

The Emerging Role of ADME in Venture Capital

a report by

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Pre-clinical ADME Tox (absorption, distribution, metabolism, excretion and toxicology testing) is emerging to take on a role in the drug-discovery venture capital (VC) industry's financial decisions that corresponds in importance and scope to its established role in the scientific decisions of drug discovery firms. Contract research laboratories that focus on *in vitro* and *in vivo* ADME Tox research are seeing increasing involvement of VC firms in all stages of the pre-clinical development process.

The VC industry is constantly looking for better ways of selecting which companies to fund, as well as better ways of managing their existing investments. The most sophisticated VC firms have now begun to grasp how pre-clinical ADME Tox can help them to achieve these objectives. VC firms are increasingly expecting *in vitro* and *in vivo* ADME Tox data not only from the firms they have funded, but also from the ones they are considering funding. In their quest to better manage their investments, they are also increasingly expecting ADME Tox to be performed in ways that not only provide quality, actionable data, but also happen to increase the control the VC firms have over their investments.

Obtaining VC funding is as crucial a factor for the success of drug-discovery start-ups as their science is. Founders can maximise their chances of initial and subsequent rounds of funding by better understanding the perspectives of VC firms on how pre-clinical ADME Tox should be implemented.

ADME Tox's Role in Reducing Failures in Clinical Trials

The performance of pre-clinical ADME Tox has caught the attention of the VC industry. In the late 1980s to the mid-1990s, 40% of all drug failures in clinical trials were due to ADME problems.¹ These failures represented a huge source of investment losses to the VC firms that had provided the funding for those drugs to enter clinical trials. Now, due to pre-clinical ADME testing, the failure rate has been reduced to 14%² and is still falling, representing a major reduction in failed investments (see *Figures 1 and 2*).

The implementation of pre-clinical ADME Tox began in the mid-1990s, when it became increasingly feasible, both technologically and economically, to perform *in vitro* ADME Tox testing at the discovery stage – long before clinical trials – in parallel with efficacy testing. These tests have become effectively predictive and relatively inexpensive,

allowing drug-discovery companies to modify or terminate research on drug candidates that are likely to fail in clinical trials for ADME Tox reasons. Consequently, almost all drug-discovery companies now perform pre-clinical ADME Tox testing.

Such a dramatic efficiency improvement has not gone unnoticed by the VC firms that fund drug-discovery start-ups. 'If pre-clinical ADME Tox can save us this much on phase I failures, what else can it do for us?' investors have asked. In response, they have come up with a number of applications of ADME Tox to help them meet their financial objectives.

Initial Funding Reviews

Before funding a start-up with some promising drug compounds, VC firms are beginning to require ADME Tox profiles of those compounds, along with proof-of-principle data. It has become so important to investors that in some cases they will even advance funds just to obtain the data; however, in the majority of cases they expect the founders to provide the data. At this stage, founders should not be too concerned about their compounds having clean ADME Tox profiles. Investors who require ADME Tox data are usually sophisticated enough to understand that it is possible to modify chemical structures to adjust the ADME Tox properties without losing efficacy. However, compounds with particularly poor profiles raise a red flag, as the likelihood of a marketable drug emerging from this research is below average.

Funding Stage

Once the start-up has been funded, investors will expect pre-clinical ADME Tox testing to be performed in parallel with efficacy testing. This is the point at which investors and founders face the decision of whether to outsource ADME Tox or carry out testing in-house. Lower marginal costs and faster turnaround time are the primary reasons for choosing insourcing, and benefit both founders and investors. In contrast, investors have several reasons to encourage or direct the start-up to outsource, including: minimising up-front investment; maximising control; focusing the expertise and management skills of the founders; and maximising confidence in the data. Lower marginal costs tend to primarily benefit the start-up, allowing a longer runway for launching a successful programme based on a fixed up-front investment. However, investors do not see this as particularly valuable; they are more interested in minimising the up-front amount at risk. What they do consider valuable is the fast turnaround time. VC firms are under enormous pressure to quickly turn over their investments. Anything that speeds up the research programme will be viewed favourably. It is this demand for speed that has led Apredica, a specialist pre-clinical ADME Tox contract research laboratory, to break from the turnaround times typical of the contract research organisation (CRO) industry to match the fast turnaround times of discovery-stage in-house ADME Tox departments.

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Investors like the ability to control spending. The costs of in-house ADME Tox departments are largely overheads, which are difficult to reduce or increase at short notice. In contrast, outsourcing gives investors the power to quickly ramp up programmes that are meeting or exceeding their success hurdles, and to staunch the bleeding of those that are failing to meet their hurdles; therefore, outsourcing is an attractive option.

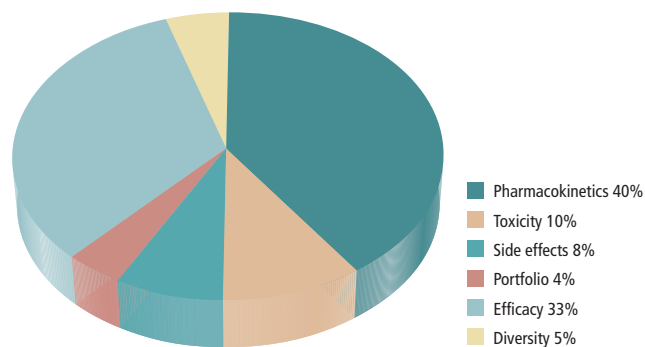
VC firms know from experience that in just a few years most of their investments will fail. In the case of ADME Tox departments, they know that whatever they start will almost certainly have to be shut down, probably due to failure but, interestingly, also due to success. They see shut-down costs as nearly certain, and not far in the future. Even the start-ups that succeed usually exhaust their research pipeline and terminate research and development operations to focus on clinical trials. Only those few firms that have developed exceptionally fruitful technology escape this fate. Within two to six years, the chances of a newly created internal ADME Tox department being shut down approaches 100%. The millions of dollars worth of equipment needed to outfit the department are now worth 10 cents on the dollar, and there will also be severance packages to pay. In successful start-ups going on to clinical trials, morale can suffer as employees see the scientists who were instrumental to the success of the company being laid off.

VC firms often have concerns about the expertise and management skills of the founders, particularly those of first-time entrepreneurs. In many cases they require the firms they fund to bring in experienced executives, or insist that the founders relinquish control once the company has achieved sizable growth. They frequently have higher confidence in work outsourced to experienced specialist firms than in work performed in-house by newly formed teams, particularly those managed by scientists who are inexperienced in the challenges and fast pace of industrial research.

One of the greatest causes for concern among investors is veracity. This comes in two forms. First is the routine overconfidence typical of entrepreneurs. The VC management team's role here is to be a counterbalancing critic, using a form of tough love to ensure the programme's success. In this respect, investors like having disinterested third-party specialists involved in the programme, such as a fee-for-service CRO, to provide feedback that can be assured not to be overly optimistic. The second concern is about deliberate deception. Were a VC firm to fall for such a deception, it would be not only financially disastrous, but also deeply embarrassing and would deal a painful blow to the company's ability to raise new funds. This is far worse for a VC firm than merely making unprofitable investments. Their whole decision-making process is geared towards ensuring such an embarrassment can never happen. Having some of the key research performed by third parties is additional insurance used by some firms to further reduce the chances of such a catastrophe.

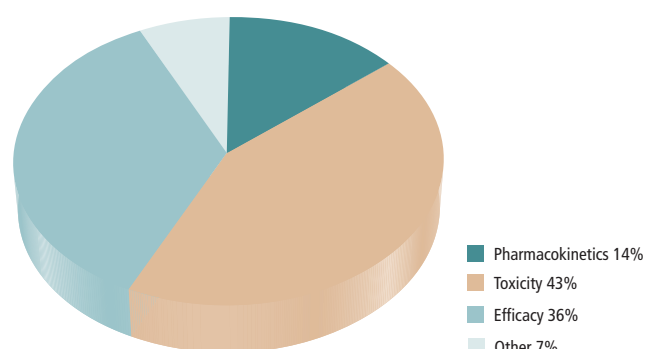
Data confidence is a substantive issue for ADME Tox testing. *In vitro* and *in vivo* ADME Tox is a correlative science involving many variables, such as what species to use for testing. When faced with results that do not support their theory, some researchers have been known to change variables and re-run the studies until they get attractive results. While the underlying science is still legitimate, each failure on the way to those

Figure 1: Phase I Clinical Trial Failures Before Pre-clinical ADME



Source: Prentis et al., 1988.¹

Figure 2: Phase I Clinical Trial Failures Since Pre-clinical ADME



Source: Kennedy, 1997² and Schuster et al., 2005.³

attractive results indicates an increased chance of future failure. If an internal department is carrying out the work, investors know that it is easy to not report failed studies, creating a skewed perception of the likelihood of future success.

Clinical Trials Stage

Many promising drug programmes have been killed because of avoidable errors, such as the contract manufacturer making a mistake with the first batch to be tested, or the strain of rodents used in the GLP toxicity studies appearing to have unexpected toxicity because it is different from the strain used in pre-clinical testing. If those laboratory animals die, the company dies with them. At the clinical trials stage, the level of financial commitment by the investors has become large; their concern is similarly heightened. VC firms that are sophisticated about ADME Tox will often want some key studies repeated, even if this presents a slight delay, as they know it is cheap insurance to run pre-clinical tests that will later be performed as part of clinical development to guard against nasty surprises and huge financial losses.

Conclusion

Founders of drug-discovery companies looking to obtain VC financing need to be aware of the increasing importance and significance investors are placing on pre-clinical ADME Tox in order to better position their firms for funding and better meet the needs of the firms providing the funding. They need to be prepared to present ADME Tox data for funding decisions, as well as after funding to keep investors informed of ADME Tox results. ■

1. Prentis et al., *Br J Clin Pharmacol*, 1988;25:387–96.

2. Kennedy T, *Drug Discov Today*, 1997;2:436–44.

3. Schuster D, et al., *Curr Pharm Des*, 2005;11:3545–59.