

# Compound Management comes of age

The changing role of compound management in recent years has seen an often under-valued and under-resourced function being recognised as a key part of the drug discovery process. This article examines the challenges faced by compound management teams and, at a high level, some of the solutions that are currently available and those that may be available in the future.

**H**igh Throughput Screening (HTS) has seen many dramatic advances during the past decade: the transition from 96-well to 384-well to 1536-well formats and beyond, the realisation of ultra HTS with throughputs of more than 100,000 compounds per assay and day, and the emergence of a plethora of new assay technologies enabling a greater range of targets to be screened. In addition, there has been an increase in potential targets from genomics, as well as advances in combinatorial chemistry resulting in more, and higher quality, compounds for screening. The pharmaceutical industry has, so far, been willing to fund this revolution. According to the PHRMA Industry Profile 2001, global spending on HTS was \$1.7 billion<sup>1</sup>. Thus far, however, the large investments in equipment and new technologies have failed to meet expectations in terms of the quantity or quality of lead compounds delivered.

It could be argued that it is too early to see the effects of the improvements in the HTS process in the marketplace, yet there is also no evidence of an increase in productivity in pre-clinical or phase one<sup>2</sup>. A possible contributing factor to this apparent lack of return could be the failure to improve the supporting infrastructure in parallel with developing the HTS process, often resulting in a

support structure that is incapable of meeting the new demands placed upon it. The corporate compound collection and its management is a prime example of this. Pharmaceutical companies often talk about their compound collections in complementary terms such as 'one of our largest assets' or the 'crown jewels'. Nevertheless, until relatively recently, many have been storing them in the equivalent of a broom cupboard under the stairs!

## The past

The management of compound collections in the past was generally a fairly low-key affair, and the groups that performed it were viewed as serving simple dispensary functions. Investment in Compound Management (CM) was small and its role not understood by many in drug discovery organisations. This resulted in some pretty terrible management of those 'crown jewels'. There is anecdotal evidence, from not so many years ago, of collections being housed in boiler rooms and Dimethyl Sulphoxide (DMSO) solutions collections that, due to water uptake, were never depleted.

Things have moved on in the last few years with the realisation that what comes out of HTS, as well as the drug discovery process as a whole, is only as good as the compounds that go in. There has been

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a definite shift from collection size being the most important factor to a more balanced view of the importance of quality and quantity combined. There are many recent examples of the industry making large investments in both compounds and the infrastructure to manage them<sup>3-5</sup>. The range of tools available to CM teams has also expanded dramatically, and compound managers now have a large choice of building blocks when implementing a CM process. CM is now an area very much in focus as a key component of a company's drug discovery process and, therefore, an important factor in its relative success or failure.

### Core principles of CM

There are six core principles that should be applied when establishing or re-engineering a CM system. Depending on the circumstances, it may be appropriate to place more emphasis on one or more of the principles. However, for a CM system to be successful it is crucial that all aspects are considered.

### Core principles of Compound Management

- Ensure compound accessibility
- Maintain compound integrity
- Enable efficient compound usage
- Flexibility to adapt to new demands
- Ability to maintain a dynamic collection
- Availability and integrity of inventory data

#### Ensure compound accessibility

It is important to ensure that CM customers can access the compounds they need, when they require them and in the format they need. This can range from small numbers of solid samples to millions of liquid samples. A particular challenge here is the need to respond to the drive towards smaller and smaller assay volumes and supply compounds at very low volumes, typically one hundredth of the assay volume, while ensuring sample delivery is accurate, precise and reproducible.

#### Maintain compound integrity

The cost of synthesising a compound ranges from \$5-12 per compound, using combinatorial chemistry, to \$5,000-7,500 per compound, using classical methods<sup>6,7</sup>. Ensuring the integrity of the com-

pounds in a collection is, therefore, of paramount importance. Equally important is the cost, in time and money, of screening, as well as potentially following up on compounds that have degraded. Maintaining the integrity of screening collections is further complicated by the use of DMSO as the solvent of choice. DMSO is used since it dissolves a wide range of compounds. However, it is also very hygroscopic and has been demonstrated to absorb 100% of its own volume within one month in open conditions<sup>8</sup>. Water uptake can lead to problems with degradation, dilution and precipitation.

#### Enable efficient compound usage

As discussed above, the compounds housed in a collection are inherently valuable. It is, therefore, vital that compound wastage be kept to a minimum. Compound wastage occurs in the CM process due to two main factors: the dead volume of labware used for sample storage and processing, and material lost during both liquid and solid handling processes.

#### Flexibility to adapt to new demands

CM facilities need to be flexible in order to meet not only the diverse day-to-day needs of its customers but also to be able to adapt to new strategies and technologies used for drug discovery. These changes can range from relatively simple ones, such as a new output microtitre plate, to more fundamental changes, such as a shift in HTS strategy. For a CM team to be successful, it has to be able to quickly respond to these changes to ensure it does not become a hindrance to the evolution of the drug discovery process.

#### Ability to maintain a dynamic collection

An obvious desirable feature of a CM system is the ability to cope with collection growth: it should be straightforward to add new samples to the collection. What is sometimes overlooked is the importance of being able to remove compounds from the collection. Samples need to be removed for a variety of reasons including depletion, degradation, discovery of undesired properties and progression into development. A problem with many systems, the majority of which are plate-based, is that the removal of samples results in a fragmented collection with a reduction in the number of useful samples but no reduction in terms of number of wells and, therefore, no savings in time and money.

#### Availability and integrity of inventory data

The final core principle of CM is the provision and maintenance of accurate and up-to-date inventory



**Figure 1**  
An automated narrow-aisle compound store under construction at RTS Life Science International

data. This needs to be available to the CM team and, in most cases, there are advantages to making this data available to the scientific customers. The lack of, or inaccuracy of, inventory data is often a major source of frustration and inefficiency. Large amounts of time and money are wasted either looking for samples that are, in reality, not physically present or resynthesising/repurchasing compounds that are, in fact, available.

### **Building a compound management solution**

CM covers a wide range of tasks ranging from supplying one or two compounds to an *in vivo* test to supplying a million compounds to an HTS screen. There is no right way to implement a CM operation. The best solution for each application is determined by factors such as the size of the collection, expected growth rate, number of customers, required access rate and budgetary considerations. It is also imperative to determine the needs of the customers: what do they expect from

a CM service? Which of the core principles are most critical for them?

Whatever the process, there are three main components that are required, the hardware, software and labware. It is important that these three components are chosen and combined in such a way as to provide the most appropriate solution for the application(s) to be supported.

#### **Hardware**

The hardware required for CM consists of two elements: equipment for storing and retrieving samples and equipment for processing samples. They can be integrated or operated independently, and there are different levels of sophistication available for each element. As with the overall CM solution, it is important that the selection of the storage and processing equipment results in a balanced solution when combined. There is little point, for instance, in having a high throughput, environmentally-controlled storage and retrieval unit if sample processing is performed manually on an open lab bench.

**Figure 2**  
A Plate  
Replication/Reformatting Cell  
from the Velocity I I BioCel  
Series™



The simplest option for storage and retrieval is the manual store. This consists of a shelving system on which the samples, usually in racks, are placed. The shelves and/or racks are optionally labelled and the required samples retrieved manually. This approach is well suited to collections that are accessed relatively infrequently. The major advantages are small size, simplicity, low cost and high flexibility. Potential problems include risk of operator error, misplaced or lost samples and difficulty in maintaining environmental conditions. Manual stores also run the risk of becoming prohibitively labour intensive if access rates increase.

A variation on the manual store is the use of automated shelving such as vertical carousel or vertical shelving units. Samples are generally still retrieved manually; the operator enters the location of the

desired sample and the correct shelf or storage tray is presented. This can be advantageous for larger collections as high storage densities can be achieved with low floor space usage. Access rates are, however, still relatively slow, cost and complexity are increased and flexibility is slightly reduced.

Fully automated storage and retrieval systems have developed rapidly in recent years and are now in use in many CM operations. The reason for this is that manual storage and retrieval is not a viable option when looking at the access rates of the thousands, tens of thousand and even hundreds of thousands of samples per day that are now required. Further advantages with automated systems include the reduced risk of error, longer walk-away times and environmental control benefits. Drawbacks with automated stores include the higher cost, decreased

flexibility and longer delivery lead times. Examples of fully automated storage and retrieval systems include narrow-aisle stores from companies such as REMP, RTS Life Science International (Figure 1) and The Automation Partnership, as well as modular solutions such as the comPOUND™ from The Technology Partnership and the TubeStore™ and PlateStore™ systems from Tekcel.

Sample processing can also be categorised into several levels of sophistication, the first of which is, again, manual operation. As with manual storage, this solution is simple, compact, low cost, flexible and suitable for low throughput operations. Manual sample processing may also be the only option for certain tasks where automated approaches are not deemed feasible. An example of this is the weighing of solid samples where, despite a number of different solutions being available, automated approaches have not been widely taken up by the industry. Manual processing suffers from disadvantages akin to those of manual storage, namely risk of operator error, difficulty in maintaining environmental condi-

tions and the risk of becoming very labour intensive if throughput rates increase.

The next level of sophistication is the simple workstation approach. In this approach, processing steps are performed with the help of small, stand-alone pieces of equipment. Simple workstations are loaded with samples and empty labware either manually, or by using stackers or simple robotic arms. The benefits of this approach include higher throughputs and a reduced risk of operator error, while maintaining the low cost and flexibility advantages. For liquid processing operations, today's compound manager has many options. Independent tip devices such as the Tecan Genesis™ are used where complex liquid handling methods are required. For rapid replication and reformatting, 96- or 384-channel, fixed or disposable tip machines are normally used. The Velocity11 VPrep™, CyBio CyBi™-Well, Zymark Sciclone and Hummingbird™ from Cartesian Technologies are just a few examples of the wealth of products available in this category.



**RTS** **LIFE SCIENCE INTERNATIONAL**

**High Integrity Automated Sample Storage and Retrieval Solutions**

[www.rtslifescience.com](http://www.rtslifescience.com)

The advertisement features a large image of a robotic arm with a yellow and blue logo, positioned over a tray of sample vials. To the right, there is a smaller inset image showing a rack of sample storage containers. The text is prominently displayed in bold, black font.

The most advanced sample processing station is the integrated work cell. Here, a number of pieces of equipment are integrated together to produce a unit that can perform multiple processing activities. A robot arm or conveyor is used to link the components together and the station is often, though not always, integrated with an automated store to provide a fully integrated storage and processing solution. Advantages include high throughput, long walk-away times, reduced risk of errors and the possibility of complete environmental control. Disadvantages include increased cost, reduced flexibility and longer delivery lead times. Examples range from custom-built solutions connected to automated stores from companies such as REMP, RTS Life Science International and The Automation Partnership to more 'off the shelf' products such as the Velocity11 BioCel Series™ (Figure 2) and the Tekcel TekBench™.

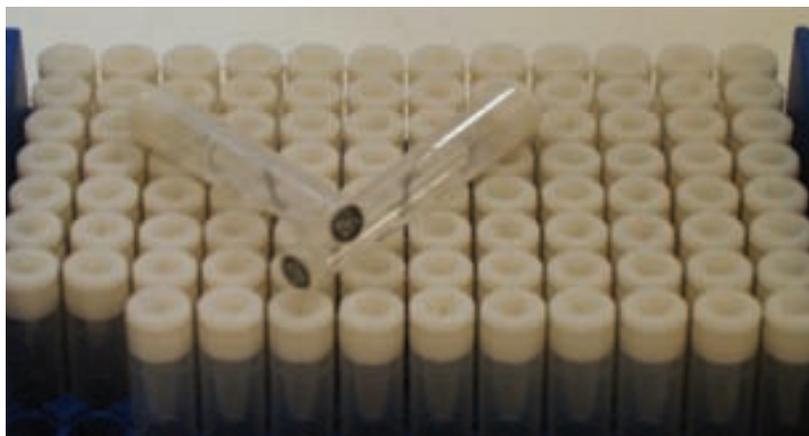
#### Software

At the heart of any CM IS system is the inventory database. As discussed earlier, it is essential that the data held within this database is accurate and up-to-date. The database not only needs to contain information about the current status of the samples, but also the history of each sample. In the case of storage systems with high access rates, the database has to be able to handle large numbers of real time transactions per day. The inventory database is, in addition, normally used to directly or indirectly populate the databases for recording experimental data against the compounds.

A mechanism for customers to place their requests is also required. For small organisations, it may require nothing more than telephone, e-mail or face-to-face contact. For larger organisations, it is necessary to have a dedicated solution that both enables customers to place and track their requests and ensures that requests are supplied to the CM teams in a standard format. A request application is particularly powerful when combined with access to accurate inventory data, allowing scientists to search for relevant compounds and then automatically request those that are available in sufficient quantity.

Finally, software is required to enable the CM teams to schedule and track the fulfilment of requests. For very small teams, it may be possible to track request fulfilment manually. More often, though, software is necessary to track incoming requests and divide them into tasks for distribution to the relevant hardware or personnel.

The choice of software will clearly impact on the availability of inventory data. In addition, it can



**Figure 3**  
The 2DCYPHER™ tube with MULTISIP™ septum plug from ABgene

potentially affect the other core principles. It is important, for instance, that an IS system does not limit accessibility by being too slow or flexibility by being too rigid (eg difficult to add new labware or new processes).

As with CM hardware there are many different solutions available. These range from combining off-the-shelf products such as e-mail, Microsoft Excel and Microsoft Access to large integrated systems such as Enterprise Substance Manager™ from Sciquest or purpose-built solutions developed in-house.

#### Labware

The labware chosen for storing compounds needs to protect the sample from water, oxygen, evaporation, dust and light. It is also essential that the labware chosen is inert in order to avoid sample contamination. As well as compound integrity, the choice of labware will also influence the other CM core principles: a container for storing solids may, due to design faults, limit processing rates that in turn limits sample accessibility. A solution storage vessel may have a large dead volume and, therefore, result in unnecessary waste. A storage vessel may also compromise flexibility if it proves to be too small to cope with larger sample quantities in the event of increased synthesis/purchase amounts. And, as discussed earlier, plate-based storage can result in difficulties in maintaining a dynamic collection.

For solid storage, there are many vials and bottles to choose from. For manual weighing operations, vessels should have a wide neck and be easy to handle. If the vessels are to be used in automated systems they should be chosen in order to best suit the weighing method and may need special features such as the Archimedes screw caps used by some automated weighing systems.

When choosing a vessel for solutions storage,

#### Websites

ABgene  
[www.abgene.com](http://www.abgene.com)  
 Boston Innovation  
[www.bostoninnovation.com](http://www.bostoninnovation.com)  
 Cartesian Technologies  
[www.cartesiantech.com](http://www.cartesiantech.com)  
 Corning  
[www.corning.com](http://www.corning.com)  
 CyBio  
[www.cybio-ag.com](http://www.cybio-ag.com)  
 REMP  
[www.remp.com](http://www.remp.com)  
 Tecan  
[www.tecan.com](http://www.tecan.com)  
 Tekcel  
[www.tekcel.com](http://www.tekcel.com)  
 The Automation Partnership  
[www.automationpartnership.com](http://www.automationpartnership.com)  
 RTS Life Science International  
[www.rts-group.com](http://www.rts-group.com)  
 Sciquest  
[www.sciquest.com](http://www.sciquest.com)  
 The Technology Partnership  
[www.ttplabtech.com](http://www.ttplabtech.com)  
 Velocity 11  
[www.velocity11.com](http://www.velocity11.com)  
 Zymark  
[www.zymark.com](http://www.zymark.com)

### References

- 1 PHRMA Industry Profile 2001.
- 2 Handen, Jeffrey S (2002). High Throughput Screening – challenges for the future. *Drug Discovery World* 3(3) 47-50.
- 3 Press Release. The Automation Partnership. Jan 29th 2001. Merck Orders The Automation Partnership's Robotic Compound Repository.
- 4 Press Release. Chembridge Research Laboratories. Jan 22nd 2002. ChemBridge and Chembridge Research Laboratories (CRL) announce a strategic multi-year discovery chemistry collaboration with Pfizer involving over 100 ChemBridge and CRL chemists.
- 5 Press Release. RTS Life Science International. 8th Feb 2002. RTS Life Science International Announces Contract with AstraZeneca.
- 6 Kuroki, Gary W (2000). Automating parallel organic synthesis. *American Laboratory* 32(7) 49-51.
- 7 Persidis, A (1998). Combinatorial chemistry. *Nature Biotechnology* 16(7) 691-693
- 8 Naylor, Stuart. (2002). Ensuring Compound Integrity with Modular, Scalable, Automated Solutions at European Laboratory Robotics Interest Group Synthesis to Screening meeting.

key factors in addition to sample integrity are capacity, dead volume, tolerances, inertness to DMSO and cost. There are a number of formats available including multi-sip tubes such as the 2DCYPHER™ tube and MULTISIP™ septum plug from Abgene (Figure 3). This tube has a low dead volume and is individually identifiable by a 2D barcode on the base. The septum plug can be accessed up to 200 times without compromising seal integrity. An alternative approach is the use of 'single-shot' containers where a small aliquot of sample is sealed within a tube and the entire tube is retrieved into a microtitre plate format carrier for downstream processing.

Plate-based storage is another option for solution storage. Plate-based collections can be replicated rapidly using 96- or 384-channel liquid handling devices making this approach attractive for collections used to produce assay plate sets for primary screening. Plate-based storage can, however, lead to problems with sample accessibility, integrity and wastage, especially if individual sample access is required. A major problem in the past has been finding a mechanism to repeatedly seal microtitre plates. Today, there are a number of solutions to address this problem such as the SealTite™ system from Tekcel and the Robolid from Corning. A novel approach to plate-based storage is the SmartPlate from Boston Innovation that incorporates both sample storage and dispensing in a microtitre plate.

### The future

There are a number of challenges that the CM teams in the pharmaceutical industry are likely to face in the near future or are in some cases already grappling with. The first of these is compound integrity. A vast amount of resources are wasted working on compounds that are low purity, or in the worst case, no longer present in the sample. CM teams should be moving towards a goal where, when supplying compounds after the very early stages of Hit Identification, they can guarantee the purity of all samples supplied. This can be achieved by a combination of improved storage conditions and the use of high throughput analytical and purification methods.

The second challenge facing CM teams is the need to support a process that is continually evolving. It is vital that CM teams implement processes that are flexible and can support changes in the organisation's drug hunting strategy without having to resort to major re-engineering. Examples of how this can be achieved include the use of 'format-free' storage methods and the adoption of a

'plug and play' approach using process modules that allow individual processes to be upgraded as required with minimal disruption and expense to the overall operation.

The need to support discovery that is spread over the globe is a challenge that some companies have been facing for a while. There is a big risk that the value of the collection is not realised as it is not possible to access compounds globally due to incompatibilities between local systems, lack of inventory data and local sample possessiveness. Distributing multiple copies of a collection around an organisation may not be a viable option due to the wastage incurred and, therefore, new, alternative approaches are required.

The final challenge is the need, as already discussed, to support assays performed in ever decreasing volumes. CM teams need not only to be able to dispense minute amount of compounds but also ensure that these compounds actually get to the assay in question. Novel solutions are, again, needed. Alternatively, there may be a shift from the pre-preparation of assay plates to an approach where compounds are added directly to the assay on the fly.

### Conclusion

CM is now recognised as a vital and integrated part of the drug discovery process. It has received the attention and resources that were often absent in the past and has progressed from a relatively low-key affair to an advanced, customer-focused, process-orientated function that is capable of providing a high speed and high quality service. With this recognition and investment comes responsibility. CM teams must now consolidate their position and justify the large investments that have been made by contributing to an increased discovery output. They need to prove that they not only are capable of managing the 'crown jewels' but also of continuing to adapt to meet the needs of an ever changing discovery process. **DDW**

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