discov*. 2004;3:711–5.
- Liu L, Di Paolo J, Barbosa J, Rong H, Reif K, Wong H. Anti-arthritis effect of a novel Bruton's tyrosine kinase inhibitor in Rat collagen-induced arthritis and mechanism-based pharmacokinetic/pharmacodynamic modeling: relationships between inhibition of BTK phosphorylation and efficacy. *J Pharmacol Exp Ther*. 2011;338:154–63. doi:10.1124/jpet.111.181545.
- Maurer TS, Ghosh A, Haddish-Berhane N, Sawant-Basak A, Boustany-Kari CM, She L, *et al*. Pharmacodynamic model of sodium-glucose transporter 2 (SGLT2) inhibition: implications for quantitative translational pharmacology. *AAPS J*. 2011;13:576–84. doi:10.1208/s12248-011-9297-2.
- Obach RS, Baxter JG, Liston TE, Silber BM, Jones BC, MacIntyre F, *et al*. The prediction of human pharmacokinetic parameters from preclinical and in vitro metabolism data. *J Pharmacol Exp Ther*. 1997;283:46–58.
- Ring BJ, Chien JY, Adkison KK, Jones HM, Rowland M, Jones RD, *et al*. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 3: comparative assessment of prediction methods of human clearance. *J Pharm Sci*. 2011;100:4090–110.
- Salphati L, Wong H, Belvin M, Edgar KA, Prior WW, Sampath D, *et al*. Pharmacokinetic-pharmacodynamic modeling of tumor growth inhibition and biomarker modulation by the novel PI3K inhibitor 2-(1H-indazol-4-yl)-6-(4-methanesulfonyl-piperazin-1-ylmethyl)-4-morpholin-4-yl-thieno[3,2-d]pyrimidine (GDC-0941). *Drug Metab Dispos*. 2010;38:1436–42. doi:10.1124/dmd.110.032912.
- Vlasakakis G, Comets E, Keunecke A, Gueorguieva I, Magni P, Terranova N, *et al*. White paper: landscape on technical and conceptual requirements and competence framework in drug/disease modeling and simulation. *CPT Pharmacometrics Syst Pharmacol*. 2013;2:e40. doi:10.1038/psp.2013.16.
- Ward KW, Proksch JW, Levy MA, Smith BR. Development of an in vivo preclinical screen model to estimate absorption and bioavailability of xenobiotics. *Drug Metab Dispos*. 2001;29:82–8.
- Wong H, Grossman SJ, Bai SA, Diamond S, Wright MR, Grace Jr JE, *et al*. The chimpanzee (*Pan troglodytes*) as a pharmacokinetic model for selection of drug candidates: model characterization and application. *Drug Metab Dispos*. 2004;32:1359–69.
- Wong H, Choo EF, Alicke B, Ding X, La H, McNamara E, *et al*. Anti-tumor activity of targeted and cytotoxic agents in murine subcutaneous tumor models correlates with clinical response. *Clin Cancer Res*. 2012;18:3846–55. doi:10.1158/1078-0432.CCR-12-0738.
- Wong H, Vernillet L, Peterson A, Ware JA, Lee L, Martini J-F, *et al*. Bridging the Gap between preclinical and clinical studies using PK-PD modeling: an analysis of GDC-0973, a MEK inhibitor. *Clin Cancer Res*. 2012;18:3090–9. doi:10.1158/1078-0432.CCR-12-0445.
- Yamazaki S, Vicini P, Shen Z, Zou HY, Lee J, Li Q, *et al*. Pharmacokinetic/pharmacodynamic modeling of crizotinib for anaplastic lymphoma kinase inhibition and antitumor efficacy in human tumor xenograft mouse models. *J Pharmacol Exp Ther*. 2012;340:549–57.
- Zager MG, Kozminski K, Pascual B, Ogilvie KM, Sun S. Preclinical PK/PD modeling and human efficacious dose projection for a glucokinase activator in the treatment of diabetes. *J Pharmacokinetic Pharmacodyn*. 2014;41:127–39. doi:10.1007/s10928-014-9351-7.