

intelligent management: moving compounds seamlessly

introduction

As the search for new and better drugs intensifies, there is an increasing need for larger libraries of diverse and high-quality compounds. However, there is mounting pressure to reduce costs while still retaining integrity and efficiency which creates a challenging and complex task for compound management.

A 2015 survey of compound and sample management professionals(1) reported that the top three requirements for a successful compound management system included:

1. accessibility (51%)
2. the ability to maintain a dynamic collection (50%)
3. compound integrity (44%)

Compound management groups need to consider flexible and expandable automated management systems, alongside meticulous monitoring of sample integrity, in order to meet these increasing needs. The survey also found that, although companies are focused on leaner solutions, 72% of participants were still planning to invest in compound management in the next year; and 33% of these predicted an investment of greater than €500,000(1).

This application note presents an example of how the TTP Labtech (Melbourn, UK) automated solution has optimised the workflow of Dart NeuroScience LLC (DNS; San Diego, CA), allowing compounds to move seamlessly through the production process and all the way into the assay plate. The marriage of software and hardware has been crucial to the success of this project.

DNS is one of the leading pharmaceutical companies focusing on the discovery and development of innovative drugs for memory disorders. The mechanisms of these new drugs are based on the genetics of synaptic connections in the brain which form memory. High-throughput screens are carried out to identify compounds that enhance or inhibit the biochemical activity of these target genes – thereby yielding memory enhancers.

improving the 'flow' in workflow

DNS made the strategic decision to protect its own IP by creating more drug compounds in house. It was expected that the compound management group would grow the size of their compound collection to 1 million. They also planned to distribute more than 100,000 compounds per year. To provide the optimal environment for this growth, DNS had a number of requirements that needed to be met:

- **an automated workflow** assuring compound integrity and protecting the overall investment
- **modular storage units** that would support long-term company growth
- **high speed and throughput**
- **low cost** in line with company budgets
- **trust and support** in vendors to successfully plan and install a complete system

A review of the current working system revealed opportunities to improve production, reduce time and save money by automating and streamlining current processes.

In order to improve the compound management workflow, DNS embraced novel and robust automated technologies from TTP Labtech in the areas of:

1. compound storage
2. compound retrieval and processing
3. creation of assay-ready plates

1. automated, high density storage

Automated compound storage ensures a safe and secure environment for samples and enables them to be retrieved whenever needed. As part of DNS's decision to create more compounds in house, a high-density and modular system was required that could store large numbers of samples. DNS chose innovative and proven pneumatic technology provided by TTP Labtech's comPOUND[®] system. The barcoded

key benefits

DNS's compound workflow was improved, saving time and cost by:

- **reducing manual labour time**
- **eradicating human error**
- **increasing throughput by parallel processing**
- **reducing reagent costs through miniaturisation**
- **automation ensures all samples are treated consistently, improving sample integrity and data quality**

samples are stored in tubes under nitrogen in a hermetically-sealed chamber at -20°C to ensure sample integrity, and can be cherry-picked and retrieved at a rate of 600 tubes/hour/unit for easy accessibility. As DNS has grown, it has invested in additional modular units to house the increasing number of compounds, spreading the cost over time.

results

Currently, DNS possess 6 comPOUND freezers that have the capacity to store and provide easy access to 1.2 million compounds with minimal hands-on time. Linking stores has also increased throughput as samples held in several freezers are simultaneously retrieved into one 96-well format rack.

“““

We have invested heavily in creating our own compounds and IP in house and we needed an optimal workflow solution that would protect this investment. TTP Labtech provided this solution!

Jose Quiroz, Associate Director at DNS

2. significant reduction in hands-on time by automating tube processing

Initially tube processing consisted of manually retrieving the rack of tubes from store, removing the caps, aspirating the required volume, recapping tubes and finally returning them to the store. Unless there were multiple personnel the process was sequential, which was both time consuming and prone to operator errors. “We needed to improve the ‘flow’ in workflow,” stated Quiroz. Reducing the time taken to process tubes would increase sample integrity, but doing so might pose informatics challenges that would need to be addressed.

DNS decided to integrate its comPOUND stores using TTP Labtech’s comPILER sample processing system to provide automated retrieval and storage of compounds and increase operational efficiency. Now, scientists at DNS submit a

list of hits to the compound management group using their proprietary sample request software. The tubes are retrieved from the comPOUND stores and automatically sent to the thawing tunnel of the comPILER. The tubes are then briefly centrifuged before removal of the caps. The open tubes are immediately gassed with argon and then the required volume of sample is aliquoted into a new barcoded tube or plate using a Freedom EVO® liquid handler (Tecan Group Ltd., Switzerland). Information regarding the change in stock contents and location, and the generation of new tubes or plates, is reported to the informatics system to reliably track the compounds. The stock tubes are returned from the liquid handler back to the comPILER, gassed with argon again and sent to the capper before being returned to the comPOUND storage freezers (Fig 1). This fully automated retrieval and storage system allows for minimal human intervention and fully traceable sample movements.

results

DNS is now able to process 30,000 tubes per day with a reduced tube pick-time from 45 minutes down to 5 minutes per 96-well plate and a saving of 1.5 FTEs (Table 1). By improving order processing, automated liquid handling and sample tracking, DNS can now process multiple requests in one run. This increases the efficiency of the process without compromising sample integrity.



Having a modular system like TTP Labtech’s comPOUND allows you to distribute the units across your lab or building – without the need to build your lab around the storage units

Jose Quiroz, Associate Director at DNS

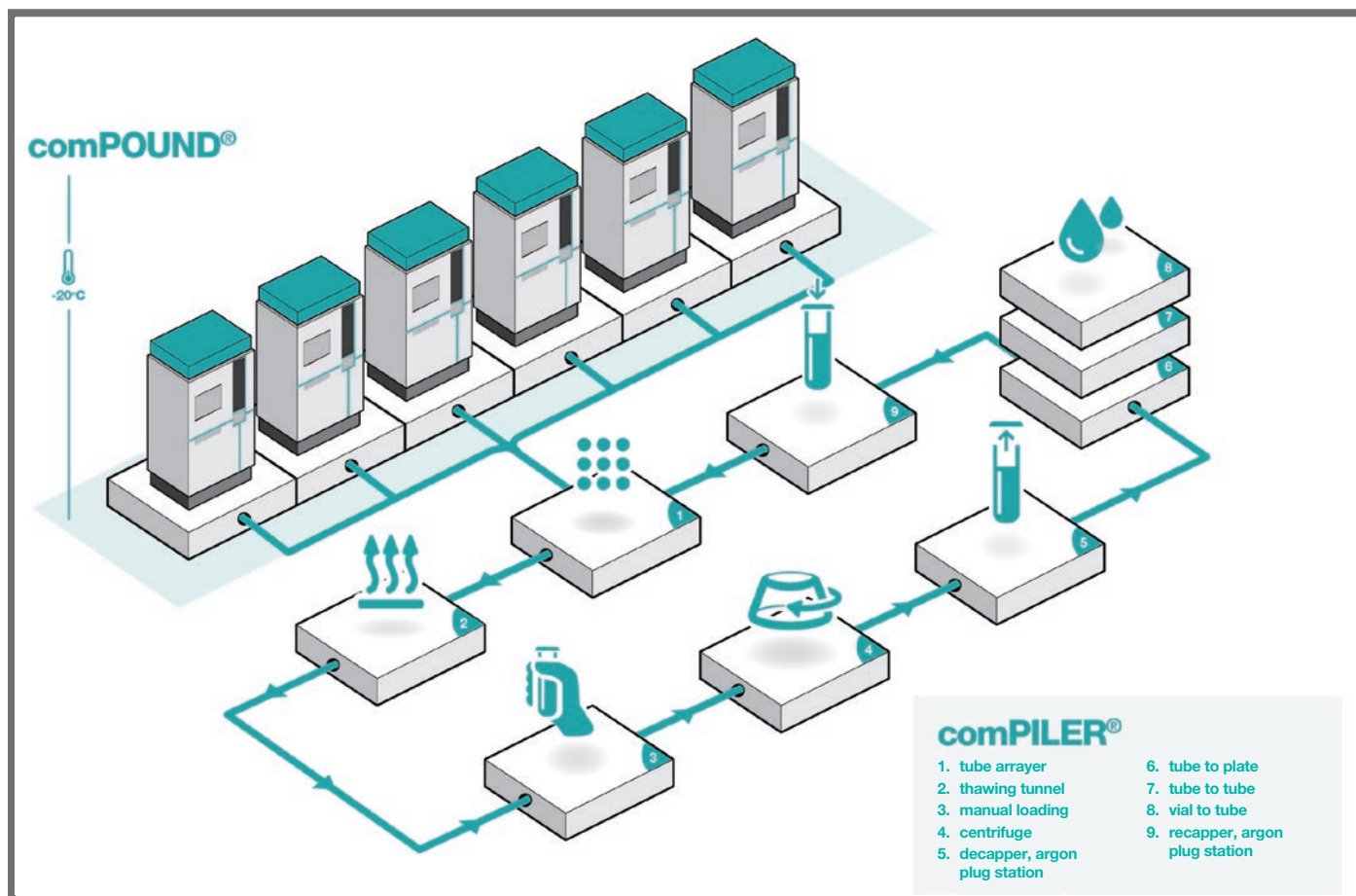


Fig 1. A schematic illustrating the use of TTP Labtech’s comPOUND, comPILER and liquid handlers in DNS’s automated tube storage and processing system.

Table 1. Optimised tube processing model

identified issue	old	new	reduction (%)
time to process 96-well plate (mins)	45	5	89
integrated system	no	yes	100
compound accessibility	slow and laborious	rapid and efficient	-
compound integrity compromised	yes	no	-

3. creation of assay-ready plates

After ultra high-throughput screening of 500,000 compounds, the average hit rate is usually about 1% (5,000 compounds). These compounds are then cherry-picked from numerous plates to be processed for further screening using serial dilutions. This normally leads to approximately 100–500 potential drug candidates stored as solid samples.

At DNS, focused libraries of 5–10K compounds are screened with hit rates of 10–20%. Previously the hit-picking

process was slow, had limited capabilities and utilised several personnel also needed in other areas. As a result, the compound integrity was compromised and a bottleneck was created in the overall workflow.

To overcome these challenges, DNS adopted a novel plate storage and processing system that consists of a plate carousel, a robotic arm, TTP Labtech's mosquito[®]X1 with a single disposable tip for plate hit-picking, and a standard TTP Labtech mosquito[®] HTS for the serial dilution of the compounds (Fig 2). This whole process is automated.

results

DNS reported the total picking time for a 5,000 hit-picking campaign was reduced by 80%, from 5 days to 1 day, and the total personnel time required was reduced by 88%, from 8 FTE hours to 1 FTE hour (Table 2). In the process of improving hit-picking, under-utilised equipment was repurposed and new capabilities were achieved, including assay miniaturisation to nanolitre volumes in 1536-well plates.

mosquito X1

cherry picking of 5000 compound hits in 1 day



plate carousel and robotic arm

mosquito HTS

automated serial dilution of the compound hits

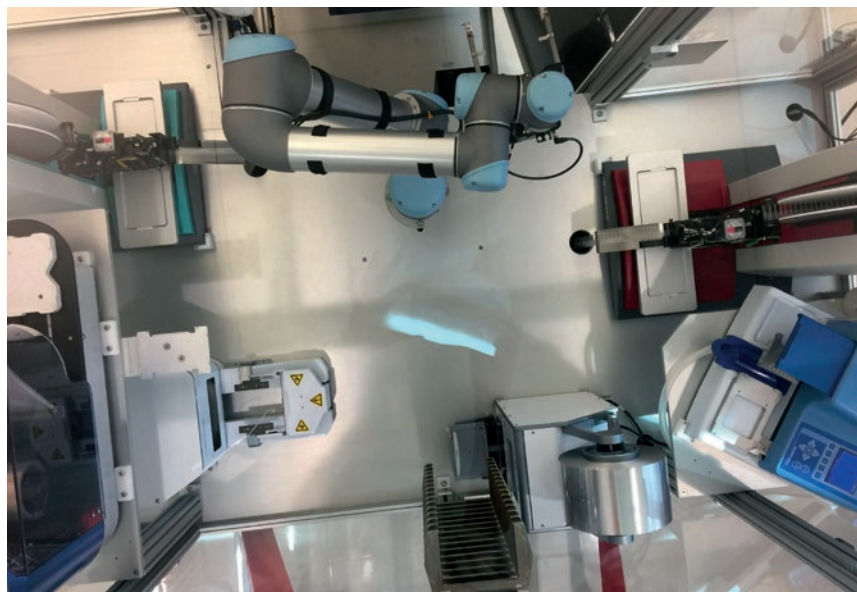


Fig 2. Optimised hit-picking and assay-plate creation: a robotic arm moves plates from the carousel plate store (centre) to the mosquito X1 (right) where individual hits can be rapidly picked from anywhere in the plate. From here the hit compounds can be transferred to the mosquito HTS (left) to set-up a dilution series.

Table 2. Optimised hit-picking model

identified issue	old	new	reduction (%)
time (days)	5	1	80
shared resources	yes	no	100
FTE time (hours)	8	1	88
integrated system	no	yes	100
compound integrity compromised	yes	no	-



There are three main reasons as to why we chose TTP Labtech as our preferred vendor: 1) The products – they had the products that did exactly what we needed them to do; 2) cost – because comPOUND is a modular system the upfront cost is reduced, but we still have the capability to expand; 3) the people – we have great trust in TTP Labtech, they have always been there when we have needed them and the service engineers go an extra mile to help customers anytime

Jose Quiroz, Associate Director at DNS

evaluate and evolve

The marriage of DNS's software with TTP Labtech's hardware resulted in a flexible and successful workflow that fulfilled all of DNS's current requirements. The modularity of the system gives scalability to support the future growth of the company.

TTP Labtech's automated solutions have improved DNS's capabilities and created faster automated hit-picking in 384- or 1536-well plates. Automating tube processing and the generation of serial dilution plates now allows the dynamic creation of small screening decks. The comPILER also provides an inert environment for sample processing at room temperature, minimising water uptake (freeze-thaw cycles in the presence

of water have been shown to reduce the solubility of compounds in DMSO and increase degradation [2]). In addition, the compound management team at DNS can now track all tube usage and plate-well creation.

references

1. Survey: Trends in Compound and Sample Management 2015. Next generation compound management - where do we go from here? PharmaIQ (division of IQPC) <http://www.compoundmanager.com/FormDownloadThankYou.aspx?target=http://www.compoundmanager.com/media/1000298/38178.pdf&eventid=1000298&m=38178>
2. Oldenburg, K et al. High throughput sonication: Evaluation for compound solubilization. Comb. Chem. & High Throughput Screen. Vol 8 (6) (2005): 499-512

designed
for discovery



discover@ttplabtech.com

www.ttplabtech.com