

# Neurocrine Biosciences: Enriching Drug Discovery Pipelines Through a Revised, Automated Process

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Neurocrine Biosciences focuses on treatments for neurologic, psychiatric and endocrine related disorders, and is firmly committed to making a difference in people's lives. In fact, this resolve is so strong, that they share valuable insights to move the entire industry forward. When the San Diego-based company suffered a setback in 2007, they remained tenacious as they took a hard look at their approach to drug discovery.

In the Chemistry group, manual chemical storage was burdensome in that users would look up a chemical in a database of 100,000 containers or more, find the grid where it was stored, search all the containers in that grid to find the right one, log how much material was used, then replace the container back

in the grid. Containers that were mislabeled, mishandled, or misplaced in the manual process meant lost productivity and replacement costs for the Company, and the lack of standardized container sizes added to the complexity. It's estimated that the Chemistry group spent 40 – 60 labor-intensive hours per month on manual chemical inventory alone.

At the same time, compound synthesis workflows were limited by the number of reagents that could be gathered and prepared for use

on a liquid handler at one time. Large numbers of compounds were created from the chemicals, but the combinatorial chemistry approach to compound creation wasn't project-specific, therefore, the time and labor needed to characterize one potent compound from among the hundreds of thousands created was extensive. In fact, with the average medicinal chemist making anywhere from 100 to 1,000 compounds per year, each new compound could cost between \$1,000 to \$3,000 each, based on the

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industry full-time employee (FTE) cost of approximately \$300,000.

At that time, Derrick Miyao, a Medicinal Chemist at Neurocrine, started to rethink ways to improve efficiency in the small molecule compound synthesis processes. “The ‘finding a needle in a haystack’ approach just didn’t work,” he recalled. “Drug discovery isn’t driven by luck, it’s accomplished by creating methods to increase efficiencies and the likelihood of success.” The change he developed for Neurocrine’s chemistry lab took 10 years from proof of concept through to full integration and Mr. Miyao expects the investment to positively impact his company’s success.

A major component of the process change included adapting workflows to automated methods. Each iteration along the way used different robots to ramp up throughput, speed, or efficiencies; and automated solutions from Hamilton Storage and Hamilton Robotics were utilized towards the final process changes. These automated sample storage and liquid handling robots also allowed Mr. Miyao’s improved chemistry workflow to be fully integrated and driven from Neurocrine’s internal laboratory information management system (LIMS).



Chemical storage containers were standardized using three vial sizes, which were then easily stored in the Verso® automated sample storage system. In addition to complete control over environmental conditions to protect sample integrity and ability to store and cherry-pick multiple sample types with different diameters, Verso provides full traceability so that samples can be quickly and accurately accessed by authorized personnel only, without the time and risk associated with manual methods.

With Verso fully integrated, the chemistry group reduced time spent on chemical inventory from 40 – 60 hours per month, to roughly two

hours per month, for an estimated FTE savings of \$130,000 per year. “More important than the cost savings, we can better allocate our time to focus on more valuable work like designing new drugs, instead of scanning sample barcodes,” Mr. Miyao commented. He notes that Verso is used to store both reagents and final chemical compounds, and picks an average of 100 – 300 containers per day.

Mr. Miyao notes that the Microlab® VANTAGE Liquid Handling System is used for about 70 – 80% of the in-house chemistry, and can synthesize up to 9,000 new project-specific compounds per day, including weekends. The system generates a report of chemicals that were used and updates Neurocrine’s in-house database in real-time with an accurate volume of material remaining to keep the chemistry lab informed and working efficiently. Microlab VANTAGE combines precision, hands-free pipetting along with multi-

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device integration on one platform for robust and highly efficient workflows. In addition to full process control and tracking, Microlab VANTAGE uses a simple, drag-and-drop graphical editor for assay programming, and can run multiple processes in parallel to further enhance assay flexibility and overall laboratory efficiency.

In addition to capturing data on compounds eliciting positive outcomes, the Chemistry group now captures data on reactants that don't work, which will further improve productivity by excluding those reagents from future similar screens. Commercial library compounds are no longer purchased from third parties for their screening platform; instead, internal library compounds are made to increase process efficiency. The group also makes new analogues within hours instead of weeks on the Microlab VANTAGE, which advances compounds at a much faster rate than traditional screening and follow-up methods.

Using the new and fully automated process, Mr. Miyao estimates that he synthesized 15,000 new chemicals for the compound library within five weeks, and created 10,000 project-specific compounds in three weeks.

Of those compounds, several yielded meaningful results that merit further exploration. "These new compounds were identified so quickly because we made them all at once rather than making a few at a time," he maintains. "This alone proves the value of the integrated Verso and Microlab VANTAGE well beyond their price tag."

The increase in efficiency is obvious within the chemistry group. The group's twelve medicinal chemists can now output 2 – 3 times more work than when the group consisted of seventy chemists before the downsizing in 2007.

The true power of the Microlab VANTAGE/Verso integration is in the software. Running the automated system doesn't require robotics expertise, and users can run the new process within one day, compared to the previous, complex processes which took six months to one year to learn. Hamilton and Neurocrine collaborated to build methods that take instructions from Neurocrine's internal database to drive the system. By linking Neurocrine's database to the integrated platform,

it created an open system for all medicinal chemists at Neurocrine to run it without any knowledge of the automation. This also allows the chemists to apply their knowledge and expertise towards interpreting results rather than manually performing the processes.

Even with the extensive enhancements, Neurocrine plans to further expand the capacity of the modular Verso, and also add a second Microlab VANTAGE to the system in the near future. Additionally, the biology group is doubling their capacity and reworking their own assay processes to keep pace with the increased chemistry output and ensure a smooth flow of data generation.

The fully automated process, including Hamilton solutions, will allow projects to be completed at a faster rate than traditional drug discovery methods, such as in one month compared to a year or more. On top of that, Mr. Miyao anticipates a return on investment (ROI) of just over one month, or approximately 65,000 compounds synthesized, for integrating Verso and Microlab VANTAGE into the process. The Company now expects to quickly achieve a rich product pipeline, and in fact, with four drugs expected to be commercialized in the next four years, Neurocrine is poised for unprecedented growth.

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