# Perspectives for ADME/Tox integration in the discovery process

ADME/T is a relatively new 'symbiotic' acronym for the investigation of basic compound behaviour in terms of absorption, distribution, metabolism and excretion, combined with assessments of toxicity. The emergence of ADMET instead of ADME reflects the growing practice of combining *in vitro* ADME and toxicology data already early on in the drug discovery process.

**By Dr Constance Höfer**

Traditionally, toxicology had late stage gatekeeper functions[1] controlling the transition to clinical use of otherwise fully developed pharmacologically active molecules. In contrast, ADME, a relatively new discipline in pharmaceutical research, is associated with early lead optimisation stages of Pharma R&D.

Searching the PubMed database, the first citation for ADME is found in 1990[2], *in vitro* ADME in 1999[3] and ADMET in 2001[4]. Similarly, entering the search term 'ADME *in vitro*' and 'ADMET' for the entire period of 1980 to 1996 yields <2000/<1000 entries, respectively, while an identical search in the period 2006-2007 comes up with a staggering 167,000 and 64,400 entries respectively (www.altavista.com). These figures alone serve as convincing evidence for the exponential increase in interest and activities in this area.

How did this almost explosive interest in combining ADME with Toxicology come about, and where will it lead?

A look at the history of both disciplines in pharmaceutical research explains how a traditionally late-stage development discipline came to be associated with the comparatively novel and almost industry-specific ADME activities in early drug discovery:

Historically, industry success in the discovery and use of new medicines seems not to have been greatly impaired either by the absence of ADME (with and without '/T') nor the late stage positioning of toxicology itself. It is not necessary here to reiterate recent analyses of industry spending and productivity in detail, but suffice it to restate that no great improvements in drug output seem to have been achieved since the 1960s, taking into account spending against productivity and returns[5].

The pharmaceutical industry originates in the chemical manufacturing industry, and was initially concerned with applying its scientific expertise to the study, purification and ultimately improvement of active ingredients in traditionally used complex biological preparations with observable medicinal effects. Therefore, the initial activities of drug development historically were analytical, preparative and organic chemistry with the aim to improve medicinal value. This gave rise to the emergence of medicinal chemistry as a formalised discipline. The other main area of activity was the study of pharmacological effects and the refinement of models to observe such effects in a reliable and repeatable

> "It is useful occasionally to look at the past to gain a perspective on the present."
>
> **F Linden**

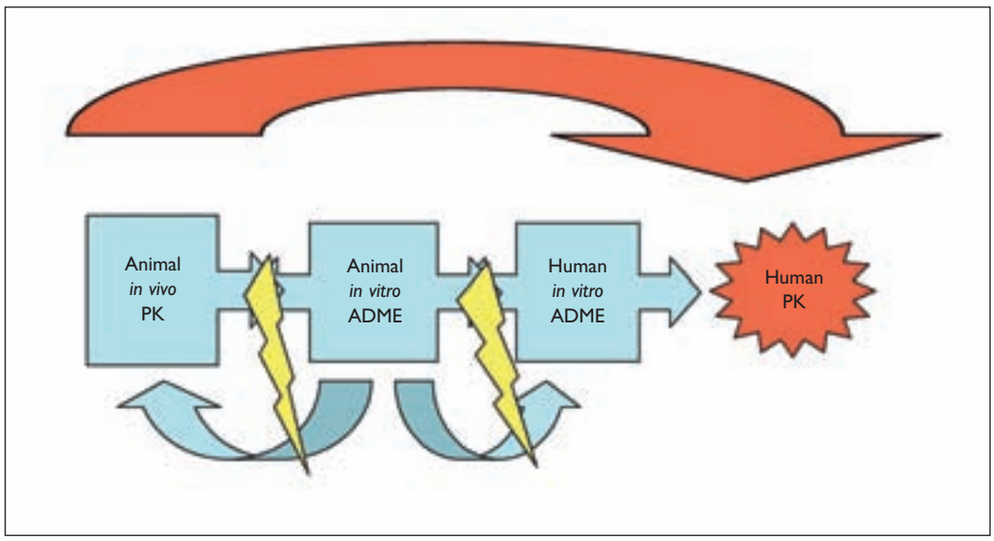



**Figure 1**
Position and role of *in vitro* ADME for *in vivo* and human PK prediction

as well as quantifiable manner, that is to say, pharmacology. Medicinal chemistry and pharmacology therefore can be viewed as the original mainstays of pharmaceutical research. Crucial to compound evaluation and selection was (and is) the assessment of structure-activity relationships (SAR). Until the advent of modern cell and molecular biology, in conjunction with huge advances in experimental techniques, SAR could only be evaluated in the most simple, and at the same time the most complex, models of pharmacological action, namely whole animals, or organ and tissue preparations. Clearly, the observation of the desired pharmacological effect implies 'good ADME' compound characteristics such as solubility, absorption, or chemical and metabolic stability. Likewise, the absence of detrimental effects on the experimental animal was taken to indicate compound safety. In this historical paradigm of drug research, where effect (efficacy) and toxicity were evaluated *in vivo* very early on, at least ADME could not emerge as a discipline because it was inherent in the process of compound selection.

Increasingly, a complete understanding of structure-activity relationships was seen to hold the key to the design of completely new drugs, ie without the guidance of 'Mother Nature's Templates'[6] and industrial drug research embraced the notion that the lack of structural knowledge of pharmacological effector molecules was limiting to the development of new drugs. One dangerous consequence of this drug development paradigm was to neglect the difficulties in translating observed effects in animals to the human clinical situation, which in time and after a number of serious toxicities observed with drugs or excipients[7,8] lead to the inclusion and regulatory requirement of conducting complex and long-term toxicology studies in a variety of animals in the hope to cover toxicity mechanisms operative in man. Thus, toxicology entered the process of drug discovery and development as a final safety check of drugs about to enter the market.

Advances in molecular biology and biotechnology soon identified multitudes of proteins and other molecular structures involved in cellular control processes. Great numbers of potential targets for disease modification became known, and the same research advances also provided the tools for the construction of detailed, highly sophisticated pharmacological models of low complexity to assess the effect of chemical structures on individual drug targets. This rapid rise in potential targets of pharmacological action and thus disease modification removed the limitation posed by the lack of new target structures. Since traditional synthetic chemistry is both time- and labour-intensive, the ability to test as many permutations of chemical structures as possible against those targets became rate-limiting, and compound availability was the new bottleneck. Combinatorial chemistry, providing libraries with millions of compounds, removed this limitation, and led to high volume rapid testing of thousands of compounds against pharmacological targets in necessarily simplified, and predominantly *in vitro* models capable of rapidly returning multiple data points. Importantly, *in vitro* potency testing became the main avenue of early compound selection.

Such high-throughput formats necessarily have to trade off complexity and accuracy for speed and

amenability to automation, and employ multiple 'reductionist' assumptions[9] on the translatability of such results to living organisms and disease processes. Importantly, this strategy does not include the investigation of (free) drug availability at the target that is automatically afforded by *in vivo* efficacy testing.

It soon became obvious that this selection process yielded many pharmacologically highly active compounds with unacceptable absorption, distribution, metabolism or elimination properties. Unfortunately, this was very often not discovered until advanced development stages, especially in the case of unacceptable human metabolism characteristics. Thus, high-throughput ADME models including basic physiochemical compound characterisation as well as animal and human *in vitro* assays were developed – or adapted from later, low throughput stages of drug development – to provide selection filters that under the old drug discovery paradigm were automatically built into early discovery stages.

ADME as a discipline in its own right could therefore only emerge as a result of the changes in pharmaceutical R&D processes.

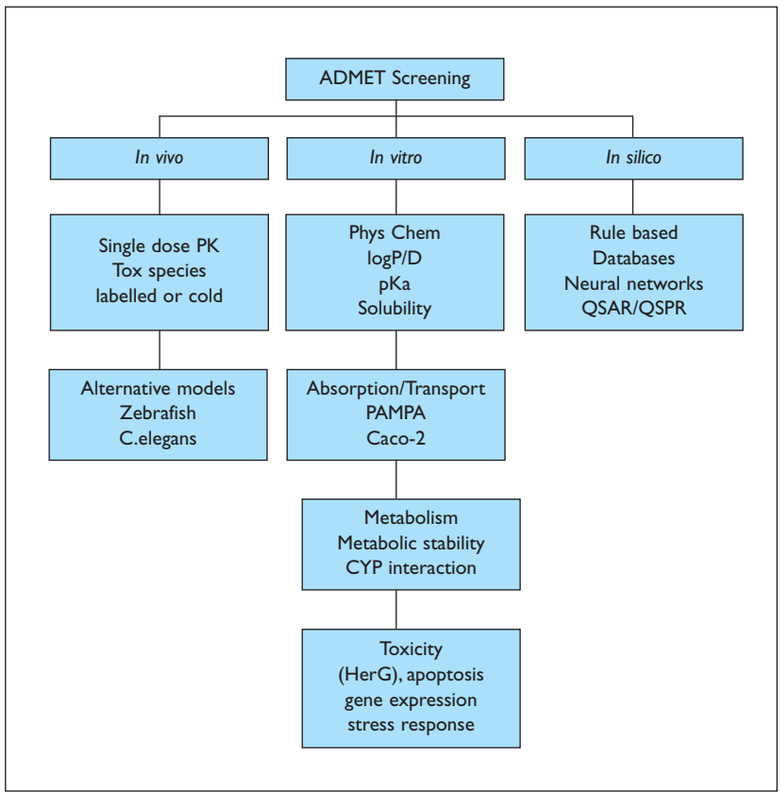
ADME holds a unique position in early drug discovery since quantitative drug movement and qualitative compound fate affect, if not determine, both pharmacologic as well as toxic drug action. Especially the ability to compare human and animal *in vitro* drug transport and drug metabolism facilitates the evaluation of early animal *in vivo* pharmacology and toxicology data (**Figure 1**).

It is now widely accepted that successful drug discovery programmes must include ADME screens (**Figure 2**) to optimise not only pharmacological properties, but also the likelihood of suitable pharmacokinetic behaviour and, to some extent, to reduce the risk of drug-interactions. The growing importance of this type of data has been discussed at the beginning of this article, but is similarly convincingly demonstrated by the rising number of specialist suppliers of high quality, high throughput ADME services, commensurate with the demand from industrial sponsors for these assay formats.

One major difficulty with the optimal application of ADME data in drug research remains its integration into the overall processes. Selection of appropriate ADME screens and evaluation of ADME data are extremely context-driven, where small changes in marketing or clinical development plans may require a restructuring of screening approaches or lead to radically different compound selection parameters. Thus, ADME knowledge management within organisations, often across virtual development timeframes of 10 years or so, continues to be a challenge to the success of ADME integration in drug research, and hence drug research productivity. This problem can best be overcome by sensitising all involved disciplines to the direct impact ADMET strategy has on final compound success, which in turn is best achieved by establishing and maintaining at least a basic understanding of drug metabolism and pharmacokinetics at all stages of decision making.

Toxicity and efficacy issues are seen as the present and future bottlenecks of successful drug research in the 21st century. Between 20% and 40% of investigational drugs are thought to be discontinued due to toxicity concerns[10]. Such toxicity in many cases is at least in part connected to drug kinetics and drug metabolism processes, as exemplified by the inclusion of drug interaction and drug induction screens under the 'T' of ADMET. These assays, however, are strictly speaking drug metabolism rather than toxicity assays. Other toxicity screening assays include assessments of cytotoxicity, cellular stress, and apoptotic changes. The emergence of ADMET thus in itself is already an example of "The future exists today. It's just unevenly distributed" (W Gibson), in that it is now

**Figure 2**
Overview of ADMET screens in drug discovery



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| Biobyte | LeadScope |
| Bio-Rad | LHASA |
| Bayer Technology Services | MDS Pharma Services |
| Cerep | Molecular Discovery Limited |
| Chemical Computing Group | Simcyp |
| ChemSilico | Simulations Plus Inc |
| Compudrug | Summit PK |
| Cyprotex | Tripos |
| Elsevier-MDL | And many others… |

widely, but not universally, appreciated that toxicity, along with ADME, needs to be addressed early on in the modern drug discovery process, despite the uncertainty regarding regulatory acceptance and to some extent, requirements in early drug development.

Prediction of *in vivo* and human drug kinetic profiles from *in vitro* data is now almost routine, but qualitatively highly dependent on the breadth and detail of the data sets and algorithms employed. Very good results are, for example, obtained where *in vitro* data sets contain solubility, absorption, distribution and metabolism data from both animal and human-based test systems, and where the model software incorporates physiological parameters of the species for which the prediction is made[11, 12]. Examples of such models include the Cloe®PK (www.cyprotex.com), GastroPlus™ (www.simulations-plus.com) and simcyp™ (www.symcyp.com) software applications.

Preclinical drug research costs have dramatically increased since 1979[5], (**Figure 2**), at least in part due to the immense costs involved in putting vast numbers of compounds through ever expanding pharmacology, ADME and lately, ADMET, screening programmes designed to be predictive of (human) clinical drug kinetics, metabolism, toxicity and efficacy. Apart from cost issues, this development entails increasing problems of capacity allocation within pharmaceutical organisations. In parallel with increased expenditure, the preclinical sector has therefore also experienced a sharp rise in the outsourcing of many preclinical laboratory activities. As discussed before, the successful application of ADME optimisation to overall compound development is highly dependent on the rapid generation, evaluation and application of such data from carefully selected experimental approaches. Only then can ADME contribute constructively to improved compound synthesis. One of the major determinants of ADME outsourcing success is thus the establishment of dedicated outsourcing interfaces between sponsor and service provider, capable of effecting the dynamic adaptation of ADME activities in line with changes in overall development plans.

A reduction in the number of compounds entering the experimental selection process represents a significant saving in cost and time. Such savings in drug development increase the economical attractiveness and viability of targeting niche markets.

One possible avenue for such savings would be to assess compound characteristics before synthesis by feeding compound structures into computational models.

This consideration is the basis of *in silico* ADMET assessment of compound characteristics, with the aim of avoiding altogether the costly synthesis and screening of compounds with predicted ADMET properties deemed to be undesirable.

A multitude of commercial suppliers offer prediction software on all or isolated aspects of ADMET behaviour (see **table**).

Approximate predictions of toxicity can be made by structural comparisons to databases of toxicologically relevant (gene expression, histopathology, clinical chemistry and morphology) observations in experimental animals in response to known toxicants and commercial drugs, (eg DrugMatrix, GeneLogic), while other programmes (eg DEREK, TOPCAT) rely on data obtained largely in non-mammalian test systems in response to a variety of non-medicinal compounds. The list in the table is by no means exhaustive but nevertheless clearly illustrates the huge number of suppliers in a highly fragmented market, where it is difficult to evaluate the strengths of the various technologies in the absence of overall benchmarking of their comparative performance when challenged with sufficiently large and diverse datasets reflecting the variable demands of pharmaceutical R&D.

Prerequisite to the successful application of pre-synthesis *in silico* ADMET (sometimes also termed

preADMET[13] is the reliable prediction of compound characteristics from compound structure alone, and the quality of that prediction in turn relies on the quality of data on which any *in silico* model is developed.

Herein lies also one of the greatest obstacles to what has been termed 'prediction paradise': the relative paucity of structural information and associated toxicity or ADME data in the public domain has naturally limited the ability to build up databases of sufficient size and with sufficient endpoints, particularly in toxicology[10]. Excretion and transport processes are currently difficult to assess using *in vitro* models, and thus will remain difficult to predict or model in the foreseeable future.

Connected to the use of ever more complex *in silico* ADMET predictions in drug discovery therefore is of course the continuing development and refinement of *in vitro* ADMET systems. Commercial development of advanced *in silico* approaches may thus be expected to be most successful in those service providers who combine the development of new *in vitro* assays with the continuing adaptation and refinement of their predictive software packages.

A major determinant for the optimal application of any ADMET strategy, especially including *in silico*-based ones, remains the clear formulation of the final ADME(T) context in which the selected compounds are to be developed, and the timely communication of any changes to allow adaptation of *in silico* strategies. In the absence of true integration of *in silico* as well as *in vitro* ADMET activities in all decision making processes, especially *in silico* ADMET would run the risk of preventing highly promising candidates from even coming into existence. To minimise this risk, highly efficient data handling and decision making structures need to be in place to translate the outcomes of *in silico* ADMET activities into optimised synthetic approaches. Automated techniques are now being introduced, eg Cyprotex Plc's Discovery Bus[14], which allow models to be built for common ADMET properties with minimal human intervention. Its novel 'competitive workflow' approach is used for the automation of

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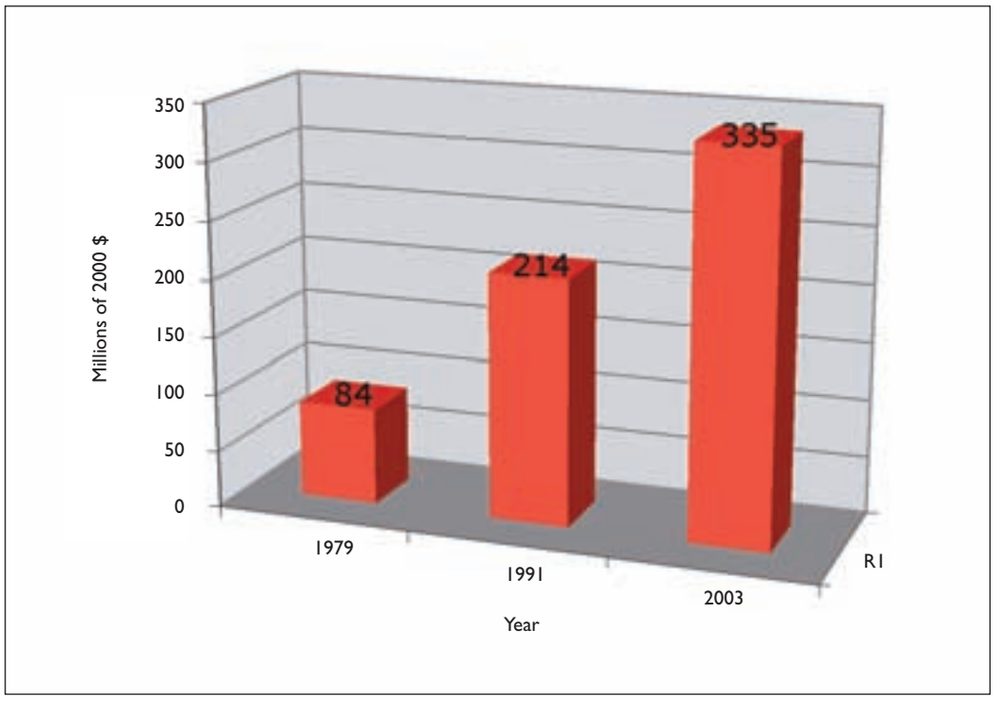


**Figure 3:** Development of preclinical and clinical capital expenditure per new approved drug, 1979 to 2003 (adapted from Di Masi et al, J Health Economics 22 (2003) 151-185, 2003. 'The price of innovation: new estimates of drug development costs'

computer aided molecular design and decision making processes. The system combines speed with the combination of numerous different chemical approaches, but is thought to be more objective in its selection procedures than a highly skilled human expert would be.

An addition to ever increasing and ever more complex ADMET discovery filters is likely to be the use of completely novel approaches focusing directly on the gathering of kinetic data in man. While the ability to clarify human PK preclinically does not remove the necessity to assess drug metabolism and toxicity, it is certainly very helpful in the predictive assessments of, for example, drug interaction risk. Subtherapeutic dosing of human volunteers or patients, known as microdosing[15], thus obtaining human PK data already in preclinical stages is gaining wider and wider acceptance, surprisingly more so in regulatory than industrial environments. A great potential advantage of embracing this strategy is the ability to directly investigate, rather than rely on PK modelling, of pharmacokinetics in 'special patient populations' usually not accessible to clinical studies, eg those suffering from organ dysfunctions, or patients outside the age range of the clinical population investigated in Phase I-III studies. Clearly, this approach is cost-intensive and implicitly relies on the prior elimination of all compounds with poor human PK profile. However, with the emergence of service providers for this technique (eg Covance, Pharmaceutical Profiles, Xceleron), and advances in associated analytics[17], it is expected that this avenue will become more popular in the future.

There are other possibilities for the future of ADMET than that described above for its further development in a predominantly target-based discovery context.

Recent publications[18] have discussed the relative advantages of employing functional over target-based approaches especially in the development of truly innovative drugs. Pursuing this strategy, it is argued, the absence of known SAR effectively extends market exclusivity by preventing competitors from being able to design improved follow-ups. Furthermore, it is argued that in the case of novel targets, the therapeutic risk is actually higher than that of functional approaches, since the latter is more closely connected to actual disease processes.

Additionally, in the absence of a known MoA, patients would benefit from a greater variety of treatment options with agents of similar function, but different modes of action.

However, due to the absence of specific targets to incorporate into screening procedures, this

approach necessitates compound activity evaluation in comparatively complex systems such as whole animals or cells. Recent advances, especially in cell-based screening, have improved the traditionally low compound throughput of these assays. The refinement of the various '-omics strategies'[18], notably metabolomics, continues to facilitate the identification of biomarkers and surrogate markers of disease/therapeutic effect[19,20] necessary for evaluating compounds in functional approaches. It is therefore likely that functional approaches will become increasingly attractive to the drug industry. Since compound activity screens would again incorporate parallel filtering for many drug-like compound characteristics in complex systems, this would effectively reverse some of the developments leading to the emergence of large-scale ADMET screening as described above. In this scenario, the main function of ADMET screens would therefore in all probability be concentrated on the comparison of animal versus human drug metabolism and toxicity to allow an accurate identification of compounds with low human drug interaction and drug toxicity risk that have successfully passed cell-based or *in vivo* activity screens. Assuming a continuation of an industry-wide trend for outsourcing of preclinical activities, service providers offering integrated and fully networked service programmes including cell-based, toxicity and metabolism models for a wide range of industrial chemicals (eg BSL BIOSERVICE, MDS Pharma Services), may be uniquely positioned to offer highly varied and flexible ranges of tests, combined with simplified administrative and logistic processes.

Early metabolomic investigations would serve to understand better the small molecule changes caused in animal and human cells in disease and as a response to drug intervention, thus facilitating the development of more relevant toxicity endpoints and more predictive assays.

Similarly to functional approaches, microdosing of promising compounds would be employed in this alternative paradigm to obtain early preclinical kinetic data in man, and used to assess the likelihood of clinical drug interactions. DDW

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