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Outsourcing to exploit a key asset

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Much has been written and debated about the economic and organizational advantages of outsourcing a growing list of operations in drug discovery. In what has been described as a modular approach to drug discovery, whole sections of the process are now handled very effectively by a wide variety of specialist suppliers to the pharmaceutical industry. Here we report on a novel outsourced solution to the challenge of consolidating and managing some of the key assets residing within a major research organization – its chemical intermediates. At Johnson and Johnson Pharmaceutical Research and Development this resource has been built up over a period of more than 40 years, and is added to daily. The challenge was to provide the company's scientists with a single source for its own and externally procured intermediates; the solution was developed working in partnership with Sigma-Aldrich.

Improving accessibility

In 2001, two Johnson and Johnson research groups, the Janssen Research Foundation and the R.W. Johnson Pharmaceutical Research Institute, merged to form Johnson and Johnson Pharmaceutical Research and Development (J&JPRD), encompassing six separate research sites across Europe and the USA. Coincidental with this was a move towards more target-oriented research and a recognition of the importance to the company's researchers of having sight of, and access to, the full range of intermediates available. Compound libraries from the different sites were being merged, but there remained the questions of how best to make these available to all and how to ensure that newly synthesized intermediates became accessible quickly. With some 20,000 existing intermediates across the sites in Europe, ranging in quantities from several grams to a few kilos, developing a centralized resource would be a far from trivial undertaking.

Perhaps even more fundamentally, it was identified that the processes involved in library design for specific projects – which typically include searching internal and external databases for suitable intermediates, ordering, inventory and management of compounds from a variety of sources – could be streamlined. As a result, a European team at J&JPRD initiated the Reagent Ordering and Tracking System (ROATS) project in 2001 to determine the feasibility and mechanisms for developing a centralized facility that would offer:

- Central storage and inventory management.
- Fast, custom delivery of single and large series of preweighed quantities.
- Selection from J&JPRD proprietary databases and commercially available monomers.

Therefore, this was not only about database management, but also covered the need for custom delivery of compounds (Box 1). The ability to place just a single order and then to receive preweighed, application-ready compounds would allow high-value scientific resources to be focused on discovery, rather than the often tedious process of reagent management and preparation. The use of preweighed compounds was also expected to reduce chemical waste.

Project development

A wide range of companies offers custom synthesis services for drug discovery [1]. However, any internet search will quickly

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1359-6446/06/$ - see front matter doi:10.1016/j.drudis.2006.04.015

BOX 1

WHY ROATS?

- Bridges the gap between reagent-selection and library design and high-throughput chemistry.
- Provides central inventory management of the intermediate store.
- Enables global J&JPRD access to all J&JPRD monomers.
- Ensures efficient tracking, ordering and gathering of J&JPRD monomers and commercial compounds.
- Provides customized delivery of monomers to meet high-throughput chemistry needs.
- Increase the efficiency of current resources.
- Reduces costs and chemical waste.

reveal a dearth of organizations able to combine the ability to procure and supply intermediates with the resources and experience to manage a discovery company's own materials. Although the team at J&JPRD was conscious of this, and also of the increasing trends towards outsourcing in pharmaceutical discovery [2], ROATS was initiated with no preconception about whether the centralized facility would be developed in-house, outsourced in its entirety, or a combination of the two. A decision to outsource completely would be a groundbreaking move because, to the authors' knowledge, pharmaceutical discovery companies have generally managed such resources in-house.

Initially, several external companies experienced in the supply of chemical intermediates were approached; major issues included their ability to implement contract agreements globally and to deliver anywhere in the world. As part of the first assessments, J&JPRD placed the same order for 50 compounds with several vendors. Fastest to respond with a quote and to deliver the order was Sigma-Aldrich. It also became apparent that this was the only company at the time set up and able to provide a fully outsourced solution for J&JPRD's intermediates management issues, and who could meet the objectives of central storage and inventory management, and custom delivery with the ability to source from proprietary and commercial databases.

It quickly became evident that one of the main benefits of working with an external supplier who could provide all these services (compared with taking this project in-house) would be the ability to make commercially available compounds accessible to everyone and promote their efficient use. Having then made the decision to fully outsource the project, J&JPRD appointed Sigma-Aldrich in late 2002, with that company's Gillingham, UK, site chosen for central warehousing and despatch. Sigma-Aldrich's position as one of the largest vendors of chemicals in the world was crucial because it was considered important for J&JPRD, as part of a major pharmaceutical company, to partner with an established chemicals supplier. The company's long-established service in supplying custom-packaged reagents for drug discovery, its own extensive reagent catalogue and proven ability to outsource from third party vendors were also key considerations.

Delivery from Gillingham can be direct to the J&JPRD sites or, for example, to custom synthesis facilities anywhere in the world. Sigma-Aldrich's established Discovery Custom Packaged Reagents (CPR) solution provided the foundation from which the J&J Monomer Store would be developed. Originally known as The Filling Station [3,4], Discovery CPR offers a complete reagent

FIGURE 1

The physical storage area, developed as a separate and secure space within the Sigma-Aldrich Gillingham facility, UK.

management service, whereby reagents from any vendor can be packaged to a customer's specifications. On this basis, the requirement to house and manage J&JPRD's own intermediates, as well as offering custom procurement and packaging, was a logical progression.

Practical developments

The first step in the practical implementation of the project was to build the physical storage area, developed as a separate and secure space within the Sigma-Aldrich facility in Gillingham (Figure 1).

Software for the database itself and for inventory management, archiving, ordering and other functions was developed by MDL, working closely with J&JPRD and with input from Sigma-Aldrich. As an existing collaborator and provider to both companies, MDL already had experience of their individual requirements, making the company's selection as partner on this project a logical step. The resulting J&JPRD CIMS_ROATS application provides a single view of all J&JPRD monomers available to the company's scientists, and the complete package allows straightforward searching and ordering of compounds.

A major operation in the set-up phase was the selection and updating of all J&JPRD's compounds. Some were already in databases and others were spread across different laboratories and sites. For every compound that the company owned, it became necessary to know the exact amount available and to have all the accompanying data. The compounds were collected, a preliminary file with structure and other key data was uploaded to the database and the materials were packaged securely and shipped to Sigma-Aldrich. With 24,000 bottles to ship, this was a lengthy but necessary process. Today there are ~27,000 bottles in store.

How it works

The first step for the ordering cycle remains the individual scientist searching multiple databases simultaneously for starting materials, but now with visibility of both commercially available

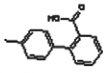
			Request											
SEL.	CHEMISTRY	MOLNAME	SM INDEX	SOURCE DB	MFCD	COMPOUND ID	BOTTLE BARCODE	CAS NUMBER	REQUESTED (mMol)	MV SALTFORM	MF SALTFORM	REQ. AMOUNT (mg)	STOCK (mg)
	 Chemistry 2	2-AMINO-3-METHOXYBENZOIC ACID		ACD	MFCD00075178	MFCD00075178		3177-80-8	1.50	167.163	C8 H9 N O3	251	
	 Chemistry 4	3,4-DIHYDRO-2H-1,5-BENZODIOXEPINE-6-CARBOXYLIC ACID		ACD	MFCD03783556	MFCD03783556		66410-67-1	1.50	194.185	C10 H10 O4	291	
	 Chemistry 6	3-METHOXY-2-METHYLBENZOIC ACID		ACD	MFCD02094039	MFCD02094039		55289-06-0	1.50	166.175	C9 H10 O3	249	
	 Chemistry 7	2,3-DIFLUOROBENZOIC ACID		ROATS		C0020760	10041370	4519-39-5	1.50	158.103	C7 H4 F2 O2	237	663
	 Chemistry 9	4'-METHYL-2-BIPHENYLCARBOXYLIC ACID		ROATS		C0020552	10039464		1.50	212.247	C14 H12 O2	318	782

FIGURE 2

Example of a quote request file.

building blocks and the full range of J&JPRD intermediates available in the ROATS database. All ordering, via a sequence of request–quote–order–receipt, employs a single electronic file (Figure 2).

The usual structure searches and filtering of reagents takes place, leading to the generation of a starting materials file. A ROATS wizard then aids the compilation of a request file which includes information such as the user's details, type of vials required for the application, selection of compound line. It also imports the information from the starting materials file, and the whole is sent automatically to Sigma-Aldrich. On receipt of a request file, availability and price information on any third party compounds is sought, and within 48 hours a quote file is returned to the requestor complete with supplier name, catalogue numbers, price and delivery times. After checking the files, and with the option to remove or replace any compounds, the order file is returned to Sigma-Aldrich through a secure website, which will take care of invoicing and order processing (Figure 3).

Sigma-Aldrich will then process the entire order, and on arrival any third party supplier compounds are loaded into the ROATS database. Suitability and updating of reactive compounds for inclusion in the database is driven by expiry dates to ensure the integrity of all its contents. Materials are weighed and packaged into the specified barcoded containers, and delivered ready to go straight into the application or for manual use. The receipt area of the electronic file is completed with details of container ID, actual amount and safety and handling information, and returned to the person placing the order. If more than one bottle of a particular reagent is needed, then two sets of details will be supplied, and different batches are not normally combined.

So although the final delivery might be made up of intermediates from J&JPRD's own collection, materials from Sigma-Aldrich's catalogue and compounds from a wide range of third party suppliers, the researcher needs to place only a single order and handle a single file. Analytical data and physical chemistry information for the compounds are available to researchers online but are not yet integrated into the system.

Overall benefits

The benefits from the ROATS project are really twofold: it is allowing J&JPRD to exploit fully the major asset that is its intermediates collection, and it is streamlining the selection, ordering, delivery and application of intermediate compounds, allowing more focus on the research effort itself. Now into the fifth year of operation, our experience with the system has been overwhelmingly positive and we are looking to extend its use.

Optimization of the design–make–test process in drug discovery has been a stepwise process in the past decade. First by the introduction of high-throughput and medium-throughput screening technology [4,5], which was fed with novel compounds through combinatorial and parallel synthesis. Together with the initial failures came the introduction of *in silico* tools to improve further on the design cycle [6,7]. In-house-developed integrated reagent and library design tools, such as REALISIS [8] and more recently Directed Diversity [9,10], were introduced to optimize the most crucial and strategic steps in synthesis planning, reagent selection and library design. However, gathering the selected intermediates still took a long time for the chemists because the compounds were stored in multiple databases scattered over the different J&JPRD sites, and were often not traceable by colleagues from other sites. As a separated action, commercial compounds were ordered one by one, whereas list ordering would be more efficient. And finally, the received monomers had to be weighed, prepared for library synthesis and registered for stock inventory. This tedious and lengthy process is optimized by the introduction of ROATS, which bridges the gap between *in silico* design tools and high-throughput synthesis or traditional medicinal chemistry. This enterprise comprises the outsourced centralized storage and inventory management by Sigma-Aldrich of proprietary

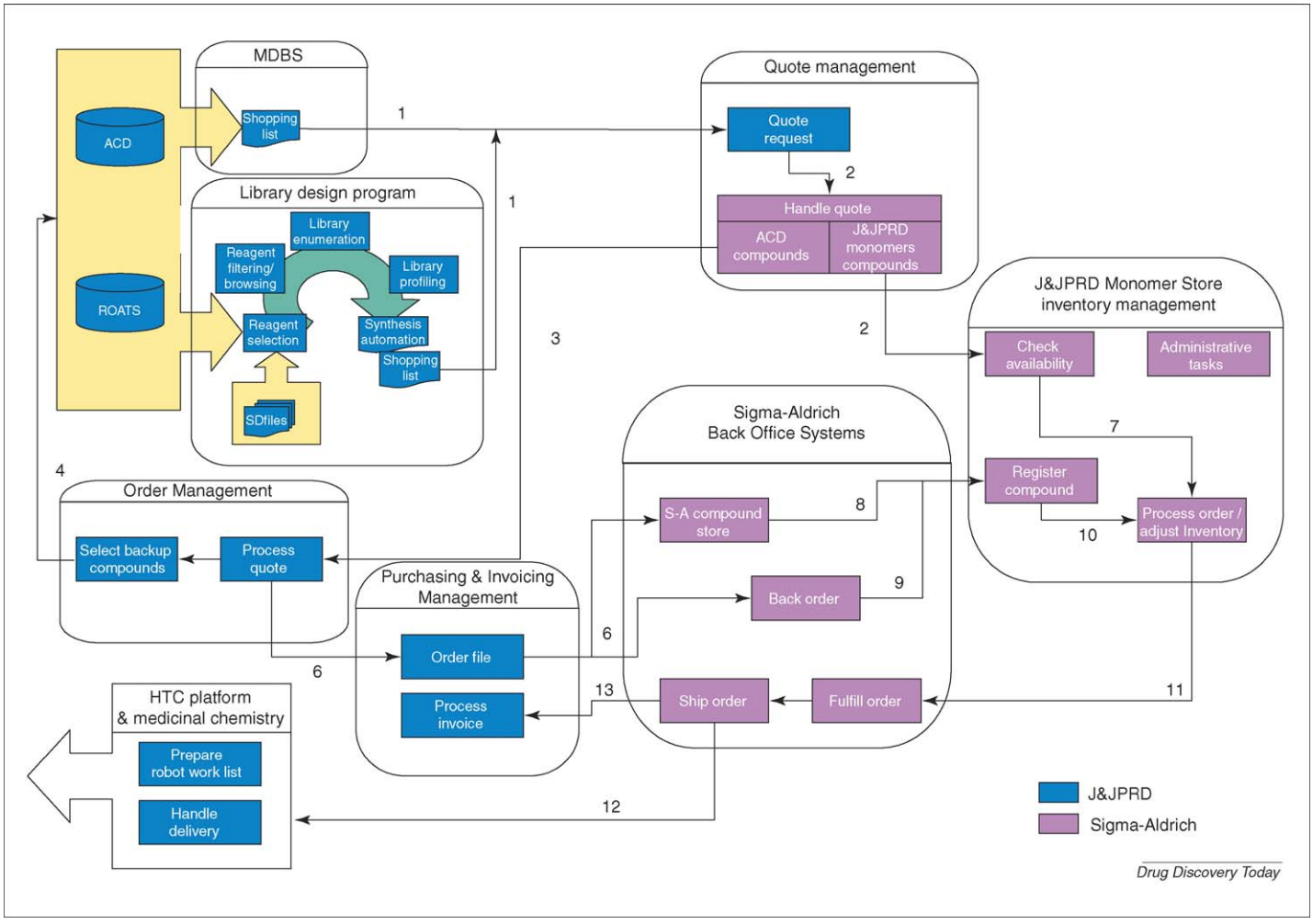


FIGURE 3

Reagent selection and ordering process. (1) A shopping list (Accord for Excel file) obtained from a library design program, from a simple multidatabase search, or from a manual database substructure search is sent as a quote request to Sigma-Aldrich. **(2)** Sigma-Aldrich splits quote request into compounds available from the J&JPRD Monomer Store and compounds to be ordered from vendors mentioned in MDL's available chemicals directory (ACD). Sigma-Aldrich checks availability of J&JPRD Monomer Store compounds and ACD compounds. **(3)** Within two working days, a total quote and delivery time for backorders is sent to the J&JPRD requestor who evaluates the price and, if necessary, seeks order approval. **(4)** A selection of backup compounds to replace commercially non-available compounds is possible. **(5)** A new quote is requested for the backup compounds (action 4 followed by action 1). **(6)** J&JPRD scientist places the order to Sigma-Aldrich using ARIBA Sigma-Aldrich punch-out. **(7)** Sigma-Aldrich collects J&JPRD Monomer Store compounds and places order for ACD compounds. **(8)** Sigma-Aldrich commercial compounds are registered in the J&JPRD Monomer Store database. **(9)** Sigma-Aldrich backorder compounds are registered in the J&JPRD Monomer Store database. **(10)** Sigma-Aldrich prepares barcoded preweighed samples in vials, as requested by J&JPRD scientist, and updates inventory. **(11)** Sigma-Aldrich sends ordered vials with corresponding Accord for Excel reception file to J&JPRD within two working weeks. A back order can be delivered within a time agreed upon by both parties. **(12)** Scientist checks delivery and uses the Accord for Excel file to prepare job list for robotic work stations (HTC) or for manual synthesis. **(13)** Sigma-Aldrich sends an invoice to the requestor.

and acquired J&JPRD intermediates, together with a service offering fast custom delivery of single and large series of preweighed quantities to J&JPRD medicinal chemists. We believe that the process of rational reagent selection supported by a centralized storing, tracking and ordering platform will further increase the speed of the design–make–test discovery cycle (Figure 4).

In the opening paragraph, we made reference to the fact that an accumulated collection of intermediate compounds is a huge asset for any drug discovery company. Increasingly, and especially with high-throughput screening, scientists will continue to revisit even old building blocks every time historical compounds in the global database are rediscovered as new hits within novel target screening. Without an accessible central database, it would be too easy for someone to be synthesizing the same compound that has been sitting on the shelf in the next laboratory for the past five years. Current resources can therefore be put to more efficient use. It is also an opportunity for scientists to share more effectively their information and materials, and everyone is being encouraged to enter newly synthesized compounds on to the database, even if physically they can only be shipped to Gillingham later. That way, colleagues have immediate access to the information and a knowledge that such a compound exists within the company.

The solution achieved here is a testament to the power of commercial partnerships in drug discovery. Identifying the most appropriate route to managing in-house intermediates in combination with externally procured materials was the first major decision. After outsourcing had been decided, close cooperation between J&JPRD and Sigma-Aldrich led to the development of a

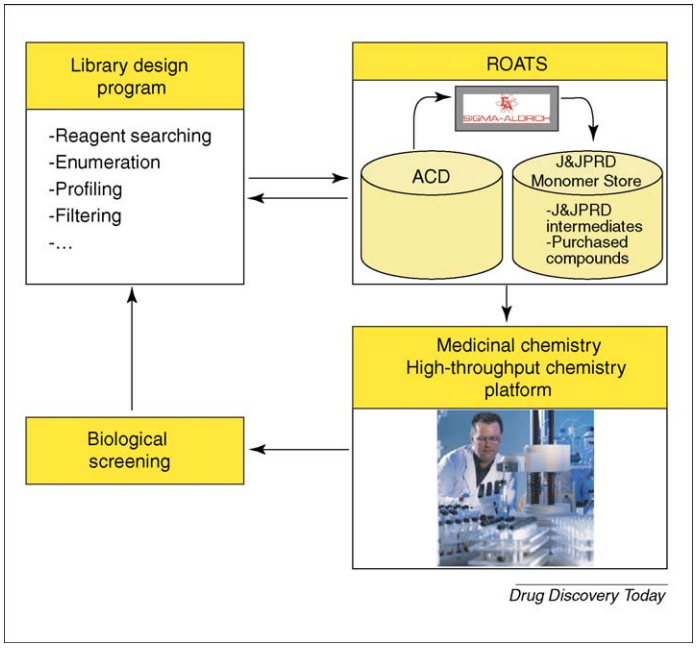


FIGURE 4

ROATS bridges the gap between reagent selection and library design and high-throughput chemistry.

truly customized solution, but one that is built on Sigma-Aldrich's proven Discovery CPR platform.

For the future

Through the establishment of the J&JPRD Monomer Store, J&JPRD scientists have constant visibility of all the chemical intermediates available to them – proprietary and commercial – with rapid ordering and delivery in the quantities and formats they need. Having developed, trialled and established the Monomer Store in Europe, there are now plans to extend its operation at J&JPRD, to provide truly global access to chemical intermediates. It would have required significant additional resources for J&JPRD to have undertaken such a project in-house, and the benefits of partnership with external companies that provide specialist expertise is evident. Strong relationships, commitment to success and excellent communications between partners are absolute requirements for long-term success as this type of complex outsourcing project becomes more commonplace, with other pharmaceutical companies seeking similar solutions.

Acknowledgements

We gratefully acknowledge Dr Jan Hoflack, Dr Luc Van Hijfte and Vic Maes for helpful discussions and input into the project.

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