

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Disease Models

Jogarao Gobburu, PhD
 Director
 Pharmacometrics
 Office of Clinical Pharmacology
 Office of Translational Sciences
 Center for Drug Evaluation and Research
 US Food and Drug Administration
 Rockville, Md.

H&O What are Disease Models?

JG Although prior information is routinely employed in making drug development and regulatory decisions, a systematic approach to maximize knowledge from prior information is critically needed. Pharmacometrics approaches can be used to quantify natural disease progression, placebo and drug effects, and trial execution variables (eg, patient discontinuation, compliance, design) from multiple trials using patient-level data. Typically, these methods are empirical or semi-mechanistic. The phrase “Disease Models” has been used to describe the aforementioned paradigm. However, it is important to distinguish these from animal disease models (eg, arthritis rat model) and mathematical representations of more complex molecular-level processes in humans (eg, whole organism physiology). It is conceivable that these more complex models and the Disease Models described above might converge in the future. The present discussion is limited to the Pharmacometrics-based Disease Models. These models are evolving and need to be updated as new information accrues. It is most prudent to start such projects by focusing on solving a narrow drug development problem and gradually populating the model further.

H&O How are Disease Models used?

JG As an example, our non-small cell lung cancer (NSCLC) model quantifies the relationship between survival, the tumor-size change, and other baseline risk factors. One can envision an NSCLC model that includes

representation of molecular-level information to drive the probability of survival, such as expression of epidermal growth factor receptor. Our main objective with this project was to develop a tool for drug developers, and regulators to use for screening drugs, selecting doses, and designing more efficient survival trials. Reports indicate that 60% of registration trials in oncology fail, despite an urgent public health need for better drugs. Tumor-shrinkage data for a new compound from an early trial and this tumor change-survival model can be used to explore registration trial designs, via computer trial simulations, to maximize chances of success and identify unanticipated risks related to a successful outcome.

H&O What is the overall goal of the use of Disease Models?

JG The immediate goal of Pharmacometrics-based Disease Models is to improve late-phase trial success rate and to derive more rational dosing strategies. On the other hand, the more complex molecular-level disease models can be used to explore potential new targets during drug discovery. I believe such models are in use, but to a limited extent. The grand vision for fully developed Disease Models would be to extend their use to identify future patients most likely to benefit (or at greatest risk), select the most appropriate treatment options, and assess relative risks and benefits across treatment options. There are a few models of this type, such as Diabetes PHD available now on the website of the American Diabetes Association.

H&O What steps is the US Food and Drug Administration taking to increase the use of Disease Models?

JG The Critical Path Initiative of the US Food and Drug Administration (FDA) identifies Disease Models as an area

of active research. The Pharmacometrics scientists within the Office of Clinical Pharmacology (OCP), together with OCP therapeutic specialists and other interdisciplinary scientists, have invested in two Disease Models: NSCLC and Parkinson disease. The goals of the two projects differ but the underlying principles are the same: improving public health and making drug development more efficient. Information on these models can be requested by sending an e-mail to pharmacometrics@fda.hhs.gov. It is important for the pharmaceutical industry to utilize these tools routinely during drug development, so we all can reap the benefits and gain and share experience. We are currently attempting to increase awareness about the availability of these models for explorative use throughout our meetings and contact with industry.

We are now planning on utilizing this approach to maximize the knowledge gained from pediatric trials in a few therapeutic areas. Approximately 50% of pediatric effectiveness trials lead to results that cannot be interpreted. The availability of patient demographic, disease progression, placebo- and drug-effect, and drop-out data from previous adult and pediatric trials for the same molecule and/or similar molecules provides a rich database. This information can then be leveraged to design more efficient and informative pediatric drug development programs, optimize dosing, and explore important genetic factors.

H&O What does the future hold for the FDA's Disease Modeling initiative?

JG The Disease Modeling enterprise is in its infancy; building quality models, moreover, is resource- and time-intensive. A dialogue between our group, industry, and colleagues at the FDA will identify diseases that would benefit most from Disease Models. The next step will be to devise generalizable guidelines on developing Disease Models, not as policy but as scientific guidelines. The goal is to facilitate clear communication on what the models mean and how to use them. Furthermore, there is a need

to develop a streamlined, well-structured source for public dissemination of Disease Models. At present, I believe the oncology community at large is not well informed about the FDA's NSCLC model initiative, and our goal is to find methods to spread our work to a larger audience. For example, at the recent Pharmaceutical Science-Clinical Pharmacology Advisory Committee meeting (March 18, 2008), we presented our NSCLC Disease Model. We hope to find methods to spread our work to a larger audience both for greater use of Disease Models and to receive feedback. Additionally, we are planning the development of a public website, which will allow easy access to newly available Disease Models. Third, it is important to note that this initiative is not only the work of the FDA. Many scientists outside the FDA have contributed, with the agency playing a central collaborative role, and the onus now is on the users, the recipients of the knowledge (ie, the pharmaceutical industry and researchers), to employ these models in their drug-development plans. In my opinion, this step is crucial for the success of the initiative. Through the use of these models by drug developers, the low success rates of oncology drug development can be improved.

Suggested Readings

Backgrounder for the Advisory Committee for Pharmaceutical Sciences and Clinical Pharmacology Meeting, March 18–19, 2008. <http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4351b1-01-FDA.pdf>. Accessed March 28, 2008.

Lesko LJ. Paving the critical path: how can clinical pharmacology help achieve the vision? *Clin Pharmacol Ther.* 2007;81:170-177.

Miller R, Ewy W, Corrigan BW, et al. How modeling and simulation have enhanced decision making in new drug development. *J Pharmacokinet Pharmacodyn.* 2005;32:185-197.

Powell JR, Gobburu JV. Pharmacometrics at FDA: evolution and impact on decisions. *Clin Pharmacol Ther.* 2007;82:97-102.

Wang Y, Bhattaram AV, Jadhav PR, et al. Leveraging prior quantitative knowledge to guide drug development decisions and regulatory science recommendations: impact of FDA pharmacometrics during 2004–2006. *J Clin Pharmacol.* 2008;48:146-156.

Zhang L, Sinha V, Fargue ST, et al. Model-based drug development: the road to quantitative pharmacology. *J Pharmacokinet Pharmacodyn.* 2006;33:369-393.