Invaluable Influences

Reducing attrition rates while managing costs is one obstacle when bringing new medicines to the pharmaceutical market, but the influence of drug metabolism and pharmacokinetics could offer a solution

Dr Richard Weaver FRSC at XenoGesis Ltd

The global prescription drug sales are forecast to grow robustly at 6.5% for the next five years, thus reaching $1.06 trillion in 2022 (1). However, it remains an increasing challenge to achieve FDA approval for a new drug application in an industry that runs high on failure rates. Figure 1 illustrates the number of FDA drug approvals from 1995 to 2016. After a high in the mid-to-late 90s, the number of drug approvals somewhat stagnated at around 23 per annum for a decade, before recovering more latterly.

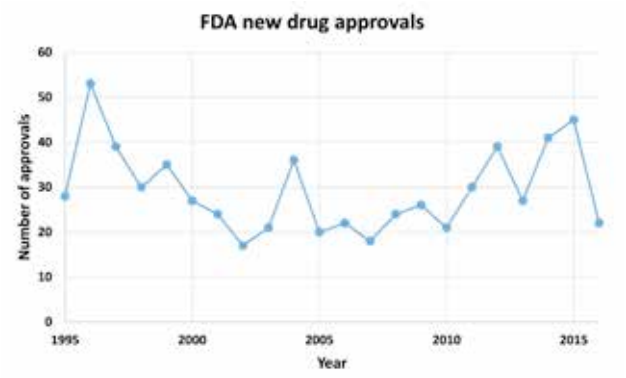

Figure 1: Number of FDA new drug approvals by year 1995-2016

Attrition in the pharmaceutical industry remains high at approximately 90% from Phase 1 through to launch of a novel drug (2). This is on the back of significantly higher attrition in the research phase. Typically 200-500 compounds are made during drug discovery, yet only one of these, synthesised in an iterative manner, will be nominated as the drug candidate. R&D spending has spiralled in recent years and has not resulted in more success.

In 2000, it typically cost approximately $1 billion to develop a new drug, versus $2.6 billion in 2015 (3). This misbalance of the books led to the dramatic change in the way that drugs are discovered and developed from traditionally pharma-in-house to often fully outsourced models, the consequence of which is the global shrinking of pharma sites and staff. Additionally, large pharma are increasingly active in acquisitions of biotechnology organisations and smaller firms to bolster their pipelines. Therefore, for the biotechs, reliance on capabilities, expertise and advice from the CRO sector is growing significantly.

Reasons for Failure

In line with the past decade – specifically 2013-2015 – the major drivers for drug failure are lack of efficacy (52%) and inadequate safety profile (24%) (4). Both of these reasons have, by definition, a drug exposure consequence. In the former, perhaps this is insufficient exposure and inferior pharmacokinetic properties, eg short half-life or poor bioavailability. In the latter, this could be too much exposure relative to 'efficacy-required' exposure.

As the drug metabolism and pharmacokinetics (DMPK) or absorption distribution metabolism elimination (ADME) properties of a drug define exactly what free-drug systemic, tissue and sub-cellular exposure is achieved, understanding and being able to predict this with confidence is essential to success.

Front-loading ADME is now commonplace in the industry. For example, *in vitro* DMPK tests, coupled with physicochemical measurements, have been proven to predict whether a drug candidate is worthy of progression to profiling in more costly *in vivo* DMPK or pharmacology tests (5).

However, in the new model of R&D, with an increasing ratio of biotech:large pharma-derived drug candidates, the real understanding and influence that ADME can have in the sector is sometimes lacking and arguably in retrograde.

It's All in the Chemistry

How the body will respond to a drug – from site of administration to elimination – is entirely defined by the chemical structure of the drug.

Therefore, understanding the chemistry of the compound in the context of ADME is an essential 'first learning' in any drug discovery campaign, and the earlier the better. If a medicinal chemist focuses on potency alone, it can often lead up a blind alley.

However, chemists are increasingly aware of how important ADME is in defining ultimate success, and compounds with more balanced overall properties are often targeted initially as hits. For example, choosing a compound or series with moderate potency and a $logD_{7.4}$ of two versus a potent compound with $logD_{7.4}$ of four is more likely to result in success.

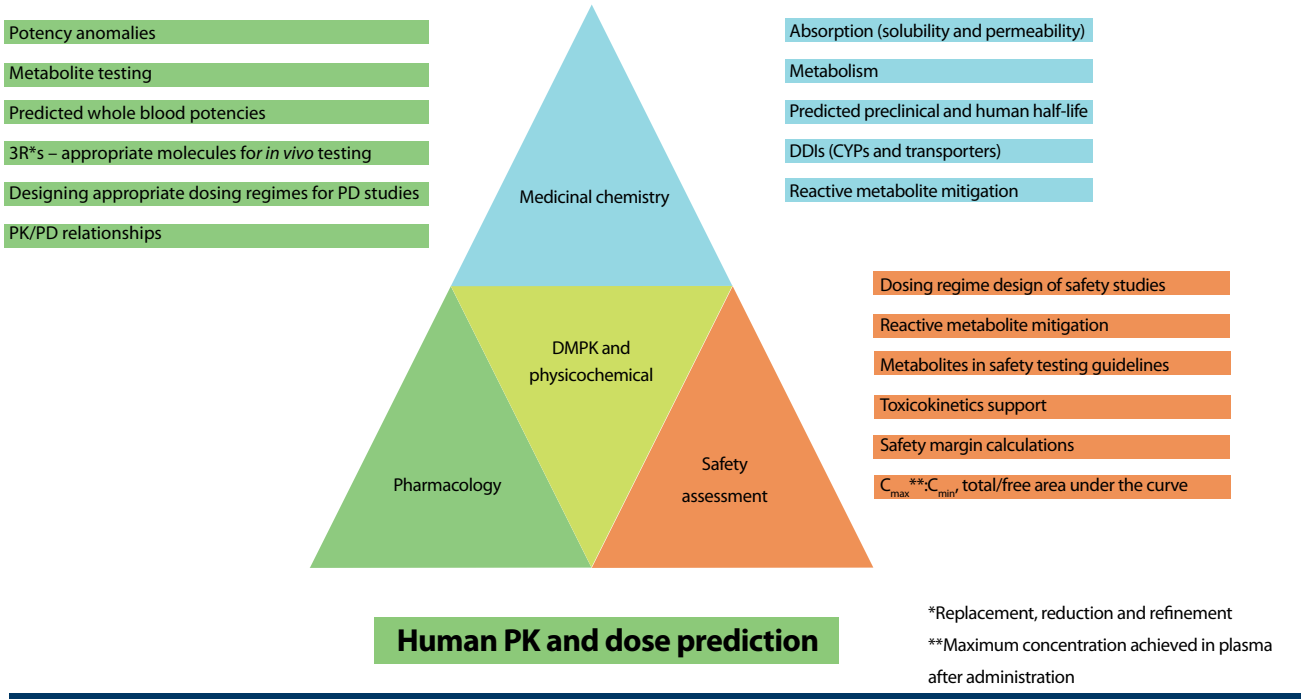

Figure 2: Influence of DMPK on all drug discovery disciplines

Understanding lipophilicity – namely logP and $logD_{7.4}$ – is fundamental to predicting the likely liabilities and strengths of a compound. Lipophilicity, a key physicochemical parameter, is often correlated with many ADME parameters. These include:

- Solubility
- Passive permeability
- Liver-based metabolism
- Passive renal clearance
- Plasma protein binding

Additionally, high lipophilicity is often correlated with higher toxicity and promiscuity of unwanted pharmacology. A compound with high $logD_{7.4}$ is likely to suffer from poor solubility, high gastro-intestinal (GI) and liver metabolism and, ultimately, poor bioavailability as a consequence. Furthermore, cytochrome P450 (CYP) inhibition will be likely, which could generate a drug-drug interaction (DDI) risk. Conversely, a compound with a very low $logD_{7.4}$ may have poor GI permeability and is subject to transporter effects, eg renal transport. Proceeding with a sub-optimal ADME profile, such as extensive formulation work to improve solubility, will require expensive rescue therapy, which can cost significant time, money and erosion of patent life.

The Cement of R&D

A successful research programme has several key core elements, along with supporting disciplines, eg pharma sciences. Specifically, the fundamental activities are (1):

- Medicinal chemistry
- Pharmacology
- DMPK/ADME
- Safety evaluation

These four disciplines should never be isolated, and representatives from each should understand the interplay and dialogue between all. DMPK/ADME is the glue that links all disciplines, primarily through the simple mathematical relationship between fully comprehending the body-exposure time profile versus wanted and unwanted effect.

To have an ADME/DMPK scientist who understands chemistry and can have a chemical structure-based conversation with a medicinal chemist – with the remit of collectively improving properties – is of significant value to a project team. Likewise, exploring the effect/exposure in a mathematical manner with pharmacology and safety assessment is essential for success. It may be surprising to some, but these relationships can start to be explored early in discovery, along with prediction to man of pharmacokinetics and dose. This is often very helpful as, even at the early stages, it can identify what needs to be improved and focused on – for instance, potency needs to increase 30-fold, poor absorption and bioavailability prediction in man or sub-optimal half-life not commensurate with once daily dosing. Figure 2 illustrates some areas that DMPK scientists can have influence on in the relative drug discovery disciplines.

All data generated within drug discovery should be evaluated in a fully integrated manner. Although DMPK data are known to be needed, which to collect and what to do with them are issues still not universally understood. For example, if a structural chemistry alert is likely to cause instability in whole blood, then this should be front-loaded as a first *in vitro* assay and certainly not progressed *in vivo* until this potential liability has been evaluated.

Building confidence in extrapolating DMPK data from *in vitro* to *in vivo* data (IVIVE) is an essential part of understanding and translation. This is firstly conducted in preclinical species and then in man. Being able to predict unbound plasma exposure from

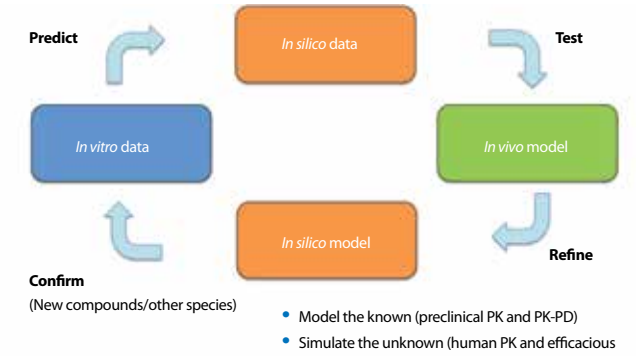

Figure 3: Integrating *in vitro* and *in vivo* data in continuous study design using *in silico* methods

an oral dose from *in vitro* data is achievable as long as certain criteria are met. Bringing in exposure and ultimately predicting human pharmacokinetics, as well as dose, is often the remit of the DMPK scientist through integration of all DMPK, *in vitro* and *in vivo* pharmacology data via simulation and modelling. Figure 3 outlines the process of integrating *in vitro* and *in vivo* DMPK and physicochemical data into study design and refinement of understanding using *in silico* modelling.

Capability Versus Creativity

As a result of the increased expenses and high attrition, large pharma has revised the R&D strategy in the last 5-10 years by downsizing substantially and increasingly outsourcing to CROs to manage the costs effectively. Historically, the expertise and experience to provide, integrate and interpret data was found within large pharma companies. However, more recently, the shift in expertise is towards the CROs and the biotechs themselves.

Consequently, the CRO market shows no sign of slowing down after its significant continued growth during the last decade. Forecasts of a 6% compound annual growth rate to 2022, with an estimated world-wide market $45.2 billion, are expected (6).

The CRO market is split into 'one-stop-shop' large organisations and more specialised/single discipline companies. The choice between them may partly depend on how much scientific input is required. For example, if the concern is simply capacity, then a lower-cost multi-disciplined CRO will likely be more cost-effective.

Nonetheless, if scientific help and advice is required on top of generating data, then greater value may well be achieved in more specialised CROs. Value should never be confused with cost in this decision-making. In the area of outsourcing DMPK, a key question may be whether one would require the CRO just to identify DMPK/ADME issues or also seek to solve them using feedback within the collective project team in the design-make-test cycle in discovery.

On the latter point, the average cost to a drug company of a day's delay in getting a new drug to market is estimated to be millions of US dollars. Accordingly, fixing ADME issues early is increasingly critical for companies' drug R&D pipelines and likelihood, time and expense of success. Even a minor improvement in early stage drug failure prediction could result in significant time and cost savings for R&D companies.

A compound can fail in *in vivo* oral pharmacology tests for two primary reasons: poor potency or inadequate exposure to drug, such as bioavailability or minimum concentration not achieved (C_{min}) relative to length of pharmacology coverage required.

In the pharma industry, the necessity of defining *in vitro* target potency before further compound progression is well-established. Moreover, acquiring this prior knowledge – along with key DMPK comprehension and data – before progressing to *in vivo* pharmacology allows real hypothesis testing and dose/route selection, while maximising the chance of success. This permits the building of a pharmacokinetic:pharmacology (PK:PD) relationship, essential for raising the platform of evidence required in a novel target area in man.

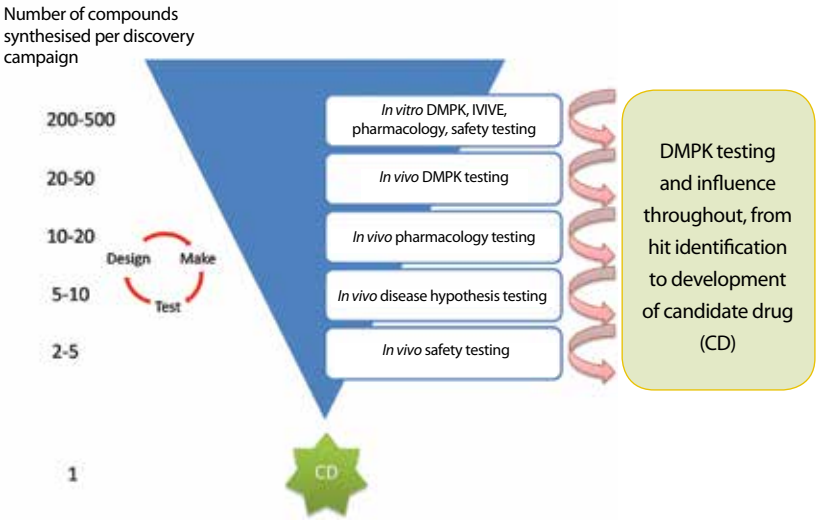

Figure 4: The influence of DMPK from hit identification to nomination of a candidate drug

Figure 4 demonstrates how this combined pharmacology/DMPK knowledge model of working fits within the drug discovery process and the typical attrition rate by compound 'drop-out' through the process.

Challenges and the Future Landscape

One of the greatest challenges in bringing new medicines to market will be reducing rates of attrition, due to lack of efficacy and safety profile, while managing costs; DMPK will be critical in aiding both these areas. Refining this exposure/effect relationship, further to key patient populations, will also involve DMPK scientists. Addressing poorly soluble compounds by advanced formulation techniques – a growing problem – will also need to be front-loaded.

The way that new drugs are discovered will increasingly rely on CRO influence, biotechs, open innovation/collaboration and risk sharing. Whether this will bear fruit and reduce attrition is yet to be confirmed. However, DMPK influence will clearly be needed more than ever.

References

1. Visit: info.evaluategroup.com/rs/607-ygs-364/images/wp17.pdf
2. Calcoen D *et al*, What does it take to produce a breakthrough drug?, *Nature Reviews Drug Discovery* 14: pp161-2, 2015
3. Pharmaceutical Research and Manufacturers of America, 2016 biopharmaceutical research industry profile, *PhRMA*: 2016
4. Harrison RK, Phase II and Phase III failures: 2013-2015, *Nature Reviews Drug Discovery* 15(17): pp817-8, 2016
5. Soars MG *et al*, Use of hepatocytes to assess the contribution of hepatic uptake to clearance in vivo, *Drug Metabolism and Disposition* 35: pp859-65, 2007
6. Visit: www.outsourcing-pharma.com/clinical-development/cro-market-to-reach-45.2bn-by-2022

About the author

Dr Richard Weaver FRSC is the Managing Director of XenoGesis Ltd, a rapidly growing CRO based in BioCity Nottingham, UK. Having joined Astra Charnwood in 1997 within Discovery DMPK, he progressed to Group and Project Leader at AstraZeneca. Richard gained a first class honours degree in chemistry, with awards for the best performance in every year, followed by a medicinal chemistry PhD with a Wellcome Trust scholarship at the University of Leicester, UK, and two subsequent postdoctoral positions at the Welsh School of Pharmacy, Wales.
Email: richard.weaver@xenogesis.com