

Lean and mean – Accelerating drug discovery

Source: www.ngpharma.com
© 2010 Grace Davison Discovery Sciences. All rights reserved.

The challenges confronting today's pharmaceutical industry are no secret. With fewer blockbusters to fund ongoing research, and more drugs preparing to come off patent, pharmaceutical companies must find new ways to work efficiently and bring new therapies to market more quickly.

One of the largest costs in pharmaceutical research is the cost of failure - if a project is going to fail, it is better that it fails early. This is driving R&D organizations to devote more resources to the early drug discovery phase to answer as many questions as possible about a target compound, as early as possible in the overall process.

The problem with asking more of the early discovery process is that it is a slow iterative phase, involving various stages of synthesis, selection, and testing of target molecules. Six Sigma-style approaches, such as process maps and LEAN analyses, are proving very useful to identify and eliminate bottlenecks that waste time and money, and slow compound submission.

One of the most recognized and challenging bottlenecks in drug discovery is purification of synthesized compounds. A target compound's successful progression from hit to viable drug candidate hinges on compound purity to successfully navigate structure-based biological activity with minimal rework. Also, during lead optimization, compound properties such as affinity, solubility, permeability, clearance, and safety are adversely impacted by insufficient purity of the target compound. Finally, requirements for higher levels of purity are continuing to raise the bar on purification processes.

Although many chromatographic techniques are applicable for routine purification in drug discovery, flash chromatography has been the primary tool to purify synthesized compounds. However, purification by flash chromatography is plagued with potential delays due to the inability of typical flash systems to deliver accurate concentrations and identify all contaminants, leading to questionable sample characterization and purity. Impure samples in turn cause delays through:

- Misleading or confusing results from bioactivity analyses
- Continuing or discontinuing an optimization unjustifiably
- Significant time wasted in re-work

Advancements in flash technology - such as improving compound purity, obtaining more information earlier in the process, and eliminating "guesswork" steps - are critical to reducing the iterative nature of drug discovery, and efficiently moving target compounds through the discovery and development process.

The bottleneck of synthesizing, purifying, and assaying only to re-do it all due to inadequate characterization of the sample can be improved. Grace Davison Discovery Sciences is using the advanced technologies available for HPLC (high performance liquid chromatography) to modernize flash chromatography.

A Step-Change in Flash Purifications

For decades, flash chromatography has been the primary tool to purify synthesized compounds in the early stages of drug discovery. Flash chromatography is perceived as a fast, inexpensive, and less complicated alternative to Preparative LC.

Current flash technology falls short, however, because today's flash systems can only detect compounds visible by UV wavelength, leaving undetected impurities in the sample and giving incomplete information about relative quantities. These inadequacies lead to time wasted in "shotgun" fraction collection and post-run analysis, inaccurate purity assessments, and can generate falsely positive results on the biological activity of the compound. This can slow compound progression through the entire drug development pipeline.

Fully addressing the problem requires a holistic view of the purification process to consider not only the separation, but also the upstream and downstream consequences. The fundamental problem is one of good chromatography - to fully characterize a sample one must achieve a good separation and take advantage of universal detection. The Reveleris™ Flash Chromatography System (patents pending) is the first flash system to overcome the limitations of traditional UV-based purifications by integrating the advanced benefits of ELS (evaporative light scattering) detection for identification of a broader range of compounds with more accurate quantitative information.

It is not as easy as connecting an extra detector, however. The Reveleris™ system with RevealX™ detection technology (multiple patents pending) uses a split fluidics design, multiple channel detection, and advanced signal processing to synchronize all detector signals to collect a single set of fractions of accurate identity and quantity. This is an unprecedented time-saving step for flash purifications, allowing chemists to get more information about their sample in a single step with no complicated equipment or post-run analysis.

When combined with the advanced separating power of Reveleris™ Flash Cartridges, the only flash cartridges designed and packed by a world-leading chromatography expert, the Reveleris™ Flash System allows chemists to work smarter:

- Fully characterize a sample – target and contaminants
- Collect only the necessary fractions, without tedious post-analysis by HPLC or TLC
- Obtain accurate purity and quantity assessments to reduce the chance of unpleasant surprises during bioactivity testing
- Submit only the most promising drug candidates for further testing

Breaking the Status Quo

Often, chemists believe their compounds are pure enough, yet the industry continues to be plagued with inconclusive testing concerns tied to purity. In bioassay testing, the questionable results that cause so much confusion in SAR refinement are often caused by inaccurate concentrations, interfering contaminants, and inadequate dissolution for bioscreening, all of which are tied to the purification process.

Until now, medicinal chemists had to rely on the incomplete information provided by UV detection, not knowing if interfering contaminants were present. The Reveleris™ flash chromatography system was designed specifically to resolve these critical concerns. Chemists can now quickly sort through potential drug compounds earlier in the discovery process, so they and their downstream colleagues can spend their time on only the most promising drug candidates, resulting in an overall acceleration of the drug discovery and development pipeline.