PERSPECTIVE

Model Informed Drug Development: Collaboration Through A Common Framework

Richard J. Anziano[1,*] and Peter A. Milligan[2]

Model-informed drug development (MIDD) utilizes the knowledge extracted from relevant data to improve the efficiency of decision making within the pharmaceutical industry. The MIDD framework creates overlap between the quantitative disciplines, including statistics and pharmacometrics, with many opportunities for collaboration. MIDD necessitates effective alignment in the thoughts and deeds of statisticians and pharmacometricians, which is not a sector norm. The challenge of greater collaboration must be met in order for MIDD to realize its potential.

In the not so distant past, trials were performed with an assumed *a priori* treatment effect that was not borne out, leading to trials being repeated (assuming the same *a priori* treatment effect). Harrison *et al.*[1] reported that 55% of phase III trials failed due to inadequate efficacy. Both of these conditions are unsatisfactory. We contend that program design efficiency is linked to effective evidence synthesis and that the risk of the above can be mitigated by appropriate evidence synthesis.

A drug's inherent "horsepower" is not something that the developers get to choose, it is something the team is continuously trying to estimate/predict. Teams are challenged with determining the probability of a drug being able to deliver clinically relevant outcomes that are meaningful to the patient, prescriber, regulator, and formulary. The Gantt chart typically details the range of activities needed (and the associate time taken) before arriving at an arbitrary decision point, putative market launch, etc. We contend that rather than "only" optimizing for speed, optimizing for knowledge to defray risk would be a long-term recipe for success. Viewing individual trials as building blocks of a knowledge base, it is quite natural to design programs that are optimized for information maximization and uncertainty minimization.

Consider two near identical assets, developed by two rival companies. DinosaurRX pursues a fast-to-market approach and initiates two parallel phase III trials with a range of doses. KMco decides that given the state of current evidence (and uncertainty), a dose-finding trial and two subsequent confirmatory trials would be prudent. The "head to head" Gantt shows KMco to be well behind the competition. We contend that presenting nonprobability adjusted timelines grossly misrepresents our level of understanding of the likelihood of future outcomes and leads to a bias toward selecting options that would otherwise appear less desirable.

(i) The planned DinosaurRX activities appear faster to completion, but the issue is that the likelihood of success is conditioned on having arrived at the right dose when the evidence base was small on information but large on uncertainty. In these conditions, with little or no trial or aggregate analysis to inform dose selection, arriving at the right dose or doses is rarely robust (low probability of a favorable outcome). If wrong about the dose, there would need to be additional trials using appropriate doses (increasing the probability of a favorable outcome). For DinosaurRX the more realistic launch conditions is the duration of the over optimistic fast-to-market approach multiplied by the probability that the dose was correct, plus the duration of the additional trials multiplied by the probability of incorrectly arriving at a dose. Because the probability of not selecting an appropriate dose is much larger than the probability of selecting an appropriate dose, the expected duration to reach a favorable outcome is much longer than the fast-to-market approach would indicate.

(ii) With KMco's approach, the expected duration is calculated similarly, with the addition of the duration of the dose-finding trial. In this case, the probability of arriving at an appropriate dose is higher and, consequently, the probability of not arriving at an appropriate dose is lower. Their

[1]Pharmetheus Inc., Killingworth, Connecticut, USA; [2]Pharmetheus AB, Uppsala, Sweden. *Correspondence: Richard J. Anziano (richard.anziano@pharmetheus.com)

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realistic launch conditions are less uncertain, more predictable, and less unlikely to deviate from initial predictions. Additionally, if both companies were to have included an interim analysis for futility, KMco would have much less "sunk costs" before determining that the drug, at their selected dose, was insufficiently differentiable.

Why does this scenario continue to play, time and time again? The answer is fairly involved, but elements including how teams are rewarded, what "success" looks like, the degree of optimism we associate with a new program, the will to advance/succeed etc., will play their part. One major contributor is that many involved in the decision making process, and the decision makers themselves, are unlikely to have been exposed to anything beyond a fundamental understanding of the quantitative aspects of variability, uncertainty, or probability. This raises the stakes and creates opportunities for those that have a greater depth of understanding to use their voices and favorably influence the development decision process. The question though is whether the statisticians and pharmacometricians are speaking up? If they are, are they being heard?

What can be done to bring derived inference from data "front and center" to navigate the many forks in the road for development teams and senior leaders? A challenge and an opportunity, MIDD necessitates collaboration between statisticians and pharmacometricians on two principal levels:

(i) The MIDD framework both encourages and demands "joined up" thinking across disciplines. The Lalonde *et al*. (2007) paper, provided a "crossover" language for discussing MIDD.[2] The paper arose out of one company's desire to create momentum for the quantitative scientists and to facilitate their greater influence within development teams and decision processes. The framework consisted of six components: trial performance metrics, decision criteria, data analysis models, pharmacokinetic/pharmacodynamic and disease models, competitor intelligence and model-based meta-analysis, design, and trial execution models. These components present many opportunities for statisticians and pharmacometricians (and clinicians) to enhance their collaborations. We can arrive at a quantitative "yardstick" for calibrating our drugs' performance against what we have defined as differentiable *a priori*. There is considerable joint work necessary in identifying and assembling the data, analyses, interpretation, and presentations to support this approach. We should always strive to avoid drawing the bullseye around the arrows that have already landed on some other part of the target. The components of MIDD enable the creation of a common lexicon for quantitative scientists, enabling more effective dialogue between statistician and pharmacometrician, and, more importantly, more impactful dialogue with the larger team.

(ii) Technical pharmacokinetic/pharmacodynamic models developed by the pharmacometrician based on the mechanism/pharmacology of the test agent are often used to produce predictions/estimates of efficacy under various dosing, population, and trial design parameters. The statistician can use clinical trial simulations to inform the design by imparting the planned analysis to determine *in silico* the operating characteristics of a given trial (including more comprehensive probabilistic determinations) to quantitatively assess the impact of changing different trial design parameters, such as duration, sample size, and choice of competitor. Each of these activities can happen independently, but, in our opinion, there are important benefits realized from greater collaboration among and between the quantitative scientists. Collaboration on technical conduct is not sufficient. The concepts, assumptions, and subsequent interpretations are complex enough that they need clear, consistent, and aligned communications. We contend that without greater alignment on methods and interpretations both disciplines fail to maximize their potential to favorably influence and impact development teams and strategies.

The authors of this paper collaborated for many years to enable the MIDD philosophy and practice to become embedded within one organization, many departments, and multiple teams. We tried to exemplify the many benefits of collaboration and partnership between statisticians and pharmacometricians. The fruit of that labor was assembled and presented in the Milligan *et al*. paper of 2013.[3] This paper quantified a diverse range of benefits obtained from MIDD application across a variety of therapeutic areas. One of the most important elements to embed MIDD was our ability to quantify the resultant savings and efficiencies derived from MIDD. Quantifying these savings and efficiencies allowed senior leaders to appreciate the value of up-front and ongoing knowledge management activities. Expressing the savings against the typical design helped create an organizational pull that complemented our push.

We recognize that our paper is not new, but, since 2013, the statistical and pharmacometric literature has not been so replete with notable examples of collaboration between statisticians and pharmacometricians. One exception was the paper by Visser *et al*. from 2018.[4] This paper sought to highlight the many similarities between the approaches documented in the clinical pharmacology and statistical literature. The outcome was to take the best of both worlds forward as a unified set of best practices that were neither "mine" nor "yours" but "ours."

Fast-forwarding to today, the authors of this paper, instead of enabling and influencing MIDD at a single company, now have a vehicle to progressively influence many companies. We recognize that the mechanics of MIDD have not so much changed, nor has the need for collaboration and a common language. Perhaps we have learned a bit more about the intangibles that give MIDD implementation more or less traction. We hope that by continuing to "live" the collaboration, we will exemplify and augment our collective quantitative voice within organizations and teams. We cannot stress enough the importance of stakeholder management when it comes to senior leaders. Having their support to sponsor and foster cross-discipline collaborations becomes more straightforward when the win-wins are clear.

Statisticians and pharmacometricians are obliged, now more than ever, to raise the bar on MIDD practice levels. The current pandemic presents many challenges for the pharmaceutical industry, and will continue to do so into the future. We know that "normal" clinical trial conduct will be compromised for the foreseeable future. It would be reasonable to expect that the supply of direct empirical evidence from a clinical setting will decrease, necessitating an increase the information yield from already studied and yet to be studied patients. All the elements exist to make MIDD the standard fare in a more rational drug development context. Regulators are playing their part by creating a pull, through pilot programs,[5,6] helping these methods gain momentum across companies. Statisticians, pharmacometricians, and clinical pharmacologists must also play their part by first recognizing the need to collaborate in a more meaningful manner, and then making it happen. This would not only be good for companies, regulators, and payors; perhaps most of all this would be good for our experimental units, yes, the patients.

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