Pharmaceutical research has a big problem. Development and Discovery are two independent activities with a very narrow bridge between them. That’s when they’re in the same company. More often nowadays, compounds are discovered and developed by different organizations. In order to deliver compounds to development organizations that are truly developable, Discovery needs to adopt a product focus, or a “developability” focus.

Certainly the first wave of this has begun: predictive ADMET, in which I include \textit{in vitro} and \textit{in silico} attempts to qualify compounds early on. There’s more to developing a drug than bioavailability and toxicity, however, and the coupling between Discovery and Development can be made much more efficient, if considerations such as formulation and manufacturing can be imparted to the Discovery mindset, and if precious know how from Discovery can roll forward into Development.

Figure 1 – A prototypical linear approach to drug discovery. In this common motif, product-focused criteria, such as patient compliance and cost-effectiveness are deferred until very late in the product development cycle. Because very few candidates are promoted to this stage of work, the development organization is forced to ‘make the best with what they get’. If more candidates were exposed to development criteria earlier in their identification process, it is likely that different compounds would be chosen for development.
Table I – Some characteristics of a successful drug product

<table>
<thead>
<tr>
<th>Effective</th>
<th>Potency</th>
<th>Selectivity</th>
<th>Sizeable therapeutic index</th>
<th>Unmet medical need</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient compliance</td>
<td>Tablet formulation</td>
<td>Convenient dosing schedule</td>
<td>Appealing taste, colour</td>
<td></td>
</tr>
<tr>
<td>Cost effective</td>
<td>Long shelf life</td>
<td>Straightforward process chemistry</td>
<td>Straightforward formulation</td>
<td></td>
</tr>
</tbody>
</table>

and CYP 3A4 metabolism (9). If our goal is to truly affect the mindset of the chemists who are innovating new potential therapeutics, surely the rules of thumb that trip off the tongue and show up as alerts or color coded indicators will win out. Interestingly, as more and more studies are done, it may well transpire that these rules of thumb are as statistically significant as the more sophisticated models. Whichever school of thought is pursued is probably less important than the essential step of taking action: equipping chemists (11), and keeping them accountable.

WHY NOT PARALLELIZE FORMULATION AND MANUFACTURING?

The rules of thumb for predictive ADMET go a long way to provide chemists with the tools to develop a product focus: tablet formulation will be more likely, and the heightened awareness of pharmacokinetic properties will lead to compounds with more convenient dosing schedules.

Indeed, the same molecular properties (solubility and logD) which govern many of the predictive ADMET rules of thumb are also cornerstones of preformulation research (Figure 2), and chemists who consult predictions of these properties regularly during their design processes will be more likely to discover compounds that can be formulated into tablets without undue fuss, leading to a lower cost of goods, and higher cost effectiveness.

Another practice that could be adopted by discovery chemists to improve the product-focus of their discoveries would be to force themselves, every so often, to produce a gram of their compound. Perhaps every chemist should synthesize on this scale once every ten compounds, four or five times a year. By being required to do so, the prudent chemist will begin to build process chemistry into his or her synthetic schemes, and focus on making compounds that can easily, rapidly and cost-effectively be scaled up to animal and first in human quantities. These compounds then create a huge advantage from the point of view of developability: not only will they be available for late-stage testing much more rapidly, but the manufacturing costs will likely be lower as well.

To this point, the discussion in this article has been focused on feeding information and ideas back to synthetic medicinal chemists. There is another way in which to tighten the integration between Discovery and Development, however: feed information forward.

THE FEED FORWARD EFFECT

A quick inspection of Figure 3 shows that as a candidate progresses toward Development, its sample size increases, and it is subject to many more analytical chemistry techniques. Looking a bit closer, there are many samples being studied that are related to one another, and many analyses that are similar (either they apply the same technique a new sample of the same compound, or they apply a complementary
Table II – The multiple relationships between Development analyses and their Discovery counterparts

<table>
<thead>
<tr>
<th>Related by sample</th>
<th>Related by technique</th>
<th>Complementary by technique</th>
<th>Complementary by underlying physics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Related by sample</td>
<td>Analogues from medicinal chemistry</td>
<td>MS for structure validation &amp; LCMS for structure elucidation</td>
<td>LCMS determinations in pharmaceutical profiling for lead selection</td>
</tr>
<tr>
<td>Related by sample</td>
<td>Metabolites from pre-clinical ADMET</td>
<td>NMR for structure validation &amp; NMR for structure elucidation</td>
<td>PhysChem determinations in preformulation &amp; Chromatography</td>
</tr>
<tr>
<td>Related by sample</td>
<td>Metabolites from clinical ADMET</td>
<td>Analytical scale chromatography for in vitro studies &amp; NMR for structure validation</td>
<td>PhysChem prediction in medicinal chemistry &amp; Solution phase characterization of active ingredient</td>
</tr>
<tr>
<td>Related by sample</td>
<td>Impurities from process chemistry</td>
<td>Semi-prep chromatography for in vivo studies &amp; Method development for QA/QC labs</td>
<td>Solid state characterization of dosage form &amp; Structure elucidation, NMR, MS for structure elucidation</td>
</tr>
<tr>
<td>Degraders from stability studies</td>
<td>Impurities from packaging</td>
<td></td>
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</table>

In another application, LCMS techniques are used to identify metabolites in a pre-clinical study. Typically, the MS experiments are able to limit the scope of possible metabolite structures, but are unable to specify points of attachment of various functional groups, or to differentiate among a few related compounds. The nature of the MS(n) fragmentation experiments does not resolve among these options. At a later date, NMR techniques will be applied to further elucidate these metabolites. This work can be greatly accelerated by feeding forward the

Figure 3 – Drug discovery and development from the point of view of the chemical sample. Notice that the amount of sample changes drastically en route from in vitro testing through animal testing, clinical studies to commercial operations. Note also that the various analyses are repeated on different scales and with different objectives at multiple stages. In each such case, specific accelerators are possible when prior experimental results are invoked. For example, the metabolite identification studies conducted by Mass Spec in early preclinical development, lead to chemical structures are partially indeterminable. These data can be passed forward to the NMR scientists in support of clinical development by a database system that stores spectra AND Markush representations of chemical structure (such as ACD/SpectManager). These spectra are also good starting points for NMR and MS scientists in later development who are dealing with impurities from process chemistry, packaging and sample decomposition. In all of these cases, the spectra and structures generated in early drug discovery provide a knowledge base that feed forward to development processes. The challenge is that these are often different scientists in different parts (locations) of large companies, or – as is becoming more often the case – the work is done by different organizations in an outsourced development food chain.
CONCLUSIONS

In summary, it is possible to envision two ways to develop a product-focused drug discovery methodology:
1) parallelize the various aspects of drug discovery and development inasmuch as possible, 2) feed critical research data forward from discovery to development to accelerate downstream processes.

We are witnessing great progress in rationalizing ADMET with sophisticated modeling techniques, but only recently are we seeing rules of thumb appear that will guide the day to day thought processes of the medicinal chemist: these all point back to the classical physical organic molecular properties. Two favorable byproducts will be a simplification of the preformulation work, and streamlined separations research. As these take hold, we can expect that clinical candidates will improve greatly in their quality as potential products.

All of this depends on two critical factors: 1) software systems that support structured, efficient pooling of research knowledge, and 2) a mindset that drives towards product-focused drug discovery. All of the software systems described herein are in existence, and being used in many research teams worldwide, but few have yet grafted them into cultural mindset that maximizes the potential.

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ACD/Labs software includes calculation of pKa’s for organic drug-like compounds, and uses these to compute the pH profiles of LogD and Solubility
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