

# Pitfalls to Using Small Animals in Preclinical Testing Are Being Eliminated

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## IMPROVEMENTS ALLOW PHARMACEUTICAL COMPANIES TO FOCUS MORE ON DRUG DEVELOPMENT

Mice and rats are the most widely used host species for preclinical drug development for a variety of important reasons. First, rodents have a comparatively short life cycle. Rodent research studies can be time-compressed to evaluate disease progression with or without therapeutic intervention. The short life cycle has also lent itself to the development of many unique inbred strains. In addition, rodents, especially mice, have been thoroughly characterized genetically and were the first animal species to be genetically modified by transgenic and gene knock-out methods.

The microbiology of rats and mice has been extensively studied. Sophisticated husbandry, biosecurity practices, and diagnostic testing effectively control environmental conditions and adventitious infections with pathogenic microorganisms that might cloud the interpretation of experimental findings.

Because genetic, environmental, and microbiological variables can be comprehensively defined and carefully controlled, data from studies using rodents are invaluable for characterizing disease conditions and therapies. Also, research reagents are more widely available for biochemical testing of rodents than for testing other laboratory animal species.

Phenotypic characterization of the behavior, physiology, and biochemistry of rodent models is crucial to their effective use in research. Biochemical testing is typically performed on blood specimens, however, the small volume of blood that can be reliably and safely collected at one time from a rodent has not been sufficient for comprehensive biochemical testing by standard immunosassays [e.g., enzyme-linked immunosorbent assay (ELISA)] and clinical chemistry methods. Therefore, most phenotypic data for rodent models are observational, which is problematic, because drug targets

and responses are biochemical in nature. Without thoroughly analyzing the biochemical phenotype of a rodent model for a human disease, the best targets for drug development may be missed. Additionally, a researcher may be working with a genetically modified animal that observationally mimics the human condition, yet biochemically is quite distinct. This could lead to the misallocation of valuable resources and result in significant time delays and increased costs at various stages within the drug development process. Potential drug toxicity might be missed when comprehensive biochemical analyses are omitted from drug safety testing, and in addition to wasting valuable resources, insufficient biochemical testing also poses a danger to patient health and a substantial liability risk to the pharmaceutical manufacturer.

Rules-Based Medicine, in collaboration with Charles River Laboratories International, is offering multi-analyte profiles (MAPs) for comprehensive biochemical analysis of genetically modified or experimental mice and rats that are now currently available. These validated MAPs can be used to precisely quantify a large number of biomarkers (88 to date) on as little as 10  $\mu$ L of plasma or serum. The MAP markers include cytokines, chemokines, growth and coagulation factors, as well as antibody assays for autoimmunity and infectious diseases.

Performing MAPs on a tiny sample is possible because of a unique fluorescence assay technology that incorporates optically encoded microspheres read in a flow-through system. The time from assay setup to result output is less than 2 hours, and up to 600 panels can be performed in an 8-hour day due to the industrialized processes used at the laboratory. Each antigen analysis is compared to two separate eight-point standard curves to provide unsurpassed accuracy and precision. Additionally, all assays are run with three separate controls. These features are critical, as in many cases, simply recognizing up-regulation or down-regulation of a

biomarker is insufficient; more precise quantification of changes in biomarker levels is required.

MAPs are cost-effective because they are offered as a service. The only ongoing labor costs are those associated with sample collection. The pre-clinical researcher has no capital expenditure costs nor is there any time- and/or resource-consuming assay research and development. Valuable research resources can be concentrated where they belong, on drug development, while still allowing the researcher to quickly, efficiently, and economically gather large amounts of biochemical data on essentially any experiment involving mice and rats.

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