Compound Hub: Efficiency Gains Through Innovative Sample Management Processes

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Abstract: While significant investments are made across the industry and increasingly also in academia to enhance or build a compound file, the efficient sourcing of compounds from in-house medical chemistry is frequently seen as a challenge. This article introduces the Compound Hub strategy developed at the Novartis Compound Archive. Central Compound Hubs in Basel and Cambridge were combined with web-based ordering of compounds and assays, providing assay-ready, solubilized samples to labs anywhere in the global research organization. Relieving scientists from time-intensive sample preparation tasks, error rates could be reduced through electronic processing and tracking of compounds/assays and the capture of medicinal chemistry compounds for the compound library could be increased by 75%.

Keywords: Compound management, compound Hub, compound sourcing, ordering software, high throughput screening.

INTRODUCTION

High throughput screening has established itself as an effective process to discover lead compounds in drug discovery. The size and diversity of the screening deck is a critical success factor and remains a topic of intense debate [1-3]. A major responsibility for the compound management group of the Novartis Institutes for BioMedical Research (NIBR) is therefore to continuously enhance the compound collection [4]. With significant investment, an enhancement program had been started that expanded the Novartis collection with commercially available compounds [5]. In parallel, we thought about ways to increase the capture of in-house compounds for the compound collection. The cost of a medicinal chemistry compound has been estimated to be up to $7500 US [6]. However, collecting these compounds is frequently challenging, since for the individual chemist the high-level goal of improving the compound collection competes with more direct pressures of an ongoing lead optimization program. The Compound Hub strategy is an attempt to resolve this conflict: scientists are offered a service that relieves them from sample handling tasks. At the same time, central sample preparation is less wasteful and preserves material for the compound collection. In this article, we are outlining the Compound Hub strategy that was developed to address these issues.

THE PAST

Internally synthesized compounds are an important source for the growth of the NIBR compound collection. In general, these compounds have been sent to the compound archive after termination of the research program, or remained in the laboratory until the retirement of the chemist. Only ~ 50% of compounds were captured for the compound collection. In our analysis, there were three main reasons for this situation: (1) no short term benefit to submitting the compounds; (2) a perceived loss of control over the compounds; (3) multiple weighing and solubilization steps consumed large amounts so that no material was left for the collection. Distribution of compounds from the lab to different destinations bears other disadvantages as well. We estimated that only approximately 10% of the stock solution is actually consumed in the biology labs. The quality of stock solutions varies as a result of different balances and non-standardized storage conditions. Inefficient shipment logistics and a lack of tracking moreover led to delayed or lost compounds.

THE COMPOUND HUB STRATEGY

A strategy to capture more compounds for the compound collection had to address these three issues. Our reasoning was that we could convince our chemists to submit their compounds if we offered them an attractive service that relieved them of the considerable workload of sample logistics, thus creating a direct benefit. A blocking functionality would enable a chemist to reserve a compound for his own use for a specified period of time. Centralized weighing and solution production for biological tests would avoid multiple weighing and dissolution steps in biology and chemistry labs and would help to reduce compound wastage. Centralization of processing steps would also raise solution quality by standardization.

Based on these considerations, a process was developed. After synthesis in the lab, the compound is placed into an access controlled refrigerator within the Chemistry buildings and is transported to the Compound Hub overnight. For transport, the chemist can choose between either glass or plastic vials, which are pre-tared and bar-coded. At the Compound Hub, the required amount is weighed out according to the desired tests chosen upon submission. Any surplus material is then stored in the Main Compound Store and can be ordered by any researcher of Novartis after expiration of the blocking period (Fig. **1**).

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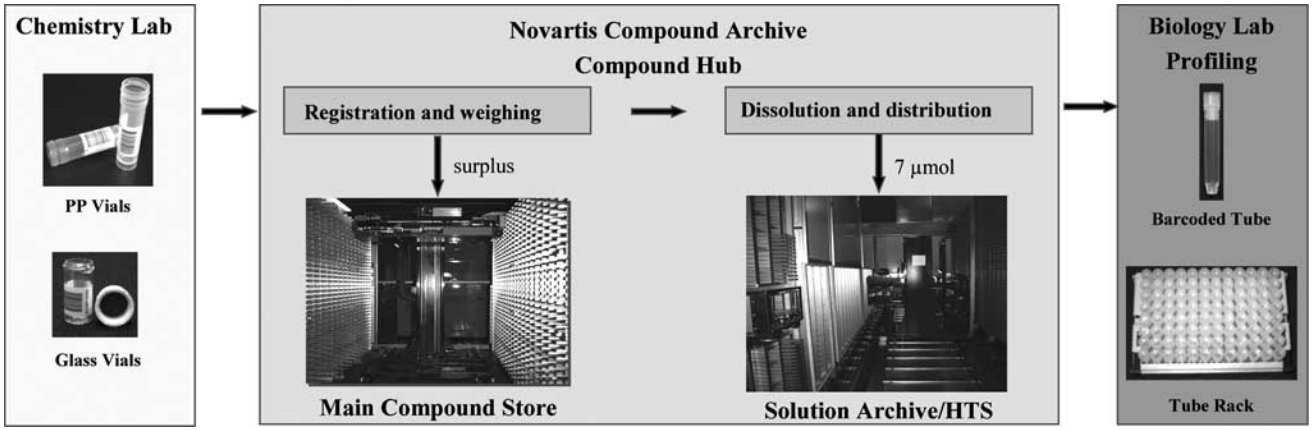

Fig. (1). The Compound Hub process.

A 10 mM DMSO solution is prepared and transferred to bar-coded tubes. On the following night, 36h after submission of the compound, these tubes and tube racks are distributed to the various biology buildings. A 7 µmol sample of the compound is integrated into the plating process that creates source plates for the solution archives feeding HTS. The time from synthesis to HTS can be reduced from up to two years to around 3 months.

THE TEST REQUEST TOOL

Prior to the Compound Hub project, scientists had to send printed substance cards and compound samples by internal mail, and had to use e-mail to clarify questions on routine compound tests. A web-based Test Request Tool was developed that facilitates the request of any assay or compound, regardless of its global location. No more printed information has to be passed on to different labs, since the global user interface of the Test Request Tool provides the chemist and biologist with all required information.

Upon submission of compounds, the chemist chooses the assays for the individual compounds within the web based software of the Test Request Tool. Along with the requested assays, the chemist provides additional information on the research program he is working in and the discovery phase of the compounds (Fig. **2**).

The chemist can also define a user group who should be informed of this request to enable team communication. An automatic validation step compares the compound identifiers with the compound database to spot mistyping and unknown identifiers before submission of the request. In addition, the molecular mass of the compound is retrieved from the database and the amount needed to produce enough solution to fill the request is calculated for each compound. Once a compound is submitted to the archive, it can easily be reordered *via* the Test Request Tool for additional tests.

The Test Request Tool also assists biology labs in planning their work. Scanning the barcode of a tube, the request information can be retrieved. In addition, a work list of all requested assays can be created (Fig. **3**).

GLOBAL IT INTEGRATION AND DATA FLOW

To set up a request, a number of data need to be retrieved from different tables of the Novartis databases. Fig. **4** shows a schematic view of the data flow.

On submission of a request, two different databases, namely the TRT database and the Global Ordering System (GOS), store all request relevant details. These databases interface a number of other core databases containing all compound-relevant data, research program codes, personal data, etc. The TRT database extracts the required informa-

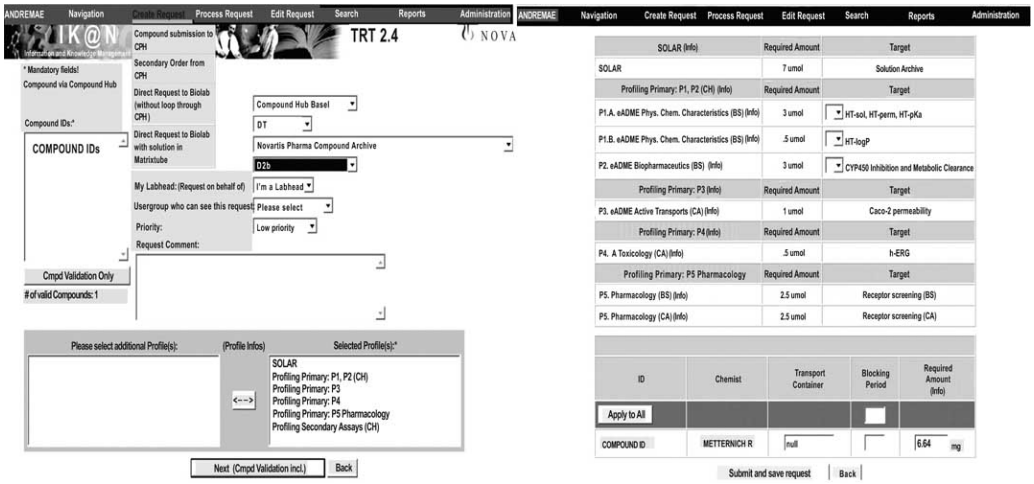

Fig. (2). Assay selection *via* Global User Interface - Test Request Tool.

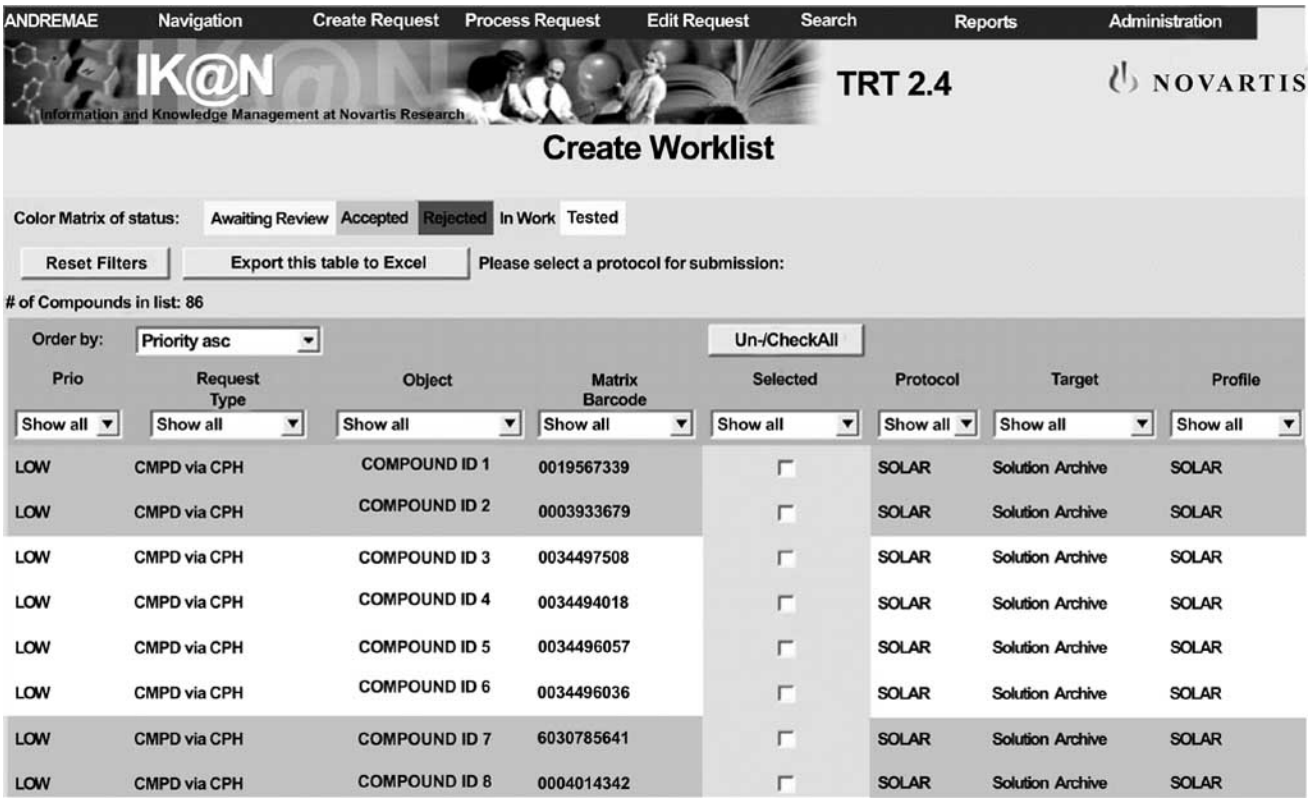

Fig. (3). Work list creation in BioLab.

tion, user information and the assay definition from these core databases. The GOS withdraws data on the compound identifier, the available quantity and the physical storage location of the individual compound. These data are then used to process a request in the Compound Hub. After the production, the tube identifiers are fed back to the TRT database and can be retrieved by the biologist for compound check-in and work list creation.

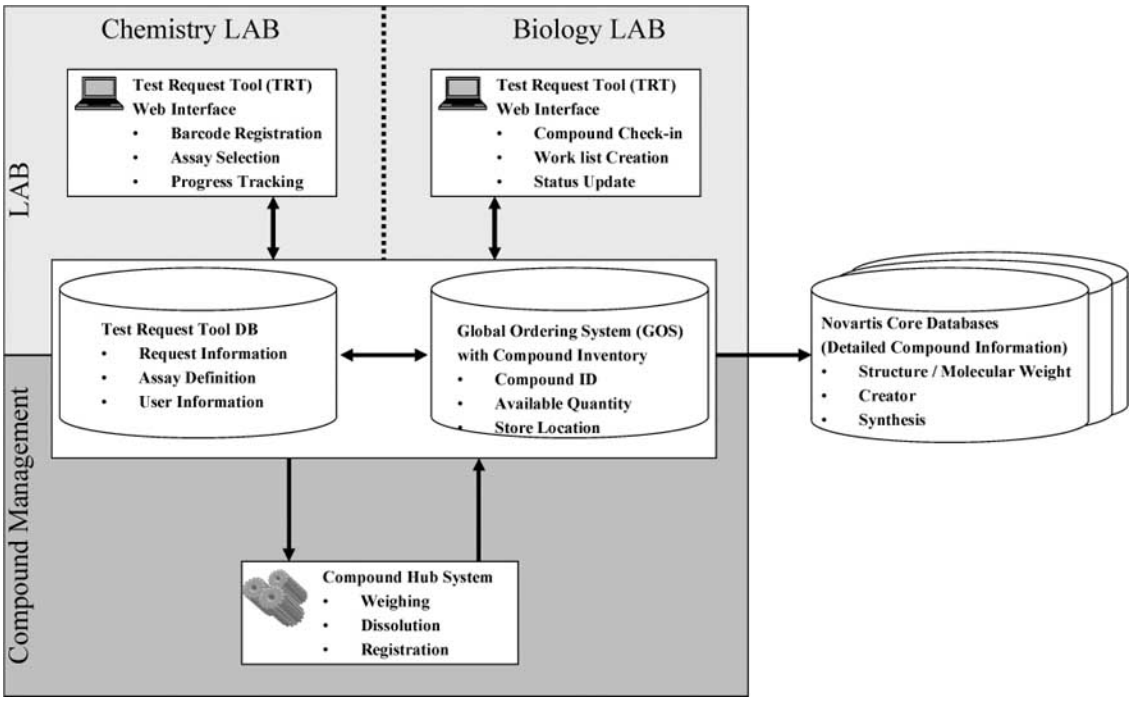

Fig. (4). Global IT integration and data flow.

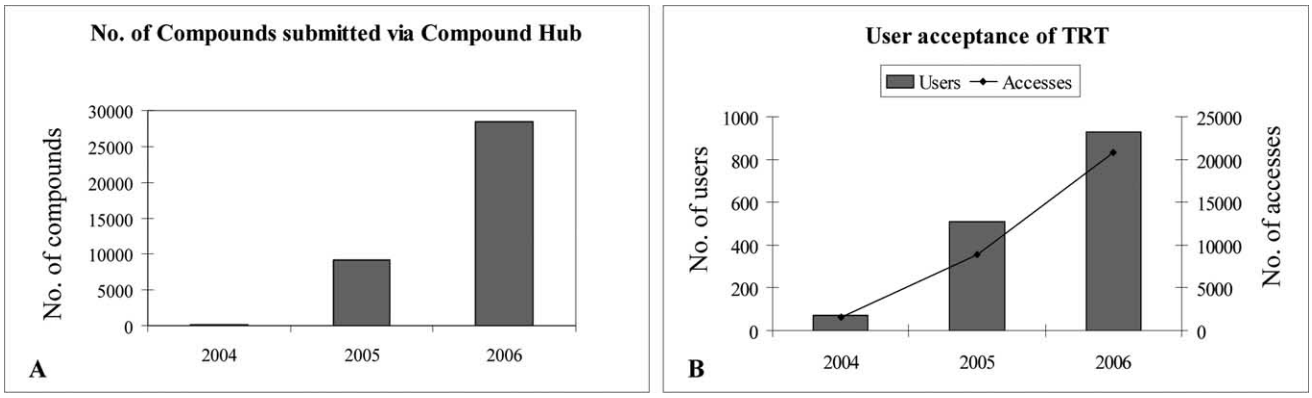

Fig. (5). A) Number of compounds submitted to the Compound Hub. **B**) User acceptance of TRT.

THE WAY TO SUCCESS

To implement this service, we started with a small test community consisting of one chemistry and one biology group. During this pilot phase, a number of improvements were identified. This early prototype testing proved to be essential for the later acceptance of the system. It was also important, however, not to over-customize the process. To achieve a high quality of service and guarantee turnaround times, a certain degree of standardization needed to be maintained. For example, a request to directly produce assay ready plates seemed to exceed the scope of the Compound Hub. Different plate layouts and types as requested would sacrifice not only the speed of the production but would also make transport of the plates more difficult. Other suggestions could be implemented. Initially the delivery vial was a plastic tube that was used for the dissolution step in the automated pipettor. The addition of a glass vial as transport container offered the option to evaporate different solvents without contamination before submitting to the Compound Hub. By carefully balancing between customization and standardization, the Compound Hub process was adapted to customer needs without sacrificing performance and reliability.

THE IMPACT OF THE COMPOUND HUB

Rolled-out globally during 2005, the Test Request Tool and the Compound Hub have led to significant efficiency enhancements for NIBR labs. Since then, the number of compounds processed by the Compound Hub has constantly increased. With almost 900 users and 20,000 web-accesses in 2006, the Test Request Tool has rapidly developed into the third-most frequented IT application in research (Fig. **5**).

The number of compounds delivered to the archive constantly increased after the start of the CPH. Fig. **6** compares the number of compounds registered in the chemistry lab to the number of compounds delivered to the archive. Two approaches were chosen to respect the different amounts available and therefore consider the different tendencies to submit them to the archive.

Only ~40% of all compounds synthesized and less than 50% of the compounds available in quantities of greater than 30 µmol were sent to the archive in 2003 and 2004. In the first year of the Compound Hub, the overall submission increased by 50% compared to 2004 and increased by another 25% in 2006.

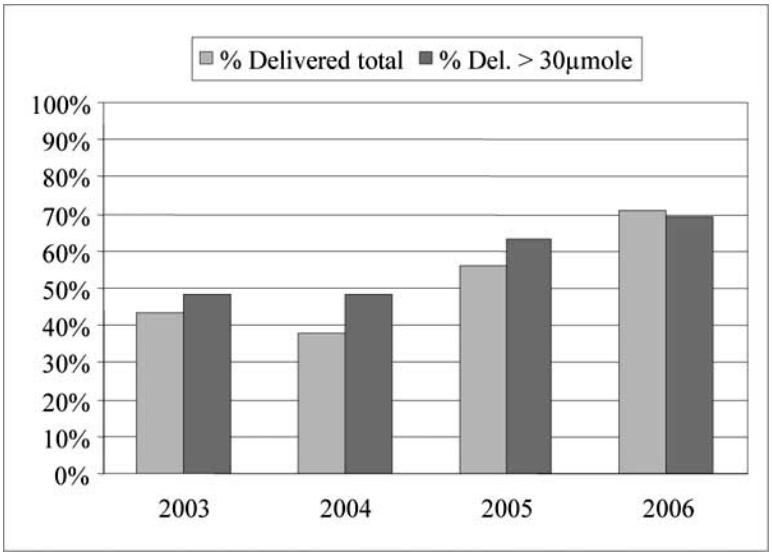

Fig. (6). Comparison of compounds registered *vs* compounds delivered to the archive.

CONCLUSION

The challenging task of collecting compounds from internal medicinal chemistry sources was addressed by the implementation of the Compound Hub at the Novartis Institutes for BioMedical Research. A win-win situation was created to help chemists with tedious weighing, dissolution and shipment and to achieve the incorporation of a larger number of proprietary compounds into the HTS library. By this directed submission channel of new substances, the time needed to integrate new compounds into the HTS library could be reduced from one year to less than 2 months after synthesis. A further benefit for the chemist is the short delivery time of freshly prepared solutions to the biology labs (within 36 h after filing of the request). The Compound Hub strategy sourced more than 50% additional compounds in 2005 its first year running and will exceed this in 2006. Most chemists globally have changed their processes to use the Compound Hub. The global user interface TRT as ordering tool quickly became one of the most frequently used applications within the Novartis research community. The globally available open IT infrastructure also allowed the implementation of the Compound Hub in other research sites.

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We dedicate this contribution to the memory of Pierre Acklin, whose vision initiated the development of this strategy.

REFERENCES

[1] Lipinski, C.; Hopkins, A. *Nature*, **2004**, *432*, 855-861.
[2] Webb, T.R. *Curr. Opin. Drug Discov. Devel.*, **2005**, *8*, 303-308.
[3] Harper, G; Pickett, S. D.; Green, D. V. S. *Comb. Chem. High Throughput Screen.*, **2004**, *7*, 771-781.
[4] Schopfer, U.; Engeloch, C.; Stanek, J.; Girod, M.; Schuffenhauer, A.; Jacoby, E.; Acklin, P. *Comb. Chem. High Throughput Screen.*, **2005**, *8*, 513-519.
[5] Schuffenhauer, A.; Popov, M.; Schopfer, U.; Acklin, P.; Stanek, J.; Jacoby, E. *Comb. Chem. High Throughput Screen.*, **2004**, *7*, 771-781.
[6] Persidis, A. *Nat. Biotechnol.*, **1998**, *16*, 691-693.

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