Pharmacometrics: A Competitive Advantage in Improving R&D for Companies of All Sizes

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An Evolving Science

Pharmacometrics—the use of modeling and simulation to support drug development and assessment decisions—has been in use for more than two decades. Today, however, the urgent need for improved R&D productivity within the pharmaceutical sector has highlighted the broader applications of this evolving science.

Pharmacometrics is becoming a competitive advantage for drug sponsors seeking a faster development process and more efficient research methodologies. Sponsors can use it as a form of “virtual reality” to envision the development path and avoid costly and unproductive action.

Long the purview of large pharmaceutical companies with the necessary computational power and crossfunctional expertise in-house, pharmacometrics holds promise for small and midsized companies, as well. Experienced partners offer smaller companies the benefits of pharmacometrics without the cost of having to develop and manage such specialized resources themselves.

Here, we explore the use and value of pharmacometrics in the drug life cycle, trends in best practices and counsel for companies requiring high-level pharmacometrics expertise without the cost of building an entire pharmacometrics function.

The Benefits to Sponsors

Pharmacometrics is a collection of model-based approaches used to characterize and predict a system’s behavior. The system can be a person, a disease or a clinical trial. The U.S. Food & Drug Administration (FDA) describes pharmacometrics as “… the science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions.”

Manufacturers use pharmacometrics to quantify uncertainty, while regulators use it to determine drug safety and dosing. The many benefits to manufacturers of applying pharmacometrics throughout drug development include:

- Speeding the delivery of new drugs. Modeling offers clarity on the relationship between drug exposure and clinical response, adverse events, or biomarkers. Sponsors can strengthen their presentations to regulators on questions of efficacy, often reducing the need for further studies that might otherwise be required.

- Improving R&D investment. The mantra in the technology sector is “fail fast,” and the same applies to drug development. It is far better to discover early in the development process if a compound is going to fail. Ideally this should occur during nonclinical development or in early-stage trials. Pharmacometrics modeling can help sponsors identify failure points more efficiently than they might in an actual clinical trial. This is especially valuable in developing novel compounds that present a higher level of unknowns.

- Refining clinical trial designs. Pharmacometrics can be used to ensure that a study design will, indeed, produce the key value needed, at the right level, within the right population.

Pharmacometrics not only offers drug sponsors greater efficiency to enhance competitive advantage, but over time, pharmacometrics expertise promises to permanently alter for the better the drug development paradigm.
The Regulatory Perspective

Regulators in the United States and Europe have advocated using pharmacometrics and sometimes ask that data from such modeling be included in a sponsor's submission package.

The U.S. FDA recognizes that trial planning may be improved by clinical trial simulations that employ quantitative methods of drug exposure-response, effects in placebo group and disease progression. The FDA encourages the best use of this science to facilitate the exploration of trial design alternatives that could increase the likelihood of successful trials.2

Meanwhile, the FDA and European Medicines Agency (EMA) have both issued direction on performing and reporting pharmacometric analyses. The FDA’s “Guidance for Industry: End of Phase 2A Meetings” provides essential context and regulatory expectations regarding the use of pharmacometrics.

Value Throughout the Drug Life Cycle

There is enormous value in being able to say, “It won’t work” rather than having to admit after the fact that “It didn’t work.” In some cases, the value can be hundreds of millions of dollars. Merck, for example, reportedly avoided $500,000 in development costs over three years by using modeling and simulations.3

Pharmacometrics analyses are typically performed in the late phases of clinical trials. However, companies can realize the full potential of pharmacometrics by modeling data throughout a drug’s life cycle, from nonclinical early stages through confirmatory Phase III, and even into post-marketing trials. Let’s look at each of the different types of models and how they can be used by drug sponsors to inform decision making:

Exposure/Response Models

These models, which describe the relationship between a drug dose, its concentration in the blood (or another such measure) and the clinical response in the patient, are the most common application of pharmacometrics. In the preclinical phase, data from animal studies can be used to predict how humans will respond when exposed to a drug. In Phases I and IIa, models can relate the concentration of the drug in the blood to safety outcomes. Exposure/response models developed at this point can be used to simulate later-phase trial designs, make dosing recommendations and predict adverse events (AEs) and efficacy. In fact, the FDA had this very application in mind when it issued its End-of-Phase 2A guidance.

With respect to dosing recommendations, exposure/response models are useful in identifying the appropriate starting dose and the maximum effective dose. The models also are of use in understanding how best to customize dosing for individual patients. This is especially helpful in determining the dose range for vulnerable populations, such as geriatric and pediatric patients. Since it may eliminate the need for as many clinical trials, pharmacometrics also can help address some of the related ethical issues. For example, the data may help prevent non-necessary, high-dose exposure to healthy volunteers or patients in the presence of a plateau effect on efficacy and could avert long and/or invasive procedures on sensitive populations like young children, the elderly or the very sick.

Pharmacometrics throughout the drug life cycle

<table>
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<th>Nonclinical</th>
<th>Scaling to humans (exposure, response)</th>
<th>Phase Ia/ib</th>
<th>Model exposure, safety. Select dose, inform trial design</th>
<th>Phase IIa/ib</th>
<th>Model exposure, response, safety. Identify covariates, inform trial design</th>
<th>Phase III</th>
<th>Confirm covariates. Dosing recommendations. Predict specific populations (e.g., pediatric, elderly)</th>
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1. The Regulatory Perspective
2. The U.S. FDA recognizes that trial planning may be improved by clinical trial simulations that employ quantitative methods of drug exposure-response, effects in placebo group and disease progression. The FDA encourages the best use of this science to facilitate the exploration of trial design alternatives that could increase the likelihood of successful trials.
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**Disease Models**

Disease models aim to describe the natural progression of a disease, the placebo effect and the treatment effect through clinically relevant markers of the disease, such as the ADAS-cog score in Alzheimer’s disease (AD).

Having models for longitudinal disease progression are essential in distinguishing a disease-modifying effect from a symptomatic-relief effect, as opposed to discrete measurements (e.g., a clinical efficacy endpoint analysis at the end of the trial). Disease progression models also can be used to estimate sample size of a trial testing a prespecified treatment effect or to estimate the needed trial duration to detect an effect.

**Clinical Trial Simulation**

Clinical trial simulation is one of the most powerful applications of pharmacometrics. Companies can run a clinical trial “in silico” to predict the kind of results they would get in an actual trial. Using their Phase III design, they can test their hypothesis surrounding exposure/response in a specific demographic, the dropout rate, trial structure and so forth. Clinical trial simulations also are used in preparing clinical trial databases and in rehearsing analysis plans.

Clinical trial simulations require the use of a disease model, exposure-response models and a trial model along with statistical sub-models, such as a patient demographics model, a placebo model and a study dropout model to simulate the natural course of a trial. The models are linked together to quantitate the study outcomes according to various design(s). An example is the Alzheimer’s disease (AD) clinical trial simulation tool from the Critical Path Institute’s Coalition Against Major Diseases (http://c-path.org/programs/camd/). This open-access tool allows companies engaged in the development of drugs against AD to prospectively calculate the sample size of the trial, determine the trial duration, decide upon the best time points to take effect measurements and compare competing trial designs quantitatively.

**Quantitative Systems Pharmacology**

Quantitative systems pharmacology (QSP) is a natural extension of two disciplines: systems biology and pharmacometrics (also known as quantitative pharmacology). Systems biology generally involves computational models of small-scale biological events at the subcellular or cellular level. Models are organized in comprehensive functional maps aimed at precisely and predictively establishing a natural (and diseased) cellular pathway of interest or an interaction between pathways. Quantitative pharmacology, on the other hand, generally uses computational models of whole organisms and broader descriptions of disease states to predict clinical utility and outcomes.

Linking the two disciplines is a logical extension based on the developing capabilities to mathematically model biological events and the ever-increasing computational capacity that modern technology allows. Nonetheless, bridging mathematical models of events and systems that exist on vastly different scales, both temporal (e.g., from milliseconds to years) and physical (e.g., from a single protein to a cell, a tissue, a whole organism or whole populations) is a massive task that we are just starting to tackle. Discussions on how to efficiently engineer QSP platforms into drug development are ongoing, as are discussions on what constitutes an adequate QSP curriculum for the development of future quantitative scientists. Most certainly, the answers lie in a plurality of expertise and systems, but the question before us is how to intelligently integrate such expertise and systems.

The appearance of QSP announces a major shift in drug development. More and more, we will see research close to what we see in the physical sciences and engineering, such as the aerospace industry. Modeling and simulation will form the foundation of drug development and in-vitro experiments, and nonclinical and clinical trials will confirm, complement and inform the models for further development. These advances mean that even before any real-life experiments take place, new drugs will be purposefully designed to act upon a specific target with the full knowledge of which pathways will be influenced and how.
Emerging Trends

Until now, pharmacometrics has often been employed “after the fact”—to extract knowledge from a trial or a series of trial results with sometime limited impact on the overall drug development process. Now, companies that rationally approach drug development are using models at each phase of development to inform and predict what will happen in the next stage, thereby guiding research investment. As the science is being applied across the development process, sponsors increasingly recognize that modeling and simulation can accelerate drug development and deliver a competitive advantage.

Companies also are beginning to apply fully integrated models rather than discrete ones at each stage of development. This is, in fact, the basic idea behind systems pharmacology. In stating its position on pharmacometrics, the FDA has said, “The single-most important strength of such analyses is [sic] its ability to integrate knowledge across the development program, compounds, and biology.”

Meanwhile, health economics and outcomes research (HEOR) professionals are starting to recognize the value that pharmacometric simulations hold. The day will surely come when the results of pharmacometric simulations populate “early” HEOR models. For example, HEOR professionals often use time-to-event models in estimating life spans. Or they tap into pharmacometrics results on exposure-response relationships to determine the cost effectiveness of an investigational drug compared to the standard of care. If the two disciplines can be bridged, companies will be in a position to determine the value of a compound early on (at the end of Phase II), rather than having to wait for the confirmatory Phase III trial results or postmarketing analyses.

To the extent that models and methodologies have been standardized, either through consortiums or within an organization, they can be outsourced. Some Contract Research Organizations (CROs) are capable of performing a range of analyses. Some, however, still require highly specialized disease or analytical expertise only found in selected academic centers. As the discipline matures, there is a movement within the industry toward continuing standardization of models and methodologies and increased collaboration. By sharing information, techniques and ideas, drug developers can save money and speed their work.

In the EU, discussions are underway on the creation of a database of statistical models. Companies are even considering ways to share anonymized data from clinical trials in initiatives such as Project Data Sphere or the independent data-sharing policies emerging from several pharmaceutical companies. Other initiatives include the Drug Disease Model Resources (DDMoRE) consortium in the EU, aimed at building a “universally applicable, open source, model-based framework, intended as the gold standard for future collaborative drug and disease Modelling and Simulation.”

In the United States, the FDA maintains a disease-specific library of models.

Advice on Outsourcing

As with other business functions, it makes sense to outsource pharmacometrics work when doing so is the most cost-effective means of accessing the necessary resources and expertise. Performing pharmacometrics—and systems pharmacology in particular—is resource-intensive and extremely challenging, which suggests that many companies may choose to entrust the work to a specialized, external team.

Although several large pharmaceutical companies have built internal pharmacometrics capabilities, small and midsized companies may find it a cost-prohibitive and lengthy process to amass the necessary talent. Logically, these companies will outsource.
But what should a company look for in an outsourcing partner? The ideal outsourcing partner to provide pharmacometrics services will:

- Have demonstrated expertise in mathematics/engineering, chemistry, pharmacology and life sciences
- Understand how to apply pharmacometrics across the entire drug development process. It is not enough to be able to express pharmacology concepts quantitatively; the outsourcing partner must be able to use this information as a springboard to plan future trial designs and to consider regulatory needs. In other words, pharmacometrics know-how must be accompanied by strong drug-development capabilities
- Maintain relationships with specialty academic centers having complementary expertise
- Have the infrastructure and computational capabilities to deal with large study databases and have an understanding of data standards
- Follow standard practices in drug development, data management and biostatistics, and have clear processes for quality control and quality assurance
- Be able to convey the complex concepts and findings in a concise and understandable way

This very specialized science must be explained in layman’s terms if it is to deliver value. Few decision makers will have the time, desire or expertise to read through equations to understand the results and the value of pharmacometrics analyses. Indeed, the failure of many specialists to convert their work into something usable by others has been one of the impediments to the more widespread use of pharmacometrics.

**Conclusion**

Pharmacometrics has been expanding into new applications within pharmaceutical R&D organizations to support a critical business imperative: improved effectiveness of the drug development process. Using modeling and simulation can characterize and predict a system’s behavior in a sort of computational virtual reality that gives sponsors advantages in both time and investment. As pharmacometric methodologies increasingly become standardized, they are no longer the exclusive purview of large manufacturers or academicians with specialized expertise. Working with the right partner, small and midsized pharmaceutical companies can now reap the same benefits that were once the exclusive advantage of the largest global enterprises.

**References**

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