

Key Findings

Future improvements in drug discovery will include the modeling of a wider range of toxicities, such as hepatotoxicity, and formations of reactive metabolites that might lead to idiosyncratic toxicity. Developments in high-throughput technologies, systems biology and bioinformatics have also enabled virtual modeling for whole organs.

High-content screening is increasingly important for identifying toxicity endpoints in a drug discovery setting. The methods use automated microscopy with image analysis to measure the effects of compounds on cell health. Improvements are required in the cell types used and the number of toxicity endpoints that can be studied reliably.

Novel in vivo models are now available including zebrafish screens, which are suited for use at the lead optimization stage or earlier.

Humanized rodent models, in which key enzymes responsible for metabolism have been replaced by their human counterparts, may also be suitable for use in candidate selection.

Pharmacometric modeling and simulation and novel study methods such as adaptive designs are increasingly being applied in drug development to make the most of the data collected and to guide the choice of dose for clinical application.

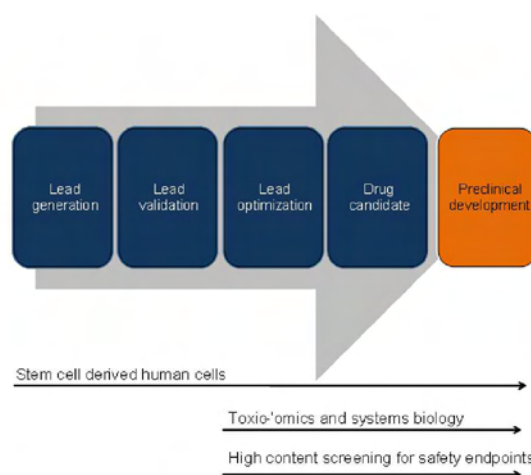


Figure 3.8: Novel in vitro methods and their use in drug discovery and development

"Cell-based assays have begun to make their mark on the discovery process. Large pharma companies have established teams to test compounds much earlier than would previously have been possible, providing greater insights into data..."

Use this report to...

- **Assess key technologies for predicting drug safety in the earliest stages of discovery and clinical development** with this report's comprehensive analysis of emerging approaches across in silico, in vitro and in vivo preclinical technologies.
- **Identify which companies are leading the field in safety prediction for new drugs**, understand the strategic implementations for large pharma companies and examine the role of public-private consortia in solving key issues within this field of predictive safety.
- **Discover the extent to which predictive safety technologies can provide potential cost savings** and improvements in attrition rates and assess the challenges and risks associated with the implementation.
- **Understand the latest strategies to improve safety evaluation in early clinical development** with this report's analysis of the latest approaches in exploratory and Phase I clinical trials.

Explore issues including...

The impact of failure; Declining productivity in the pharma industry has intensified the need to create innovative solutions to reduce new compound failures. The current likelihood of a project progressing from Phase 1 to approval is roughly 20%, although in some therapeutic areas this may be as low as 8%.

The importance of collaboration; Sharing information and expertise across companies can drive the field forward in a way that is impossible for these organizations individually. Biomarker data from some of the major consortia has been submitted to regulators, and this represents significant progress, most notably within the field of renal toxicity.

Better predictive animal models; Rodent and non-rodent models used in drug development are expensive and the results do not always translate well to the human situations. A survey carried out in 1999 reported a true positive concordance rate between animal and human data of 71% for rodent and non-rodent species (63% for non-rodents and 43% for rodents alone).

The need for early assessment of key clinical attributes; Exploratory trials are particularly useful for gaining early insight into human ADME characteristics including mass balance, metabolite and absolute bioavailability parameters that would not traditionally be collected until Phase 2 or later. These studies use microdoses and can explore more candidates at a lower cost than a traditional 'First in Man' study.

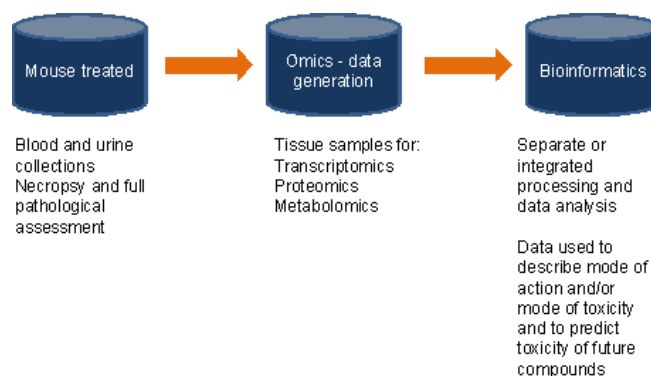


Figure 3.9: A typical toxicogenomics workflow in the pharma industry

"The principal 'omic technologies are used regularly in preclinical drug development. Such experiments aim to gain insight into the mechanism of action or mechanism of toxicity of a new compound. Alternatively, the experiments may be conducted with the aim of identifying predictive markers of toxicity in humans."

Discover...

- Which technologies are leading the way in predicting potential safety problems in the earliest stages of drug discovery and development as possible?
- What are the contributions of in silico, in vitro, and in vivo methods in the non-clinical stages of drug development?
- What are the goals of public-private consortia in driving the discovery of methods and biomarkers and how much have they achieved to date?
- How can the data collected in early human clinical trials be improved to better inform decision-making about potentially safe candidates?

Sample Information

Chapter 6: Strategies to improve safety evaluation in early clinical development

Pharmacometrics – modeling and simulation to improve Phase 1 safety

Pharmacometrics, or Quantitative Clinical Pharmacology, is quantitative pharmaco-statistical analysis to answer clinical drug development questions, regulatory questions and influence decisions. It examines the variables that influence drug pharmacokinetics and pharmacodynamics, using disease, drug and safety models. The application of pharmacometrics in early clinical drug development has the potential to improve the quality of the data collected in Phase 1 trials.

Over the past few years, the use of pharmacometrics has grown rapidly due to increases in computing power, growing expertise among pharmaceutical scientists and an increase in the understanding of drug mechanisms and systems biology in general. Efforts to standardize ontology have also been important. Initiatives include the Gene Ontology Consortium, which addresses the need for consistent descriptions of gene products in different databases. With standards in place, researchers can be more certain that a search on a particular topic be comprehensive.

Before a drug reaches clinical development, disease-drug models can be used to elucidate mechanisms of action, potential determinants of drug safety and efficacy and the initial choice of dose for clinical trials. The sophisticated mathematical models take into account No Observed Adverse Effect Levels (NOAELs) from toxicology studies, which were traditionally used as the basis for choice of dose levels, as well as information on the sensitivity of receptors involved in drug efficacy and allometric scaling using data from relevant animal

species (Figure 6.17). These models aim to provide more justifiable predictions of doses for use in humans, improving safety in early clinical trials, and can be used to support regulatory submissions including INDs and NDAs. They can also be used to predict the outcomes of clinical trials with various designs, inform patient selection and enable molecule selection from efficacy and safety perspectives.

The level of sophistication achieved by models varies according to therapeutic area. Models of HIV and bacterial infections are now well established and are able to predict clinical outcomes based on preclinical data. Other therapeutics areas, perhaps with more complex disease etiology, lag behind these areas and are the focus of current research.

Figure 6.17: Information utilized in model-based drug development

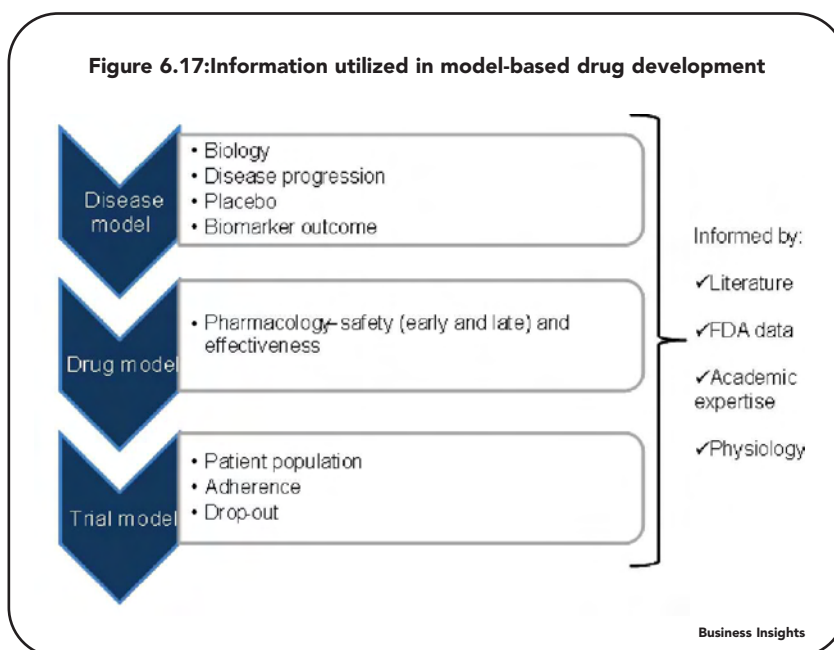


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