charles river

Summary

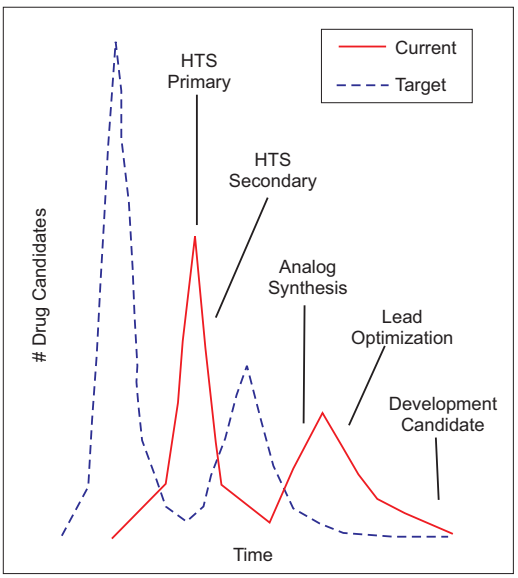
The iterative nature of *in vivo* pharmacokinetic screening requires rapid cycle times. When combined with our discovery bioanalysis, Charles River can provide standard PK parameters within five days of dosing.

Rapid Pharmacokinetic Screening for Drug Discovery

To reduce the cost of overall drug development, it is essential to focus resources on those drug candidates most likely to succeed; therefore the pharmaceutical industry persistently looks for ways to reduce drug candidate failure as early in process as possible. One key factor in the early assessment of any compound is its *in vitro* ADME and pharmacokinetic profile. Inappropriate *in vitro* metabolism and pharmacokinetics such as poor solubility and stability plus low bioavailability, short elimination half-life, and high clearance respectively are major causes of drug development failure.

Charles River Laboratories has streamlined numerous early processes that can aid highly confidential discovery programs from hit screening to candidate selection and lead optimization using HT-ADME, *in vitro* ADMET assays and rapid *in vivo* bioavailability programs. (Figure 1) The combined strength of our experienced metabolism and pharmacokinetics departments, discovery scientists, and state-of-the art bioanalytical chemistry laboratories help identify molecules which possess suitable characteristics to make acceptable drugs.

Figure 1: The Drug Discovery Process

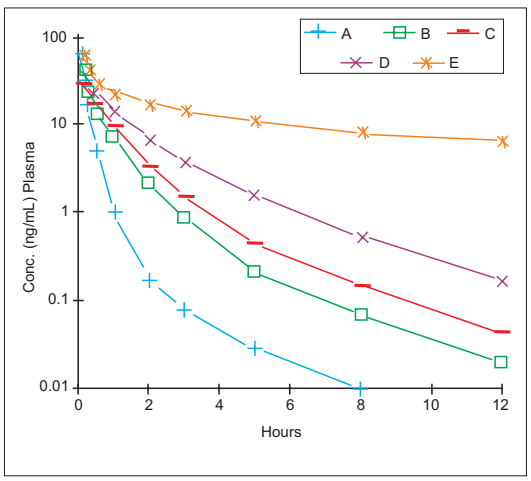


Hit screening advancements have dramatically increased the number of compounds generated and our streamlined *in vivo* high-throughput screening process and sample analysis can maximize this combinatorial chemical synthesis and shorten the time frame to a development candidate.

Study Design

Hit screening, lead optimization, and the candidate selection processes can each take on a variety of forms. In addition to a battery of standard study designs, our scientists can design and execute a custom protocol tailored to meet each program's requirements. For rapid screening, all routes of administration can be performed with either single treatments in multiple animals, multiple compounds in a single animal, or a combination of treatments in a crossover design (see Figure 2). In many cases upon completion of an initial protocol, we can quickly begin programs for different drug candidates by amendment within two to three days of each subsequent request.

Figure 2: Intravenous Pharmacokinetic Screening



Five analogs were evaluated in single animals for changes in terminal elimination half-life.

To expedite each program, we maintain a standing supply of rodents and house a sizeable colony of large animals at multiple laboratories. Colony animals are ready for immediate use in discovery screening or pharmacokinetic studies at specific Charles River sites. Use of these animals helps clients avoid both the high cost of naïve animal purchase and quarantine delays.

Sample Collection and Analysis

Sample collection and data evaluation is critical when selecting a lead candidate. Our study designs range from full kinetic curve collection of blood and urine for up to 24 hours, to abbreviated sample collection regimens used to assess relative bioavailability. Our team is equipped to help clients accelerate the lead optimization process and can design studies to minimize cost and time and to maximize critical information.

The speed of lead candidate selection via rapid pharmacokinetic screening has been matched by an equally rapid analytical tool, liquid chromatography with tandem mass spectrometry (LC-MS/MS). The LC-MS/MS system provides critical pharmacokinetic data for single or multiple drug discovery candidates with minimal sample preparation and method optimization.

Charles River houses many LC-MS/MS instruments around the globe and this proximity allows constant communication and rapid information exchange as well as sample transfer for analysis. In addition, the data is quickly provided to the study director for pharmacokinetic analysis via the WinNonlin or Watson LIMS™ and insertion in the *in vivo* study report.

The analytical chemistry department employs a number of highly qualified individuals who specialize in the mass spectrometry area. Our scientists have developed analytical procedures to measure dosing solutions, urine, blood, plasma, or serum concentrations of multiple drug analogs simultaneously in a single analytical run. The LC-MS/MS data can be further supported by protein binding techniques such as ultracentrifugation and equilibrium dialysis.

Ensuring that compounds succeed during ADME and pharmacokinetic screening studies is our primary focus at Charles River. By taking advantage of both standard and custom study designs, clients can be absolutely confident that studies will be completed on-time and furthermore, avoid costly pitfalls.