

**2008
Upcoming Drug
Discovery Events**

**9th International
Conference on
Alzheimer's Disease
Drug Discovery**
October 6-7
New York, NY

BioPartnering Europe
October 12-14
London

**15th North American
Regional ISSX Meeting**
October 12-16
San Diego, CA

AAPS Annual Meeting
November 16-20
Atlanta, GA

Dr. Burton presenting
"Strategy for Characterizing
Substrate and Inhibitor
Potential for Sparingly
Soluble Drugs"

Bio-Europe 2008
November 17-19
Mannheim, Germany

**The 8th World
Drug Discovery &
Development Summit**
December 2-3
Prague, Czech Republic

Introducing... Your Drug Discovery Partners



Philip S. Burton, PhD
Co-Founder, CEO, and CSO
psburton@admetrx.com



Jay T. Goodwin, PhD
Co-Founder, President and COO
jtgoodwin@admetrx.com



Michelle L. Peterson, MS
Director, Profiling Services
mlpeterson@admetrx.com



James W. Nielsen, BS
Director, Analytical Services
jwnielsen@admetrx.com

We are absolutely committed to working with you in discovering solutions to your drug development challenges here at ADMETRx! And, through *ADMETRx Now* we hope to enrich your knowledge of who we are and what we do beyond that current project. In this semiannual publication, you can expect to receive relevant information about industry related events and advancements, educational information, and announcements from time to time of increased capabilities and expertise that ADMETRx is adding to better serve you. We hope you enjoy the condensed white paper that Dr. Burton wrote for the Cambridge Healthcare Institute in this inaugural issue. He welcomes your feedback and questions!

The goal of ADMETRx is to provide you with the best discovery support possible so that your organization maximizes the potential of its drug development candidates.

We welcome the opportunity to partner with you in finding the answers you need.

The BEST answers.

Contact us to see how we do it!

What clients are saying about us:

"ADMETRx's accessibility and expertise provides an additional clarity in our decision making that has provided us with answers to our go/no go questions and lead optimization."

Manager, Drug Evaluation
Inspire Pharmaceuticals

The Challenge of Improving the Drug Discovery Process— An Early ADME Perspective

Philip S. Burton, PhD

The following is a condensed version of an opinion piece that Dr. Burton wrote for Cambridge Healthcare Institute.



R&D spending has increased steadily and substantially, but the number of new drug applications and approvals in recent years have been flat at best. New drug development costs continue to soar and there are concerns about stagnation, as evidenced by the recent launch of the FDA Critical Path Initiative.

The success of current candidates in surviving through Phase I clinical trials may be due in part to strategies implemented in the mid 1990s to address an earlier productivity problem. A 1991 analysis of failures found 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, constituting part of the so-called “fail fast—fail cheap” approach resulting from high throughput profiling.

A similar analysis of clinical failures in 2000 found that ADME/PK failures have 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 failures. However, according to a Merrill Lynch analysis of trends in major pharmaceutical companies, failures today appear to be occurring in Phases II/III and are primarily due to lack of efficacy and toxicity.

There is a critical need for additional tools for predicting efficacy and toxicity. There is also a need for more effective models for using all of the data available for a particular molecule or series of molecules and for improving decisions about which candidates to advance.

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 deciding what to measure and how, 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. The impact of accuracy on

compound selection performance can be minimized somewhat by improving assay accuracy, generally at the cost of throughput. However, the problem of uncertainty propagation remains.

An example of a potential solution to using such data in a multi-criteria decision-making mode is the Analytic Hierarchy Process (AHP) which deals with decision problems that can be structured hierarchically [Maggiore, GM (2002) “Computer-aided decision making in Pharmaceutical research,” Proceedings of the Beilstein-Institute Workshop, May 13-16, Bozen, Italy]. In a typical three-level hierarchy, a “Goal” is evaluated with respect to several “Criteria” that each subsumes the entire set of “Alternatives.” The objective is to prioritize the alternatives with regard to meeting the goal.

This approach consistently uses all the information pertinent to making such a decision and, in constructing the hierarchy, builds a consensus among the stakeholders with regard to the relative importance of the criteria. 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.

FOR A COMPLETE COPY of this paper, e-mail:
mwarren@admetrx.com



Visit the ADMETRx facilities Kalamazoo, Michigan.
Contact us for assistance with your travel arrangements.



4717 Campus Drive
Kalamazoo, MI 49008
269.372.3272
www.admetrx.com
clientrelations@admetrx.com