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Outlook for Predictive Safety Techniques

Author: Hermann A.M. Mucke, PhD

PREDICTIVE SAFETY

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Executive Summary

Unexpected toxicity is the single most significant constant of attrition to drug development pipelines. It can hit throughout the course of in vivo development, from the first rodent toxicity tests to Phase III, and even when a drug is already on the market.

Although the average preclinical program that will allow a drug candidate to enter clinical Phase II will consume about 1,300 rats and 90 beagle dogs, it offers no guarantee that the compound will not present safety problems in human tolerance and proof-of-principle studies that are significant enough to warrant discontinuation—causing a total commercial write-off of all resources spent so far.

This alone warrants investments in strategies and technologies that will allow drug developers to predict the "safety-related developability" of a compound as early as possible. However, there is another reason: such approaches could lead to a significant reduction in research animal use, meeting the increasingly outspoken demands of the public as well as government agencies. Even though it is unlikely that regulatory authorities will step back on current animal safety testing requirements in the near future, good discovery-stage predictive safety assessments could help the industry to focus these studies on those compounds that will most likely pass these assessments.

This report provides an overview of the newest developments in discovery-stage and preclinical predictive safety assessments, from in silico safety-driven lead selection and optimization to high-content screening (HCS), toxicogenomics, and advanced animal models. We have assembled a "virtual round table" where leading experts from pharmaceutical companies, contract research organizations,

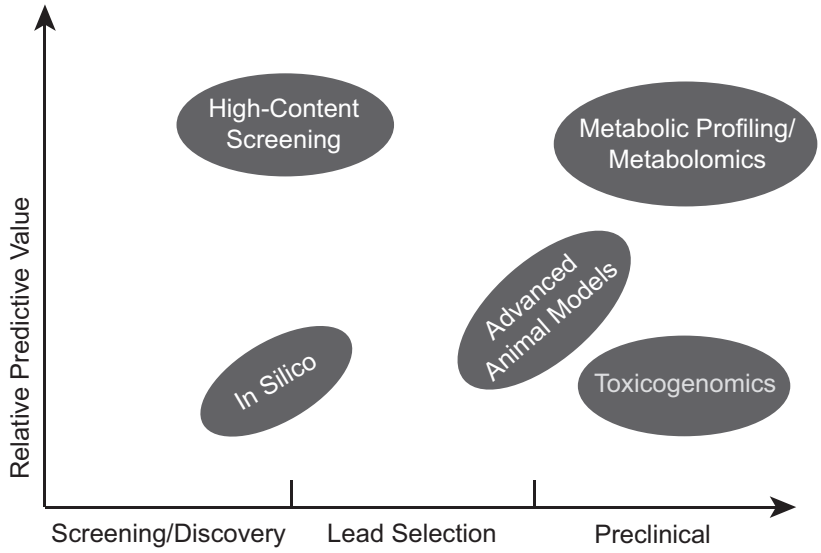
and the FDA provide their opinions in response to 10 questions presented by the author. The results and analysis of a Web survey Cambridge Healthtech Associates conducted in September 2006 are also integrated into this report, which will tell you what is "hot" in predictive safety testing today, and which directions the evolution of this field is going to take within the next 5 to 10 years.

An Overview of Predictive Safety Testing Approaches

The pharmaceutical industry is responding to the enormous challenge that is presented by the necessity of moving safety assessments to the discovery and early preclinical stages of drug development. As with all complex responses to complex challenges, its implementation could not be a matter of snap decisions – especially not in such a tightly regulated community. Rather, what we have been experiencing during the past few years is a slow and partial migration of resources from the later preclinical stages (as far as these studies are optional, and not mandated for regulatory filings) to the discovery and lead selection stage.

The figure below illustrates that the major techniques currently in use for predictive safety testing cover the entire "value space" from the discovery to the advanced preclinical stage if applied properly. HCS and in silico methods can eliminate toxicity-prone candidates in the library screening or lead selection stage; advanced animal models can assist in lead selection and allow to draw more information from routine animal safety pharmacology, which is the domain of toxicogenomics, metabolite profiling and metabonomics (although these can also be applied to cell and tissue cultures).

Figure. Relative Predictive Value of Predictive Safety Assessment Methods from the Discovery to the Preclinical Stage

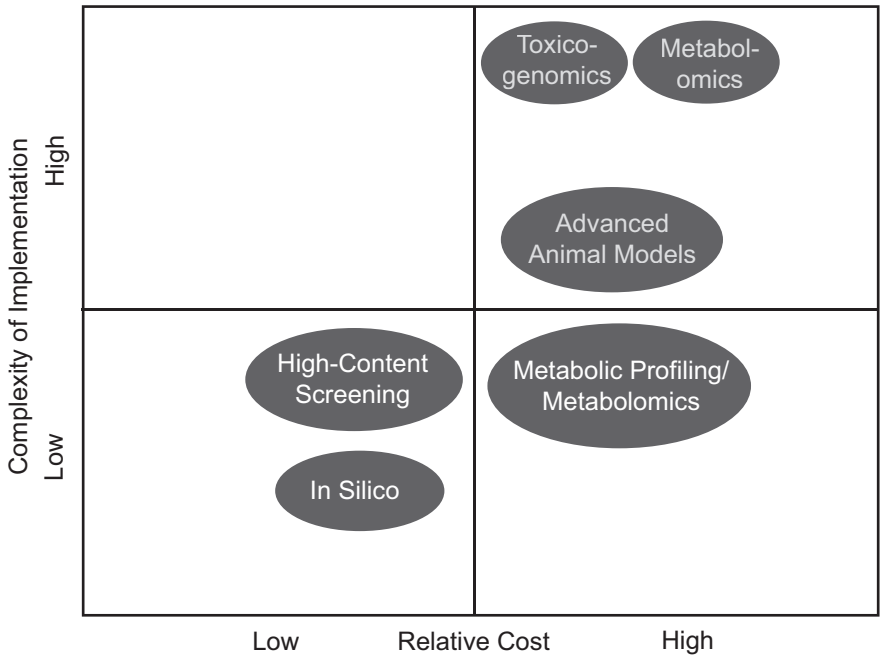


Source: Cambridge Healthtech Associates Advances Reports

To fully embrace predictive safety testing in drug development, the pharmaceutical industry must know the "total cost of ownership," a term that describes the totality of costs that arise from acquiring, implementing, maintaining, and using such procedures.

Software solutions that can perform tests for certain types of toxicity in silico require limited investments and are easy to implement if turnkey solutions are acquired; once deployed, these systems do not incur significant costs related to the number of compounds screened. For HCS solutions, deployment and integration as well as maintenance is more difficult in terms of hardware, software, "wetware" (i.e., the biological material), and user training, but in general these are still relatively cheap and straightforward systems. Toxicogenomics and metabolomics are at the top end in every respect of ownership costs (see figure below); however, their benefit is high if their output is fully linked to preclinical in vivo results obtained in parallel.

Figure. Complexity of Implementation for Predictive Safety Assessment Methods in Relation to Relative Cost



Source: Cambridge Healthtech Associates Advances Reports

Our analysis of responses from a Web survey (see Appendix) and from personal phone interviews (see Chapter 6) indicates that apparently most predictive safety testing is conducted in the development of molecular entities and/or drug targets that are new, at least for the respective organization (see figure below). Safety screening of drug candidates that are directed at well-established targets, but also of compounds that originate from known structural classes, seems to play a relatively minor role. This makes sense for companies, since resources relevant to predictive safety testing (which in large parts is ultimately still experimental) would be spent on high-risk projects rather than on those where much more background information is already available, and where a considerable amount of data on structure-activity and structure-toxicity relationships is already available.

Figure. Survey Results: Primary Targets of Predictive Safety Testing

Source: Cambridge Healthtech Associates Advances Reports, Predictive Safety Survey, September 2006

Such relationships are best explored with software-based methods. Large companies seem much more likely to exploit those than small ones, who tend to be skeptical of their predictive value and in any case would rather restrict their use to lead prioritization than to employ them for library streamlining. Indeed predictivity of commercial in silico turnkey solutions is still relatively limited unless these systems can be calibrated and fine-tuned with experimental data from related compounds.

Almost half of the Web survey respondents said they had some type of predictive safety assessments deployed, while 30 percent were planning to do so within the next 3 years, and the time horizon was beyond 3 years for about one-quarter of companies. Large pharmaceutical companies were more likely to use in silico methods for safety-related purposes than small ones, and they were also more likely to use high-content safety screening while they were less likely to continue those assessments while animal pharmacology was already under way. This dichotomy indicates that big pharma is more inclined to use equipment-intense applications that are easily scalable to the degree of throughput that is required in large library-based drug development programs.

In the "wet laboratory," metabolic profiling was more popular than toxicogenomics and metabonomics, although toxicogenomics (whose popularity had somewhat suffered during the early years of the decade) has made a remarkable comeback. While metabolic profiling is obviously most immediately useful for the safety-related decisions that are to be made during the early stages of development of new molecular entities, the "-omics" approaches profit from the fact that the US Food and Drug Administration (as well as other regulatory bodies) is universally perceived as being on the path toward making submissions of standardized pharmacogenomic and toxicogenomic data mandatory within the next 5-10 years—but only among small pharmaceutical companies, while the majority of large companies and full-service CROs apparently does not believe so. (At present, such submissions are voluntary unless the underlying data are an integral part of clinical trials or their evaluation.)

Direct linkage of these and other safety-related data to animal safety data captured by conventional (mandated) animal safety pharmacology studies was generally perceived as being insufficient. Several respondents stated explicitly that including such "extra" data in regulatory filings would give the developer no benefit while carrying a considerable risk of causing delays if FDA wants some aspects of these data, which might not be completely understood in all their implications by anybody, to be followed up with more conventional testing.

The great majority of opinions were in favor of early-stage predictive safety testing to potentially result in significant overall savings but were skeptical of its potential to reduce research animal use. Indeed we are convinced that the number of animals used will not significantly diminish (or might even increase) because the necessity to conduct the mandatory preclinical safety pharmacology will persist for many years. This view was shared by most large companies and full-service CROs, and predictably the 2 FDA officials also stated that for the foreseeable future these methods would not result in waiving requirements of current animal safety testing. This reinforces our view that savings in animals used as well as in corporate spending will be derived from the early elimination of compounds that are potentially doubtful with respect to safety issues, while those candidates that are actually carried through development will experience little benefits in terms of direct savings.

Future improvements in predictive safety testing are generally expected to be derived from incremental improvements rather than from research or technology breakthroughs. Remarkably, the consensus value of the current market for safety testing not related to animal pharmacology was estimated only at a few hundred million dollars annually (range, $100-$750 million), indicating that its potential for growth could be extreme once methods become better targeted and more predictive, given the fact that investments required to deploy and run most types of early stage predictive safety testing are low in comparison to the potential savings resulting from not advancing compounds with a likelihood of failure in late-stage preclinical testing, or in clinical trials.

In our opinion, systems biology-based high-content screening approaches using cells, tissues or perhaps model organisms such as the zebrafish could push the market to at least $5 billion until 2015. In contrast, we believe that in silico toxicology methods, if improved constantly, will ultimately find a large niche in lead optimization and target prioritization. This could nevertheless allow this sector some limited growth. Computation-based advances will be most pronounced in systems biology, where constructing of physiological and metabolic network representations (and assessing the modulation of these networks by drugs) exceed the capabilities of the human mind.