

The Challenge of Improving the Drug Discovery Process - An Early

ADME Perspective

Philip S. Burton, Ph.D.

Chief Executive and Scientific Officer

ADMETRx, Inc.

4717 Campus Drive, Suite 600

Kalamazoo, MI 49008

It is well recognized that productivity in drug discovery has been disappointing in recent years. Despite steady and significant increases in R&D spending the number of new drug applications and approvals has been, at best, flat. This has contributed to the relentless increase in new drug development costs and concerns about stagnation in the drug industry. Evidence of this concern is clear in the recent launch of the FDA Critical Path Initiative to revitalize the discovery and development process, and begin to improve the introduction of new medicinal agents to meet unmet medical needs.

Given this considerable interest in the industry productivity predicament, it is informative to more carefully explore the nature of the problem and its historical context. As documented in a recent Merrill Lynch analysis of trends in major Pharmaceutical companies, the number of IND's approved per year has kept pace with the increased R&D spending. This supports the contention that Discovery has been effective in

introducing potential new drug candidates. Thus the productivity problem does not seem to lie in identifying and advancing new candidates.

Further, those candidates tend to survive through phase I clinical trials. In phase I, general tolerability and pharmacokinetic characteristics of potential drugs are evaluated in normal human subjects, prior to testing for efficacy in the target population. This success may be due, at least in part, to strategies implemented in the mid 1990's to address an earlier productivity problem. In 1991 when major causes of clinical failure of drug candidates were evaluated, fully 40% were due to unacceptable pharmacokinetic characteristics unidentified in the preclinical development programs [PMA/FDA Survey, 1991]. This led to the development and universal implementation of all the *in vitro* absorption, distribution, metabolism and excretion (ADME) models to help identify these potential liabilities early and eliminate those molecules from further consideration. This constituted part of the so-called "fail fast - fail cheap" model resulting from high-throughput profiling of early discovery compounds.

To its credit, this strategy has proved effective. A similar analysis of clinical failures in 2000 found that ADME/PK failure had been reduced to about 10% [Pharmaceutical R&D Benchmarking Forum, General Metrics 2001]. Clearly these *in vitro* models have been effective in reducing ADME/PK failure of candidates advanced into clinical development.

So where, and why, are candidates failing now? In the Merrill Lynch analysis, failure appears to be occurring in Phase II/III and primarily for reasons of lack of efficacy and toxicity. Given that overt, acute toxicity is expected to be identified in Phase I, the high toxicity failure may be influenced in part by idiosyncratic toxicities which are harder to identify in preclinical studies. Furthermore, lack of efficacy suggests that the best candidates are not being taken forward into clinical development programs.

It is tempting to speculate that the high attrition of later Phase candidates is due, at least in part, to the fail fast - fail cheap model used in the earlier research profiling activities. While the experimental models have been effective in reducing specific causes of clinical failure, by possibly being too restrictive, or inappropriately applied, they may have contributed to the elimination of viable clinical candidate; effectively throwing the baby out with the bath water. Such a scenario has been suggested recently, and is a conclusion that this author firmly believes.

The solution to this predicament is at least several-fold. First and foremost, additional tools for predicting efficacy and toxicity are critically needed, and are identified as such in the FDA initiative. However, in addition, more effective models for utilizing all the data available for a particular molecule, or series of molecules, to improve decisions about which candidates to advance are needed. It is the composite profile of a molecule, rather than any specific attribute, which dictates its success as a drug. Models that accommodate deficiencies in one dimension but are compensated for in another will improve significantly the advancement of better development candidates.

In general, an ADME profile of a typical drug candidate will consist of solubility, permeability, metabolism, protein binding and probably CYP inhibition and induction data. Increasingly, affinity for the growing number of drug transporters such as P-glycoprotein (P-gp), multidrug resistance associated protein (MRP), breast cancer resistance protein (BCRP) and others, is also evaluated.

After the decision of what to measure and how to measure it has been made, the challenge of how to use the data remains. The concept of minimally acceptable values for the individual properties has been used to advance or reject candidates in a more or less linear fashion. A problem with this approach, particularly in high-throughput assays, is the issue of propagation of uncertainty error in the measurement. That is, even if each individual assay is 90% accurate in differentiating between acceptable and unacceptable values in the property, by the time several properties have been selected for, the “yield” of compounds meeting the desired profile is significantly reduced. The impact of accuracy on compound selection performance can be minimized to a certain extent by improving the accuracy of the assay, generally at the cost of throughput. However, the problem of uncertainty propagation remains and becomes more significant with increasing number of properties to be profiled. Further, if one accepts that minimally acceptable limits are context dependent, at best, with respect to other characteristics of the molecule, alternative methods of using the data to make advancement decisions are necessary.

Several potential solutions to using such data in a “multicriteria decision-making” mode, in order to make better decisions about candidate advancement, have been presented in recent years. One example is the Analytic Hierarchy Process (AHP) which, as the name implies, deals with decision problems that can be structured hierarchically [Maggiore, GM (2002) “Computer-aided decision making in pharmaceutical research”, Proceedings of the Beilstein-Institut Workshop, May 13-16, Bozen, Italy]. In a typical three-level hierarchy, for example, a “Goal” is evaluated with respect to several “Criteria” that each subsumes the entire set of “Alternatives”. The objective is to rank, or prioritize, the alternatives with regards to meeting the goal. The relative importance of each criterion to the goal is determined by pairwise comparisons based on judgments of the relative importance or dominance of one criterion with respect to another. Each alternative has a value for each of the criteria. The rankings of the alternatives are then determined by the sum of the products of the criteria scores and criteria rankings for each alternative individually, by means of multilinear regression.

As an example of how this may be applied in a discovery setting, one could consider the “Goal” of oral bioavailability to be dependent upon the “Criteria” of solubility, intestinal permeability and metabolic stability (first pass metabolism), at a minimum. These properties are measured in the laboratory by well established *in vitro* methodologies for each compound (“Alternative”) in the discovery program. The AHP model is then used to prioritize the compounds with respect to bioavailability before the first in animal study. The method of pairwise comparisons and ranking scores allows for compensatory

interrelationships among the properties, such as solubility and permeability, for example, to be explicitly taken into consideration.

One of the strengths of such an approach, in addition to consistently using all the information pertinent to making such a decision, is that in constructing the hierarchy, all the stakeholders in the goal need to come to consensus with regards to the relative importance of the criteria, and this ultimately aids in making consistent decisions. Furthermore, it is expected that such a strategy will result in better overall candidates rather than attempting to profile for those with exceptional characteristics in all dimensions. To use Rob DeWitte's Tour de France analogy, sometimes the overall champion does not win any individual stage in the race but is a steady, consistent performer in all [DeWitte RS (2002) "On experimental design in drug discovery", *Curr. Drug Discov. Feb*]. The challenge to the drug discovery community now is to identify the winners earlier and advance only those into clinical development. Many of the tools are already available, particularly in the ADME area, but the challenge of better use of the data remains.

Philip S. Burton, Ph.D.

Dr. Burton is currently Chief Executive and Scientific Officer of ADMETRx, a specialty research company focused on preclinical biopharmaceutical property profiling and modeling. Phil received his PhD in Medicinal Chemistry from the University of Florida. After completing a postdoctoral fellowship with in the Department of Chemistry at Harvard University, he joined The Upjohn Company in 1983 as a research scientist. He remained with Upjohn through its mergers with Pharmacia and Monsanto as a Senior Scientist in the Drug Absorption and Transport Group. He also formed and led the Computational Biopharmaceutics Group from its inception in 2000 until the Pfizer acquisition in 2003, when he left the Company. Phil received the Meritorious Manuscript Award in both 1994 and 1998 from the American Association of Pharmaceutical Scientists (AAPS), and was elected Fellow of the AAPS in 1999. He is currently a member of the American Chemical Society, AAPS, New York Academy of Sciences, AAAS and ASPET. He has served as Associate Editor for the Journal of Pharmacology and Experimental Therapeutics since 2000, and on the editorial board of the Journal of Pharmaceutical Sciences since 2001.