Expediting the preclinical development process

The concept of the meeting entitled *Accelerating preclinical development by successful integration into drug discovery* on 25–26 February 1999 in Nice, France was ambitious, as it covered a wide range of aspects from re-engineering a company, regulatory aspects of pre-clinical packages and safety evaluation, through to details of which drug metabolism pharmacokinetic (DMPK) studies should be carried out and how to perform them.

It could be concluded from the presentations that DMPK has, at least in part, responded to the challenge of the new approaches of combinatorial chemistry and high-throughput screening (HTS). However, toxicology has been slower to respond, creating a new bottleneck in the process of accelerating compounds into the clinic and proof-of-concept studies.

Developing *in silico* modelling techniques to predict drug absorption and permeability

Michael Abraham from University College (London, UK) presented an approach to calculating a number of properties important in drug metabolism based on five descriptors: excess molar refraction, polarizability, H-bond acidity, H-bond basicity and the McGowan volume. The first and the last of these descriptors can be calculated, but to-date, the other three are usually determined experimentally. It was proposed that the same five descriptors could be used to predict a number of processes that are transport-related, namely solvation, Log P (the logarithm of the partition coefficient of a solute between two immiscible solvent phases), blood–brain distribution and skin permeation. This methodology has been extended by estimating the values of the descriptors for different functional groups, allowing rapid calculation of the transport-related processes on the basis of a SMILES (simplified molecular input-line entry specification) structure.

Implementing physicochemical metrics for estimating solubility and permeability

Chris Lipinski (Pfizer, Groton, CT, USA) gave a thought-provoking analysis of the drug discovery process at Pfizer, which included a retrospective analysis of the duration of the lead discovery and optimization phases. Of particular interest was a comparison of the physicochemical properties of the clinical candidates from Pfizer and Merck, both in the US. Compounds from both companies have shown an increase in molecular weight in the past 30 years. However, whilst the Pfizer compounds have been accompanied by an increase in the Mariguchi Log P of +1, the Merck compounds have shown no change in lipophilicity but an increase in the number of H-bonding groups. This was attributed to lead generation being based on HTS at Pfizer whilst Merck rely more on a structure-based design process. By contrast, researchers at the Sandwich site of Pfizer (UK) have been following the Merck structure-based process more closely, and the trends in the physicochemical properties of compounds from Sandwich are much more similar to those of Merck than of their colleagues in Groton.

Lipinski highlighted that although historically, the lead identification process is consistently 5–10 months, lead optimization has been much more variable, ranging between 15 and 35 months. He attributed this to the difficulty in getting reliable *in vivo* behaviour. At least part of the problem is compound absorption and this is highly dependent on the physicochemical properties of the compounds. Hence, the problems in absorption for Merck could be caused by too many H-bonding groups in their molecules, whilst at Pfizer Groton, the problems might be caused by poor dissolution.

Lipinski summarized his, now famous, 'rule-of-five' for drug absorption, which states that compounds that have:

- More than five H-bond donors (e.g. -OH, -NH)
- A molecular weight greater than 500
- A calculated Log P of greater than five
- A sum of N and O atoms of greater than ten

will potentially be poorly absorbed.

Early positioning of high-throughput pharmacokinetic and metabolic screening

Irvine Silver (GlaxoWellcome, Research Triangle Park, NC, USA), gave a presentation on positioning high-throughput metabolism studies early in the drug discovery process as part of a combinatorial lead optimization programme. The programme includes the assessment of physicochemical properties, permeability and toxicity testing, and pharmacokinetic and metabolism studies. The purpose of these high-throughput screens is to rapidly evaluate molecules in a number of parallel screens, and then choose the quality compounds, hence preventing the formation of a bottleneck in the lead optimization process. GlaxoWellcome is also looking to the future, however, and intend to use the data generated to improve understanding and possibly enable the prediction of properties based on structure.

These high-throughput approaches are being used for a number of types of study:

- Measurement of metabolic stability
- Identification of pathways of metabolism
- Identification of sites of metabolic lability

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- Determination of species differences in metabolism
- Finding the potential for CYP450 inhibition
- Identification of which cytochromes are responsible for metabolism.

High-throughput *in vitro* metabolic stability screens are run in 96-well plates on Tecan (Switzerland) robots. Reactions are analyzed by high-performance liquid chromatography (HPLC)–mass spectroscopy (MS), either with single-ion monitoring, or by using triple-quadrapole or ion-trap MS by cassette analysis. Cassette analysis is an approach where, on completion of incubation, samples from different studies are mixed together and analyzed as a single HPLC–MS run, relying on the MS to provide separate simultaneous analysis of each component. The importance of good automated data handling to enable the analysis and review of results from multiple screens of hundreds of compounds was stressed. All the data (e.g. metabolic stability and permeability) are used to select compounds for further testing, which usually consists of *in vivo* pharmacokinetics in the rat and dog.

Questions to the speaker made it clear that, although these high-throughput methodologies are being used within GlaxoWellcome in a very pragmatic way, more thoughtful and/or classical approaches are still running in parallel.

Incorporating toxicology evaluations into drug discovery

Colin Brown (Inveresk Research, Tranent, UK) highlighted the importance of good supporting toxicokinetics and mechanistic understanding of toxicology, giving an example of a compound that was about to fail because of toxic signs until it was realized that, on further dosing, the exposure levels in the test species were likely to drop. This led to a reduction in the apparent toxicity and enabled the study, and presumably the development programme, to continue.

The importance of speeding up the whole process was emphasized by a consideration of the chances of making a profit from a new chemical entity (NCE). For a compound that generates peak sales of $100 million per year, it is unlikely that any profit will be made if the development has taken 12 years. Surprisingly, at least to this author, it was claimed that the success rate for getting a compound from preclinical development to the market was one in eight for the UK, compared to 1 in 22 in the US. Furthermore, the duration of development for a leading medicine was reported to be 7–9.5 years, whereas for other medicines, it was 8.5–12 years.

Emerging technologies for accelerated toxicity evaluation

Roger Ulrich from Abbott Laboratories (Abbott Park, IL, USA), provided a review of some of the new technologies that are becoming available to enable early toxicity screening of compounds in the research phase. With some knowledge of the likely mechanism of toxicity for a class of compounds, rapid screening could be possible using cell models such as primary cultured hepatocytes. It was suggested, however, that only approximately 20% of the results seen in the clinic are being correctly predicted. Gene expression-based assays can provide screens for a variety of cellular responses such as cell growth or death, CYP450 induction and peroxisome proliferation. As all toxicity leads to a change in gene expression, it should be possible to screen for adverse effects by examining the DNA, RNA and/or the proteins. Some aspects of large-scale transcript imaging using microarrays and proteomic approaches were discussed. However, their use in drug discovery is yet to be proven and the methodologies to cope with the vast quantities of data generated are not yet in place. Nonetheless, these approaches are most likely to provide the high-throughput screening that the pharmaceutical industry is seeking.

Re-engineering the organizational structure

Philip Birch (Nycomed Amersham, Little Chalfont, Buckinghamshire, UK) proposed that the target for altering the organizational structure to enable effective integration of preclinical development into drug discovery is to manage change whilst maintaining momentum. Birch suggested that several activities that are traditionally associated with the development phase are incorporated into, or at least influence, research projects. Aspects such as project management, portfolio management and strategic marketing were cited. It was proposed that to get a seamless transition from research to development, it might be useful to have the development teams within the drug discovery unit. At the very least, management must ensure that the necessary core competencies are available across all phases of research and development. To manage the changes necessary for a seamless transition, it might also be useful to have an internal consultancy or reference group. Research workers need to be aware of their role and/or project in the overall business context, as well as their company's portfolio.

Thus, it would seem that the industry still has a significant way to go to ensure that compounds that enter development have a high expectation of appropriate pharmacokinetics and bioavailability, as this is still the largest single cause of failure.

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