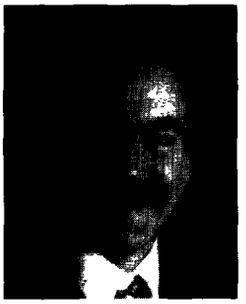
Meeting client needs in combinatorial chemistry: a service company perspective



'The drug discovery process is now following the established outsourcing pattern'

The science and innovations surrounding combinatorial chemistry and high-speed parallel synthesis have emerged as some of the most significant developments in the drug discovery process in recent years. The potential benefits of these innovations are now shaping the strategic thinking of discovery chemistry managers in large and small pharmaceutical and agrochemical companies alike. The drivers for taking up these new technologies are purely economic. Even a medium-sized pharma company will be aiming to take 20 new chemical entities into preclinical development per year, and the associated costs are becoming prohibitive.

Scientists engaged in the drug discovery process can tap into several of the technology products of this area, each of which has been embraced with varying degrees of enthusiasm by the industry. In addition to dedicated in-house resources, smaller service-based companies offer resources and products that can complement, compete with or even replace the internal efforts. Where a company, perhaps through size constraints, has not invested in such expensive and resource-intensive technologies, the service-based companies can offer a highly cost-effective 'alternative' medicinal chemistry department.

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The drug discovery process is now following the established outsourcing pattern set by the drug development departments, and an appreciation of clients' requirements is essential for the development of successful relationships from the viewpoint of the service-based company. An analysis of the distinct areas of lead discovery and lead optimization from a perspective of the client requirements vs service company offerings is given below.

Lead discovery libraries

According to current perceived wisdom, for each new target screen, around 100,000 compounds must be screened to obtain one quality lead compound worthy of an optimization programme. Several large companies have indicated that it is their intention to develop a large corporate compound database derived from combinatorial/high-speed chemistries to support this demanding screening effort. The size of such a compound collection varies from company to company, but numbers of 1–3 million have been discussed. Companies are addressing this goal through a combination of in-house synthesis, collaborations with combinatorial service companies and direct compound purchase.

Although the debate is ongoing, certain key requirements are emerging for the lead discovery libraries of the future. The libraries should consist of single compounds that have been individually analysed and prepared to a minimum purity specification. The individual compounds may be pooled together in mixtures for screening to improve throughput. The compounds should be focused on 'drug-like' structures and be based on novel building blocks, to ensure that the screening entities are not only structurally diverse but are capable of being optimized to exploratory development candidate status as rapidly as possible.

The issue of what makes a compound 'drug-like', and the relevance of this to library design are also under scrutiny. Within Oxford Diversity, we have adopted the concept of 'privileged structure' libraries, where compounds are not only selected for optimal structural diversity but are based on templates that offer a varying degree of conformational restriction. Some other service companies offer products that are conformationally promiscuous so as to maximize the potential of binding to target proteins. Whatever the approach, companies are demanding a high-quality product for lead discovery from the service providers (whether in-house or external) with high

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  1359-6446/96/$17 00 PII: S1359-6446(97)01070-2

purity to limit the frustration arising from false-positive results and the ability to measure 'diversity' or 'dissimilarity' to enable structural 'gaps' in the corporate database to be filled.

For in-house groups engaged in discovery library generation, a plethora of new technologies has to be addressed, resourced and put into practice before obtaining large lead discovery libraries can become a reality and an impact is made upon the corporate library database. The key issues confronting these groups are:

- the availability of technology,
- the multidisciplinary nature of the science,
- the speed and cost associated with setting up such a group, and
- the ability to engender a 'production mentality' within scientists engaged on the project.

The technologies needed for large library production require scientists and organizations to learn or acquire new skills. Unusually, much of this technology has been developed within industry, rather than academia, and there is little information in the public domain. This represents a significant challenge even for the largest pharmaceutical organizations and may present insurmountable entry barriers to smaller organizations.

The skills required to produce large compound libraries include advanced skills in organic and medicinal chemistry, polymer science, automation and robotics, computational chemistry and data management. Some of these skills currently reside in a typical medicinal chemistry department, but some do not. For the client, a major risk is that the costs associated with recruiting and resourcing an in-house team are not reflected in productivity gains in compound production and lead discovery. Hence, potential clients of service companies operating in this sector will expect to have access to experienced and talented teams of scientists with a proven track record.

The preparation of lead discovery libraries is highly dependent on access to sophisticated yet robust automation and novel building blocks. Additionally, it requires a cultural environment where the repetitive tasks and associated simple manual operations do not conflict with the more cerebral aspirations of highly trained medicinal chemists. Such a cultural approach is rarely found in a pharmaceutical discovery environment.

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The unique challenges associated with preparing lead discovery libraries are clearly an attraction to scientists within pharmaceutical and agrochemical companies, and there is an understandable desire to keep a knowledge base in-house. Also, there is a well developed 'Not Invented Here' syndrome within the industry when considering whether to partner or subcontract to a third-party service company. Significantly, we have detected that the experience of several companies engaged in this process is leading to a change of strategic emphasis from 'can we do this?' through to 'do we really want to do this?'.

Lead optimization libraries

One of the original perceived advantages of high-speed chemistry technologies was the reduction in time required to optimize around a structure discovered through primary screening. The multiparallel nature of the methodology potentially means that many hundreds of related structures can be prepared in the time taken by traditional medicinal chemistry to prepare a handful of compounds. In reality, the effort required to develop a synthetic route to the hit structure that is flexible and robust enough to prepare a truly representative collection of compounds for meaningful SAR studies is frequently too great to achieve the required results within a project's timescale. The danger is that, by the time the chemists have made their lead optimization library, the biologists have moved on to another target.

In order to meet the strict deadlines set by today's projects, the service company operating in this sector must have at its disposal an armoury of methodologies and technologies to reduce the time taken to validate the chemistry before the library is produced. Companies must either invest considerably in the development of such technologies, with all the caveats discussed above, or partner with a service-based company that has already developed an advanced 'toolbox'. Central to the toolbox concept is the development of a sophisticated array of solid-phase chemistries. For example, through collaboration with Pfizer, Oxford Diversity has generated an impressive range of proprietary chemistries that can be used for the preparation of lead optimization libraries for other clients within the industry.

The purities required by clients for lead optimization libraries are frequently higher than those specified for lead discovery libraries. The onus is on the service company to prove that compounds supplied meet the desired specification – a challenge that in-house groups do not necessarily have to meet. To achieve the quality expected by clients, service companies have had to invest in the development of relatively high-throughput purification systems, which are generally not 'off the shelf' products but require significant innovation.

An ongoing revolution

Against the backdrop of the technical challenges associated with developing combinatorial/high-speed parallel synthesis expertise within major or emerging pharmaceutical companies, there is a revolution in the way in which the industry is viewing its core activities within drug discovery. Every activity is being carefully scrutinized to determine whether it is most appropriate to perform it in-house or whether it is more effective to partner or subcontract with a third party. Service companies that operate to meet the requirements of potential clients in this sector must offer technical advantages and cost–benefits to the process and must also have the flexibility to address particular client wishes in this fast-moving field.

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