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Pharmaceutical Profiling Case Study in Disruption

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■ ORIGIN

Recent history has been disruptive for medicinal chemists. Despite these distractions, the imperative to discover drugs continues. Patients with one of 6000 rare diseases (e.g., sickle cell), neglected diseases affecting millions (e.g., schistosomiasis), or under-treated diseases (e.g., Alzheimer's) hold out their hands to medicinal chemists for hope. So, we persist, partly by considering that recent disruptions that seem extraordinary (e.g., new modalities, genetic targeting, outsourcing, layoffs, designers vs synthesizers, initiatives in government and nonprofit research) are, arguably, on the trajectory of past disruptions. Certainly, each disruption will persist or recede by the resulting efficiency improvement and patient benefit.

Here, we consider a disruption that began in the 1990s, the transfer to medicinal chemists of responsibility for pharmacokinetics (PK) and safety (tox). It added to the responsibility for novelty, efficacy, and selectivity. Chemists shouldered this responsibility because 50% of development failures were attributed to inadequate PK and tox.[1] A major hurdle, however, was that at the time, negligible PK and tox data were available to medicinal chemists. In response, the measurement of PK and tox indicators during discovery expanded and has been termed "pharmaceutical profiling" or "discovery ADME".

■ EVOLUTION

The first question was how to prevent candidates with poor PK or tox from progressing to development. "Kill fast and cheap" was an early solution during the boom of combinatorial chemistry and HTS, when candidates seemed unlimited. Chemical series with poor PK or tox were abandoned. Later, it was reasoned that good leads with target binding are precious, so the strategy evolved to "data-driven optimization" of PK and tox for active chemical series.

This generated a new question: how do we optimize PK and tox, which are complex phenomena resulting from many diverse interactions in living systems? A "mechanistic" solution emerged, in which underlying physicochemical (e.g., solubility, permeability) and biochemical (e.g., metabolic stability, transporters) interaction properties were used as indicators. Just as in vitro assays for binding supported structure−activity relationships (SAR), structure modification for efficacy optimization, and compound prioritization, pharmaceutical profiling implemented in vitro assays, SARs, structure modification, and compound prioritization for PK and tox optimization.

Subsequently, the pharmaceutical profiling disruption evolved into a multitier process, each tier providing increasing knowledge and complexity. On the first tier, molecular properties of structures are readily assessed by counting hydrogen bonds, molecular weight, and simple Log P and

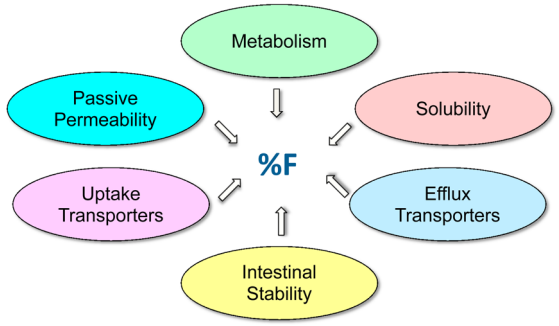

Figure 1. In vivo pharmacokinetic parameters result from multiple underlying physicochemical and biochemical interactions, any of which may require in vitro measurement and structure optimization. One example is bioavailability (% *F*).

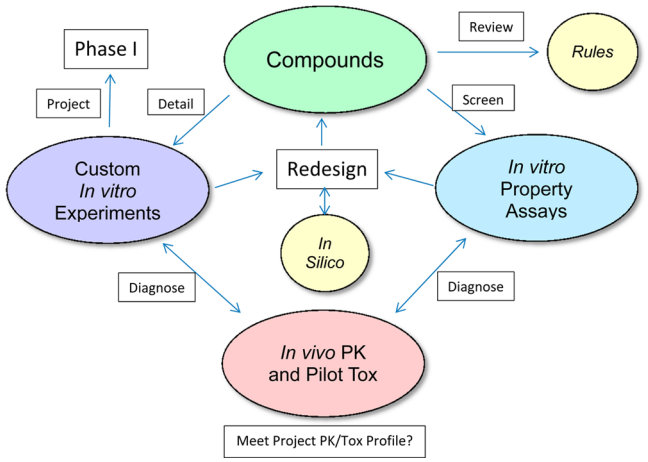

Figure 2. Process of PK and tox optimization during discovery.

TPSA calculations. Their correlation to PK and tox indicators was formalized by Lipinski, Lombardo, and colleagues[2] into the highly successful "Rule of 5". Other effective rule sets have also been described for indicators from bioavailability to toxicity.[3] *Rules* are very efficient for focusing effort on the most productive chemical space for PK and tox.

On tier 2, *in silico models* use structure or measured properties to predict higher level properties, such as solubility, metabolism, or blood−brain barrier permeation. They are useful for comparing various structures that might be synthesized, so that synthesis time can be spent on the most likely to succeed.

Next, *HT in vitro assays* measure key PK and tox properties. They are applied simultaneously with bioassays so that all of the

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data can be used in holistic structure redesign. Such assays use generic protocols, lab robots, and submilligrams of compound. Key properties are profiled, including microsomal stability (correlated to clearance[4]), passive diffusion permeability (correlated to intestinal absorption and cell assay permeability), and kinetic solubility (correlated to absorption and bioassay precipitation). The data support hit selection, structure redesign, bioassay optimization, and prioritization for advanced studies. In some enterprises, dedicated computational scientists develop and update in silico ADME models based on property data. HT assays have benefited from an influx of analytical technologies, such as lab robots, plate readers, and LC-MS-MS. However, technology only enhances speed, sensitivity, and precision. The most important part of an assay is incubation conditions, under which the compound interacts with physicochemical or biochemical models of living systems. Correlation to PK or tox observations in living system is the most important characteristic for reliable in vitro data that enables decisions.

Custom in vitro experiments provide enhanced detail and answer specific questions from discovery projects.[3] Often, these questions arise from inconsistent or unexplained observations. The specific experiment conditions are selected to address these questions, such as phase II metabolism, which transporter mediates permeability, or which analogue is more stable in plasma. Planning and interpreting such studies benefit from collaboration of experienced DMPK or pharmaceutics experts. The data answer important questions, guide redesign,[5] and enable human PK projection.[4]

In vivo studies examine a model species end point for PK or tox. Initial in vivo protocols screen PK and tox using generic dosing and fast analysis schemes for higher throughput. Later protocols offer enhanced specificity based on the biology of the project and planned human dosing route for increased understanding and human prediction.

In different enterprises, these tiers are organized in different ways, often distributed among DMPK, medicinal chemistry, and pharmaceutics departments. Nevertheless, no matter the organization, it is imperative that the functions work collaboratively to support each stage of drug discovery, help answer questions, and support medicinal chemists throughout candidate selection, optimization, and human projection.

INTEGRATION

Several factors have assisted the integration of the pharmaceutical profiling disruption into drug discovery. The first was *acceptance*. Initially, profiling was viewed as a threat to traditional benchmarks for medicinal chemists (e.g., patentable compounds with excellent target binding). There was concern that it would kill chemical series that had taken years to craft. A shift occurred as those benchmarks changed to clinical success of compounds, which required good PK and tox. Properties were more broadly applied as *case studies* appeared in chemical literature and projects succeeded.

Another integration factor was recognition that physicochemical properties can be responsible for *inadequate biological assessment*. Insoluble compounds precipitate and do not interact with the target in vitro or are not well absorbed in vivo. Chemically unstable compounds degrade. These all cause underestimation of intrinsic activity. Active compounds can be saved by solubility improvement.

Integration was also aided by demonstration that compounds with druglike properties have advantages.[3] The development failure rate owing to inadequate PK and tox has dropped dramatically. Development is faster and less expensive. Better discovery biology data are generated. Partnering opportunities for smaller enterprises are improved as big pharma companies review clinical candidates with quality PK and tox. Patient compliance is higher with less burdensome dosing regimens for drugs that have lower clearance, better absorption, and longer half-lives.

Many large companies have implemented sophisticated profiling functions. However, considerable medicinal chemistry is done by companies and academic groups with fewer resources and lower PK and tox expertise. The leads from these groups might have inadequate PK or tox if not addressed during research. Smaller enterprises can make the most of less expensive tools: use the rule sets to keep compounds focused in productive chemical space; calculate molecular properties of compounds inexpensively using ChemDraw or Web sites; use less expensive in vitro assays (e.g., kinetic solubility, microsomal stability); assess permeability using lipophilicity ($0 < \text{Log D} < 3$) and TPSA (<140 Å^2); and select an example compound for in vitro assays or simple PK study by a CRO. Efficient use of resources to discover holistically improved compounds improves chances for finding an interested partner.

STRATEGIES

Several key strategies improve success with candidate optimization.[3] Obtain in vivo PK and tox data on a key series example to check if it meets the desired profile. If not, break the complex in vivo processes into its component properties using in vitro tests to identify the liabilities. Apply structure modification (e.g., H-bonding, lipophilicity, TPSA, pK_a, MW, electron withdrawal, steric hindrance, shape, reactivity, and MW) for redesign and test the new compound for improved performance.[3,5] Balance properties, activity, and selectivity to obtain the best overall candidate. Improve bioassay conditions for solubility and chemical stability. Use formulation to solubilize compounds for dosing.

FUTURE PROSPECTS

The success of the pharmaceutical profiling disruption continues to encourage new innovations, which are occurring now:

- Practical understanding of the many properties that affect a desired in vivo end point, such as brain target exposure,[6] give medicinal chemists guidance for systematically optimizing leads.
- Free drug concentration in the therapeutic target biophase is driving in vivo efficacy optimization (rather than free fraction or serum shift).[7]
- Multiparameter schemes are impacting optimization and selection.[8]
- Innovative in vitro assays provide increased detail to predict human PK, such as the clearance of highly stable compounds.[9]
- New assays for toxicity indicators enhance safety.
- Outsourcing of high-throughput assays increases, freeing scientists for high-impact custom experiments to answer project questions.
- Software continues to improve for predicting PK or tox, to assist medicinal chemists with structure optimization and to plan human clinical studies.

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- Improved understanding of transporters revolutionizes compound optimization, increases target delivery, and enhances tissue targeting.
- Underlying properties affecting PK and tox of new drug modalities (e.g., proteins, peptides, antibodies, and RNA) are being characterized and assays developed to support PK optimization.
- Pilot toxicity studies in discovery are common and enable tox optimization during discovery.

CONCLUSION

Instead of author-based conclusions, every medicinal chemist is encouraged to personally evaluate whether the pharmaceutical profiling disruption has improved efficiency and benefited patients. This will also help us apply lessons learned to current and future disruptions.

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