The 3 I's of Imaging: image why, image what, image when?

Imaging has become an integral part of the drug development process. This report details the value imaging adds at a time of exponentially rising costs, and outlines how its application can enable confident decision-making.

Image Why?

The drug development pathway remains plagued by high cost and low success, leading to a steady decline in pharmaceutical R&D productivity over recent decades. Yet, patent cliffs and the ongoing need to replenish pipelines force pharmaceutical companies into ever-increasing spending. A study from the Tuft’s Center for the Study of Drug Development (CSDD) in 2014 puts the cost of developing a prescription pharmaceutical at $2.6 billion (DiMasi JA et al. 2014). Taking inflation into account, this represents a rise of 145% over the estimate made by the CSDD in 2003.

The escalating costs have been attributed to increasingly high standards expected of new drugs, ever-more cautious regulators, wasteful investment and high expectations put on the results of basic research (Scannell, JW et al. 2012). Despite increasing time and money invested, failure rates for new drugs remain high, with research in 2010 estimating that the clinical approval success rate for central nervous system (CNS) drugs is just 8% (DiMasi JA et al. 2014). A drug failure during late stages of development entails huge losses – potentially costing ten years of development and $1 billion development costs, besides the lost revenues from a successful new molecular entity.

Growing efforts to bring greater efficiency to pharmaceutical R&D have not reduced the cost of drug development. Attrition increases costs for both payers and patients, making it increasingly difficult to reach project profitability and destroying value for pharma companies. On average, the rate of return for small molecule drugs is just seven per cent, and the long-term cost capital of the industry is eight to ten per cent (DiMasi JA et al. 2014). Shifting the major fraction of compound attrition to the early phases of drug development will lead to significant savings in time and money. To achieve this shift, significant improvements in early phase decision-making are required, to kill compounds that are destined to fail in later phase. Technologies that allow these go/no go decisions to be made earlier and with more certainty, will reduce overall drug development costs.

Go/no go decisions are difficult to make for both small and large biopharma companies. A review of 44 Pfizer Phase II programs concluded that in 43% of cases, it ‘was not possible to conclude whether the mechanism had been tested adequately’ (Morgan, P et al. 2012). Morgan and colleagues have formulated a concept of three ‘Pillars of Survival’ providing information required to give confidence that an early-stage drug can make it through to proof-of-concept. The three pillars, are:

- Drug Exposure – at the target site of action for the desired length of time
- Target Engagement – Drug binding to the right target at clinically meaningful doses
- Pharmacological Activity – Proportional to the demonstrated target exposure and target binding

These questions can often be best answered by the judicious and timely use of imaging methodologies, in particular, quantitative PET.
Without imaging, the drug development pathway (see Figure 1 below) contains a ‘black box’ preventing the direct examination of drug interaction with its molecular target in human. Molecular and functional imaging in vivo can open up the black box to direct examination and validation of the three ‘Pillars of Survival’.

Figure 1: The ‘black box’ preventing the direct examination of drug interaction with its molecular target that can be visualised with imaging.

Image When?

The right information on drug performance in man, obtained as early as possible is extremely valuable. Application of PET imaging in parallel with the first-in-human single ascending dose (SAD) safety trials, allows the determination of the relationship between plasma concentration of the drug and target occupancy over time. A combination of these data with peripheral pharmacokinetic data enables the estimation of target occupancy following repeat dose administration. Such information will allow a
reduction in the size and expense of the multiple ascending dose (MAD) safety and tolerability studies, as well as the Phase II proof-of-concept. Alternatively, if it is felt that adequate target engagement cannot be achieved at clinically relevant doses, termination of the candidate molecule can take place immediately after the SAD study.

In order to ensure that the full impact of PET imaging is brought into the early phase, any development of novel biomarkers (if required) must commence at least 18-24 months before first-in-human studies, preferably at the same time as lead compound selection.

Imaging applications can benefit later phases of drug development as well, though the study design and methodology used should be carefully focused to answer the specific questions faced by a particular phase of development, as illustrated below in Figure. 2.

Figure 2: Types of imaging studies relevant to particular phases of drug development.

Image What?
The ultimate aim of imaging in early phase drug development is to:

1. Obtain information on drug distribution to the target organ
2. Quantify target engagement, and
3. Detect post-target effects of the drug indicative of pharmacodynamic effects relevant to its proposed clinical mode of action

Each of the aims above will require a specific study design using focused methodology.

Quantification of target occupancy

Demonstration of an interaction of a drug molecule with its target in a tissue should be considered the approach of choice for defining drug–target pharmacokinetics, and will provide valuable information on both drug distribution and target engagement. Target occupancy studies require a well characterised radioligand (or tool compound) that can be used to quantify the availability of the target of interest before and after drug administration. A typical study will evaluate target occupancy following the administration of different single doses of the drug, at various time-points post administration to determine the relationship between plasma concentration of the drug, target occupancy and time post-dose, to deliver a an appropriate biological model to predict target occupancy following repeat dose administration (Abanades, Van Der Aart et al. 2011). Adaptive-optimal designs can minimise the number of subjects required and maximise the information related to the plasma concentration-receptor occupancy relationship, thus providing an efficient means of conducting PET receptor occupancy studies (Zamuner, S et al. 2012). Target occupancy studies can be efficiently combined with functional imaging methods, such as blood oxygen level dependent functional MRI (BOLD-fMRI) or arterial spin labelling (ASL) to provide information on the post-target pharmacodynamics effects which can be related to target occupancy (Rabiner, B et al. 2011). Such a multi-modal imaging study will cover all three ‘Pillars of Survival’ and represents the ideal at this phase of drug development.

Biodistribution

While a target occupancy study is an ideal study to conduct, it requires a suitable PET radioligand, which is often not available. In the absence of a PET radioligand, suitable to quantify target availability, direct information about drug penetration into the organ of interest can be obtained by radiolabelling the drug of interest with a PET radionuclide. In conjunction with associated measurements of the drug concentration in blood, it is possible to use bio-mathematical kinetic models to derive estimates of the clearance from plasma to tissue (a function of the blood flow and the tissue extraction of the molecule from the blood) and the ratio of the concentration of labelled drug (and drug metabolites) in tissue to blood that would be achieved at equilibrium (the tissue: blood partition coefficient). Associated HPLC analysis of blood samples ex vivo allows additional consideration of any metabolism of the radiolabelled compound. A combination of a PET distribution study with such a labelled drug, and information on drug free fraction in blood and tissue (obtainable from in vitro equilibrium dialysis) can relate drug plasma concentration to tissue free drug concentration in vivo. The tissue free drug concentration may be combined with in vitro affinity estimates to provide an indirect estimates of target occupancy (Gunn, S et al. 2012). While such data rely on in vitro affinity estimates (which often differ from in vivo ones), in the absence of the capacity to do an occupancy study, a biodistribution study may provide an acceptable alternative.
Pharmacodynamics response

The pharmacological effects consequent on drug binding to a target can be related to the levels of target engagement, which, in turn, enables the levels of target occupancy needed for pharmacodynamic effects to be estimated (Gunn, R et al. 2013). Pharmacodynamic effects can be indexed by targeting second messenger systems (such as the phosphodiesterase enzymes), changes in neurotransmitter concentration (such as increased monoamine concentrations caused by stimulants or selective serotonin re-uptake inhibitors), tissue metabolism (using 18F-FDG), or for drugs that target the CNS, changes in blood flow/blood oxygenation via functional magnetic resonance imaging (BOLD-fMRI or ASL) (Mullard, A).

Although measurement of pharmacodynamics responses can be useful in assessing the utility of novel drugs, care should be taken in study design to ensure that any changes in tissue metabolism or blood flow can be related to the drug studied rather than various confounding variables.

Development of target-specific radioligands for PET

Given the potential value of PET imaging to drug development, there are surprisingly few validated PET ligands available. In order to support first-in-human studies against novel targets, it is necessary to start planning biomarker development during the early drug discovery phase.

PET ligand development has many similarities to that of drug development, and often a suitable candidate can be identified from the compound library used for selection. Like the drug, the PET ligand should be selective for the target of interest and have a high affinity. In contrast, a shorter half-life is more appropriate for a PET ligand than for most drugs and, because the PET ligand is administered as a microdose, toxicity is generally not an issue. Additionally, a PET ligand can be administered intravenously, thus intestinal absorption will not prove problematic. These factors mean that development of a novel PET ligand – selected from an existing compound series – can take around 18 months to clinical validation, compared with the 10-14 years that it takes to develop a novel pharmaceutical.

With appropriate data on target and compound properties, in silico biomathematical modelling can be used to predict the behaviour of potential ligands and rank them in terms of likely success before the determination of labelling feasibility and routes of synthesis. PET radioisotopes typically have short half-lives, so it is important that the label is added during the final synthetic stage.

The next step is designed to evaluate the performance of the selected PET ligand candidate in a suitable preclinical species, and will generally involve the quantification of the magnitude of the displaceable signal, as well as an estimate of the reproducibility of its measurements.
Before the PET ligand can be used in the clinical setting, a single dose toxicity study should be performed, as outlined in the ICH M3 guidelines for preclinical safety testing. In parallel, while the toxicity study is being performed, the synthesis of the PET ligand must be implemented to Good Manufacturing Practice (GMP) standards.

Figure 3: This diagram captures the full process of developing a PET imaging probe in humans. The process starts by obtaining target in silico and in vitro measures around the target protein and candidate compounds (Step 1), before proceeding through biomathematical models that identify the most likely compound to work in vivo (Step 2), identifying possible routes and reactions for radiolabelling (Step 3). Subsequent phases involve synthesis of the chosen candidate (Step 4), before evaluation in an appropriate preclinical species (Step 5) and translation to humans (Steps 6 and 7).

Case Study
A recent trial on a drug candidate targeting the Adenosine A2A receptor for treatment of neurological disorders, carried out by biotechnology company Vernalis and imaging company Imanova (Brown, AP et al. 2013), provides a clear demonstration of the utility of imaging in early phase drug development to reduce both the cost and time of entering proof-of-concept studies. In this instance, a PET ligand suitable to evaluate occupancy at the A2A receptor was available.
Using an adaptive trial design, the an occupancy study was performed in parallel with the single ascending dose (SAD) study, in order to relate occupancy at the A2A receptor in the brain with drug dose and plasma concentration. Each subject underwent three PET scans: at baseline; three hours and at 23 hours after drug dosing, as shown in the Figure. 4 below. For each PET scan, A2A receptor occupancy was related to the plasma drug concentration measured at the time of the PET scan.

Figure 4: Images from a representative subject. The upper three rows show summed PET images. Baseline images (top row) show regional heterogeneity consistent with the expected distribution of A2A receptors, which is significantly reduced three hours (second row images) and 23 hours (third row images) after drug administration. Corresponding baseline structural MRI scans are shown in the bottom line for anatomical reference.

The data generated clearly demonstrates the relationship between plasma concentration and receptor occupancy in the central nervous system (CNS), showing that the drug crosses the blood brain barrier and interacts with the target receptor. The information acquired was used by the study sponsor to support the progress of the drug into Phase II studies. Importantly, the quantitative data generated from the occupancy study, was used to determine the dose to be used in patient studies for efficacy, thus reducing the number of doses to be tested.
Figure 5: Estimates of receptor occupancy plotted against plasma drug concentration. The vertical line shows the estimated EC50 and its 95% confidence intervals.

This study clearly demonstrates the value imaging can add to aid a number of critical decisions. In this way, imaging holds the key to considerably reducing time and costs of drug development overall.

Beyond the Brain

While imaging has become an essential part of CNS drug development, the utilisation of these techniques for non-CNS applications has lagged behind.

The lack of well characterised ligands for non-CNS targets, the greater availability of alternatives such as biopsy, and the relative lack of expertise in the use of imaging among non-CNS scientists all contribute to the lower utilisation of imaging for these drugs. Nevertheless, the principles in common use for evaluation of CNS targets, can be easily translated to other therapeutic areas.

A range of PET ligands developed for the CNS have been applied to imaging non-CNS targets, and a broad range of therapeutic areas, including autoimmune diseases and inflammation, fibrosis and oncology appear to be fruitful candidates for the utilisation of imaging techniques.

By raising awareness of the applications of imaging within the debate about R&D productivity, there is an opportunity to transform the drug development process. Drugs that do not interact sufficiently with their target in the clinic can be dropped from further development, allowing drug developers to focus resources
on compounds that are likely to be successful. In addition, the information gained from a timely and well-designed PET imaging study can be used to make decisions about further development, such as drug dose – saving both money and time.

References


DiMasi, JA et al, Cost to develop and win marketing approval for a new drug is $2.6 billion. Visit: http://csdd.tufts.edu/ news/complete_story/pr_tufts_csdd_2014_cost_study


Mullard, A. Molecular imaging as a de-risking tool: coming into focus? Nat. Rev. Drug Discov: 12, 251–252, 2013

