Translational Pharmacology:

The Key to Ensuring Safe and Effective Dosing

By Biologics Consulting Group, Inc & Quanticate, Ltd.

Introduction:

The relationship between dose, systemic exposure, and both safety and efficacy are the most important elements in biopharmaceutical/drug development. The key is to attain adequate systemic exposure to mediate a clinically effective response while avoiding a level of exposure that results in toxicity. Understanding these relationships constitutes the central dogma of product development from preclinical studies and on through to Phase 1, 2, and 3 clinical trials, and is still important in post-marketing studies and pharmacovigilance.

In order to proceed successfully through clinical development, it is necessary to accurately assess and demonstrate a favorable risk/benefit relationship at each milestone. This begins at the preclinical level, where appropriate pharmacodynamic, safety pharmacology, pharmacokinetic, toxicology and toxicokinetic studies are performed in various animal species. The results of these studies are used to demonstrate proof-of-concept for the proposed indication and to support safety for first-in-human administration in a Phase I clinical trial. These preclinical study results are also used to determine the no-observable-adverse-effect level (NOAEL) and estimate the "Maximum Safe Clinical Starting Dose" which are then used for determining the dose range to be tested in the Phase I clinical trial[1]. Thus, the FDA depends heavily on the preclinical pharmacology-toxicology program to support safety and plan the Phase I clinical trial. Results of the preclinical pharmacology-toxicology program are submitted to the FDA as part of an Investigational New Drug (IND) Application to support the proposed first-in-human clinical trial. The focus of the FDA's clinical reviewers when assessing a Phase I IND application is whether the first-in-human clinical study is designed to demonstrate safety in a small number of subjects without putting these subjects at unnecessary risk.

Although safety is the main focus in the preclinical studies and early clinical trials, the sponsor should also be thinking in terms of defining the relationship between dose, exposure and efficacy. Historically, one of the main reasons for the high rate of drug attrition in clinical development was undesirable pharmacokinetics (PK); from 1964 to 1985, approximately 39% of drug candidates in the UK failed clinical development due to their PK characteristics[2]. This is no longer a major issue due to improved approaches to drug design and candidate selection increasing the bioavailability of new chemical entities. More recently, Phase 2 clinical trials most often fail because insufficient attention was paid to accurately translating preclinical

efficacy findings to clinical doses that are not just safe, but have a high chance of demonstrating efficacy[3,4]. In fact, the incidence of failure due to efficacy in Phase 2 clinical trials is actually increasing based on an analysis of 2008-2010 data. Figure 1, drawn from a recent article by Arrowsmith (2011)[3], indicates that 51% of 87 Phase 2 trials conducted between 2008 and 2010 clearly failed because of efficacy. The authors report that an additional ~ 29% were categorized as failures due to "strategic" reasons that likely resulted from failures due to efficacy (as well as safety). Thus, the overwhelming majority of Phase 2 failures were related to efficacy.

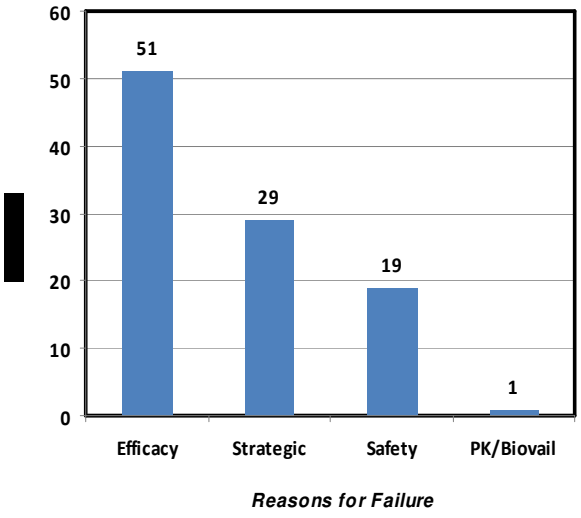


Figure 1. Phase 2 Trial Failures: 2008-2010. Revised from Arrowsmith et al.(2011)[3] reporting data from 108 failed Phase 2 clinical trials. The reasons for failure were reported for 87 of the 108 failed trials and presented as the percentage of the failures in each category. The numbers above each bar are the percentages.

Analysis of Phase 3 trial failures between 2003-2007 indicate that ~45% are unsuccessful because of failure to demonstrate efficacy compared to placebo[5]. These data for Phase 2 & 3 failures are very sobering to CEOs and investors when considering the prospects for success and return on investment. Looking at the top 50 companies and all classes of drugs, it is estimated that approximately 1 drug in every 6 candidates that enter clinical testing receives approval by FDA[6]. Since most of these drugs fail at the level of Phase 2 clinical testing, it is critical that companies employ strategies that increase the chances of obtaining efficacy. This will provide a much stronger basis for undertaking the major commitment of time and resources required for Phase 3 clinical testing and reduce failures due to efficacy. An extremely important part of this strategy is dose optimization, which represents one of the main causes of efficacy-related failures in late-phase clinical testing. In fact, the FDA guidance on end-of-Phase 2A meetings[7] specifically states: "*Accurate dose-response information is important for understanding how patients should take drugs to maximize desirable effects and minimize*

undesirable effects. Dose selection for Phase 2 and Phase 3 trials is a challenge in many drug development programs, and poor choice may lead to trial failure. Improving early dose selection may increase the likelihood of future trial success".

It is estimated that no more than 8% of drugs entering clinical testing for oncology indications ever receive licensure. This dismal record is viewed by some as simply unsustainable. To help address these issues, PK data should be analyzed in tandem with pharmacodynamic (PD) data to assess the pharmacokinetic/pharmacodynamic (PK/PD) relationship throughout the entire drug development process. We address this problem early in preclinical and clinical development, and are providing sponsors with the translational pharmacology resources to successfully optimize their chances for success in their critical Phase 2 and Phase 3 clinical trials.

Preclinical and Clinical Pharmacokinetic/Pharmacodynamic Studies

We view preclinical and clinical PK/PD studies as a continuum that permits optimal translation of dose from animal studies to clinical trials and finally to clinical practice. PK/PD analysis should not be performed as an afterthought or simply to meet regulatory requirements, but rather must be carried out with careful planning from early development through product approval. The fundamental principle of translational pharmacology is to design pharmacokinetic and toxicokinetic studies in the preclinical setting and early Phase 1 clinical trials with the purpose of accurately and effectively modeling the dosing so that critical clinical trials maximize their chance of success with respect to both safety and efficacy. Therefore, the goal of translational pharmacology is not simply to design preclinical studies to demonstrate safety for first-in-human clinical administration, but to design studies that, together with Phase 1 clinical data, will be used to maximize the chances of success in the Phase 2 and Phase 3 clinical trials. It is worth noting that preclinical, first-in-human and other Phase 1 studies can be particularly well suited to PK/PD analyses since a wide range of dose levels are often assessed and blood sampling tends to be intensive (data rich). Furthermore, depending on the therapeutic area, biomarker data can be incorporated into such studies relatively easily and biomarkers can play a role in bridging animal and human pharmacology, toxicity/safety evaluation, dose selection, patient selection. The use of biomarkers can be an integral part of reducing the risk of Phase 2 trial failure[8]. Later in clinical development, we utilize data gathered across clinical trials to characterize the relationships between dose, safety, efficacy, biomarkers and key population covariates. These data are used to help define dosing guidelines for use in clinical practice following approval. Biomarkers have played a key role in accelerated approval.[9]

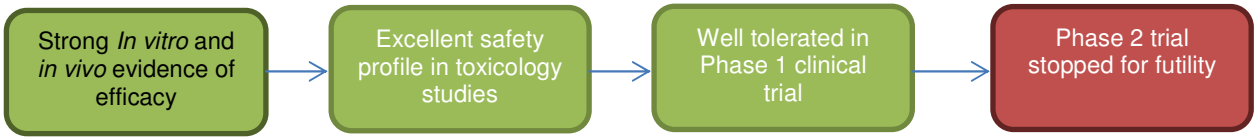
The following case study illustrates the need and critical role that PK/PD assessments and modeling can play in increasing the chances for success in the development process. This particular example is for an oncology drug, a therapeutic area which has one of the highest failure rates (estimated at ≥ 90%[10]).

Case Study

A new biopharmaceutical for treating cancer has shown evidence of efficacy in both *in vitro* cell culture studies and *in vivo* xenograft models of pancreatic tumors, including evidence for synergism with both first line and second line therapeutic agents. Toxicology and toxicokinetic data suggested that this new biopharmaceutical may have a very favorable adverse event profile since it produced severe toxicity only at very high doses of drug. FDA allowed this drug to enter a first-in-human Phase 1 clinical trial in advanced pancreatic cancer patients and the results showed it to be well tolerated suggesting that this new agent was safe and could be tested in a Phase 2 dose escalation trial. This Phase 1 trial demonstrated significant evidence of safety at the doses tested and the investigators felt it was not necessary to add additional dosing cohorts in an attempt to establish the maximum tolerable dose.

A Phase 2 clinical trial followed from this study and targeted pancreatic cancer patients based on efficacy that was demonstrated in *in vitro* and *in vivo* proof-of-concept pharmacology studies and the good tolerability and safety profile from the Phase 1 trial. The Phase 2 trial confirmed the tolerability and safety profile of the drug, but was stopped because of futility to demonstrate efficacy based on the prospective frequentist (non-Bayesian) design of the study (Figure 2.).

Figure 2 A Common Scenario



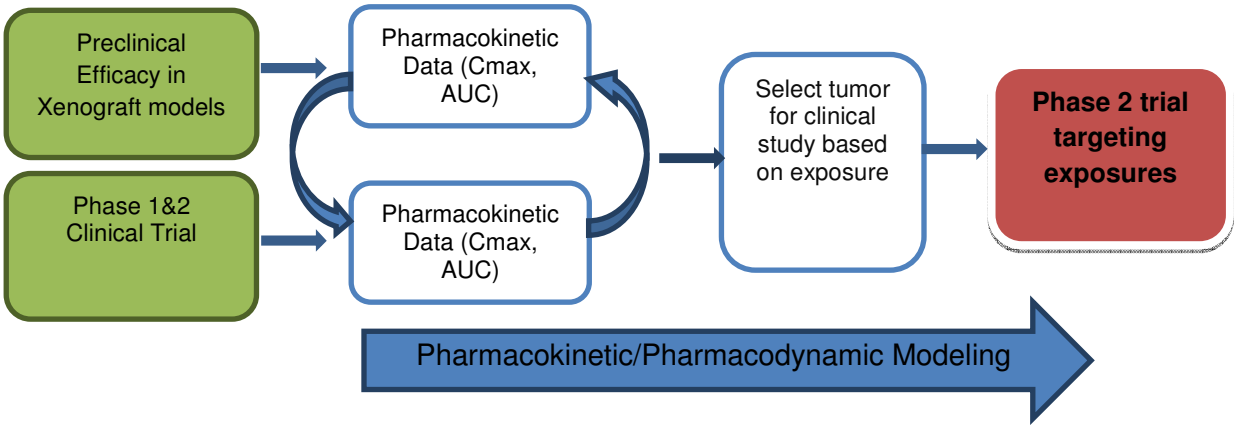
Retrospective analysis of the PK data from the mouse xenograft models and the human PK data from both the Phase 1 and 2 trials revealed that exposures (AUCs) were considerably lower in humans than exposures observed with the pancreatic tumor lines that had demonstrated efficacy in xenograft models. In fact, the results of this analysis indicated that the levels of exposure attained in humans correlated with exposures seen in mouse models showing slightly less efficacy in colon cancer cell lines. These data suggested that the wrong type of tumor (pancreatic vs. colon) may have been selected for clinical investigation. Originally, the basis for selection of the disease (particular tumor) for study in clinical trials was the tumor that showed the highest percent tumor growth suppression (E_{max}) in xenograft mouse models in the absence of significant toxicity. However, this selection was premature and ignored the difficulty of translating exposure in animal models to that achievable in humans. The selection should have been based on a comparison (using appropriate allometric corrections) of the exposures achieved in the Phase 1 clinical trial and those observed in preclinical studies demonstrating efficacy in xenograft tumor models.

Additionally, this retrospective analysis of the data revealed that increasing the maximum dose used in the Phase 1 clinical trial could have achieved the exposures associated with efficacy in the xenograft mouse models of pancreatic cancer. Because the appropriate analyses had not been performed on the preclinical and Phase 1 PK/PD data, the design of the Phase 2 trial did not target a potentially efficacious dose. The investigators did not realize that further dose escalation in the Phase 1 trial may have resulted in the selection of a dose for the Phase 2 study with a higher chance of demonstrating disease activity.

All too often the focus is solely on establishing the MTD in Phase 1 clinical trials and the assumption that maybe some indications of potential efficacy will be obtained. While the number of patients in a Phase 1 trial is not sufficient to demonstrate statistical evidence of efficacy, it is important to establish that the exposures achieved in patients are in the efficacious range established in the preclinical models. In addition, assessments of biomarkers can provide further evidence of the potential for efficacy and make the transition to Phase 2 clinical trials more successful.

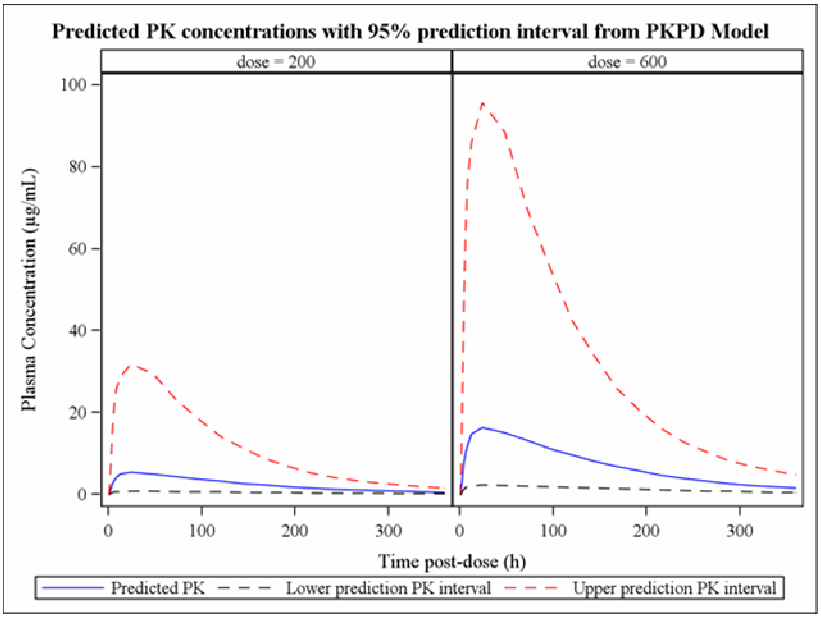
Fortunately, in this particular case, the preclinical pharmacokinetic studies were designed such that complete pharmacokinetic data were obtained allowing for robust estimates of the relationship between efficacy and exposure to the test drug. These preclinical data, combined with the human PK data, could thus be used to select the optimal tumor for further clinical study. In addition, PK/PD modeling was used to determine the optimal study design for the next clinical study, in particular the dosing range required to maximize the chances of observing efficacy (Figure 3.). In this case, a Bayesian design with appropriate interim analyses was selected to most efficiently show efficacy in the second Phase 2 study.

Figure 3. Utilizing PK/PD to Achieve Accurate Translation of Efficacious Dosing



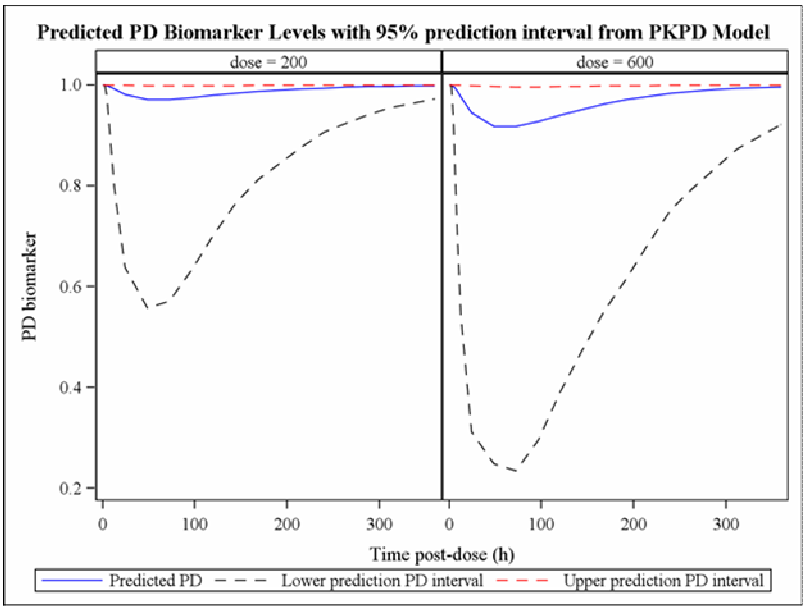
The data in Figure 4a show the plasma concentrations predicted for two concentrations of drug to be used in the Phase 2 clinical trial including the 95% prediction intervals for these individual plasma concentrations. Data like these can be not only important to establishing exposures that

Figure 4a.



are likely to be efficacious, they also help to warn against the possibility of achieving drug exposures in the toxic range for these patient populations. When the data was combined with the reduction in expression of the tumor biomarker from the mouse xenograft models, it was possible to predict the reduction in the appearance of this biomarker in patient plasma as shown in Figure 4b. The data in Figure 4b show the predicted pharmacodynamics response for single dose treatment at two different doses (200 and 600 mg) of drug.

Figure 4b.



With the actual PK and PD data from patients it is possible, using the Bayesian approach, to select the optimal dose as well as the most susceptible/responsive patient subpopulations for expansion in the Phase 2 clinical trial. The Bayesian approach utilizes prior data and assessments, in this case the Phase 1 study patient PK data and data from the ongoing Phase 2 trial patients, to provide better estimates of the treatment efficacy using biomarker assessments. This approach continually learns and improves as the trial progresses to target the optimal dose and most susceptible patient population in the Phase 2 clinical trials and ultimately for testing in one or more Phase 3 clinical trials.

Commentary on the Case Study

This example illustrates how: 1) insufficient attention to PK/PD analysis and modeling all too often contributes to the failure of Phase 2 trials and; 2) careful planning and study design that results in robust PK/PD data from preclinical and Phase 1 clinical studies is critical to designing successful Phase 2 and 3 clinical trials. For small companies, efforts to move forward with additional clinical studies following failure of a Phase 2 clinical trial can be associated with significant difficulties and delays that often prove unsustainable. At a minimum, one can expect difficulty convincing investors to fund further studies due to the loss of confidence in the candidate drug after a Phase 2 trial has been stopped due to futility. This loss of confidence is also seen in the reduced enthusiasm of key opinion leaders and clinical investigators to participate in further clinical testing. Furthermore, regulatory agencies may become much more critical about what will be required for a sponsor to proceed with further clinical trials when efficacy has been brought into question in the clinical setting. The assumption of efficacy based on the preclinical data becomes a weaker argument for the efficacy potential of a product once it is in clinical trials. These are extraordinarily difficult barriers to overcome and, at a minimum, will constitute significant program delays and unplanned additional costs. For small companies, practically speaking, there is really only one chance to get this right.

For small biotech companies, in particular, it is critical to establish integrated program design from the beginning that optimizes the use of all prior data to avoid the myriad of pitfalls and target successful clinical trials. This approach also permits the design of a development program with the fewest number of studies and at the same time highest probability to succeed, saving time, resources, and optimizing investor dollars.

Discussion

The importance of preclinical and clinical pharmacokinetics to designing a successful clinical trial design cannot be overemphasized. The expense associated with PK/PD analysis and modeling is trivial compared to the cost of failed clinical trials and the potentially devastating consequences for small companies. Therefore, the careful planning of a translational

pharmacology program that spans preclinical through clinical studies and provides information that maximizes the chances of success in the clinic is a service that adds great value to a clinical development program for a biopharmaceutical or drug.

Accordingly, our approach is to establish a program that utilizes state-of-the-art PK/PD analysis and modeling that will target and optimize the likelihood of demonstrating efficacy as early as possible in clinical testing. Application of pharmacometrics across the entire development life cycle is critical to: 1) the design and execution of a preclinical pharmacology-toxicology program; 2) the design and execution of successful clinical trials; 3) achieving a positive benefit/risk balance supporting licensure; 4) and establishing an effective post-marketing and pharmacovigilance program. Thus, PK/PD models are becoming increasingly critical knowledge-building tools, not only for late phase clinical trials, but throughout the entire drug development process.

Biologics Consulting Group and Quanticate welcome the opportunity to bring their combined unparalleled depth and breadth of experience to navigate the major challenges inherent in the development pathway to new therapeutic drug/biopharmaceutical licensure.

With over 18 years of experience with FDA registration of Biologics, Drugs, and Devices, BCG has contributed to 10 of the last 12 BLA approvals by FDA. BCG supports product development from pre-clinical pharmacology through clinical design and product registration. To find out how we can support your programs, please visit us at www.biologicsconsulting.com.

Quanticate's strong Biostatistical heritage and depth of experience offers statistical consultancy in novel areas such as adaptive design methodology, PKPD modeling, trial design, DSMB/DMC, and phase I-IV clinical and safety data analysis. To find out how Quanticate can augment your internal trial teams please visit us at www.quanticate.com.

Bibliography

[1] FDA Guidance for Industry. Estimating the maximum safe starting dose in Initial clinical trials for therapeutics in adult healthy volunteers. July 2005

[2] Prentis, R. A., Lisand, Y., Walker, S.R. Pharmaceutical innovation by the seven UK-owned pharmaceutical companies (1964-1985). J. Clin. Pharmacol. 25, 387-396,1988

[3] Arrowsmith, J, Phase II failures: 2008-2010. Nature Review [Drug Discovery] 10:May 2011

[4] Rubio-Viqueria B and Hidalgo M, Mouse xenograft models for drug discovery in pancreatic cancer. Chapter 2 In *Drug Discovery and Pancreatic Cancer* H. Han, P. Grippo (eds.) Springer Science + Business Media LLC,p 29-49, 2010.

[5] Invention Reinvented: McKinsey Perspectives on Pharmaceutical R&D, McKiney and Company, 2010

[6] Pharmaceutical Research and Manufacturers of America, *PhRMA Pharmaceutical Industry Profile 2011* (Washington, DC: 2011).

[7] FDA Guidance for Industry: End-of-Phase 2A Meetings, 2009

[8] Hurko, O, The uses of biomarkers in drug development. Ann. N.Y. Acad. Sci. 1180: 1–10, 2009

[9] FDA Guidance for Industry. Clinical trial endpoints for the approval of cancer drugs and biologics, 2007

[10] Dimond, P F What's wrong with phase II trials? Genetic Engineering and Biotechnology News. Feb 28, 2011.