Benchmarking chemistry functions within pharmaceutical drug discovery and preclinical development

Different companies have employed various techniques and strategies for addressing productivity issues in the chemistry functions within pharmaceutical discovery and preclinical development. We benchmarked lead optimisation, clinical candidate selection, and chemistry support for preclinical development before IND filing in nine major pharmaceutical companies. Results from the benchmarking analyses of strategies, processes, resources and organisational structures in the chemistry functions are presented and discussed in terms of their implications for improving delivery of chemistry capabilities in early drug discovery.

By Dr Roger A. Edwards, Dr Kai Zhang and Louise Firth

How productive is pharmaceutical R&D? From 1990 to 2000, pharmaceutical R&D spending worldwide rose from approximately $10 billion to more than $25 billion[1], but the number of new bio-pharmaceuticals has not kept pace. While many hypotheses exist regarding why this has occurred, few analyses have been undertaken. Prior work[2] notes "insufficient knowledge about [about the cause of] existing bio-pharmaceutical R&D productivity and innovation creation". Other explanations include the lag associated with applying the voluminous amounts of new information generated by the genomics, transcriptomics and proteomics tools. Any examination of the R&D process is difficult, given the context of rapidly evolving technologies and decade-long product discovery and development. But benchmarking provides one way to better understand R&D by identifying best practices and areas for improvement. Since the chemistry capability is a vital function, we initiated benchmarking efforts in this area.

The purpose of this study was to benchmark the chemistry functions within lead generation in the pharmaceutical industry. We examined current industry trends and individual company positions regarding lead optimisation, clinical candidate selection and chemistry support for pre-clinical development before an investigational new drug (IND) filing.

Approach

We conducted detailed interviews with individuals from nine leading pharmaceutical and emerging

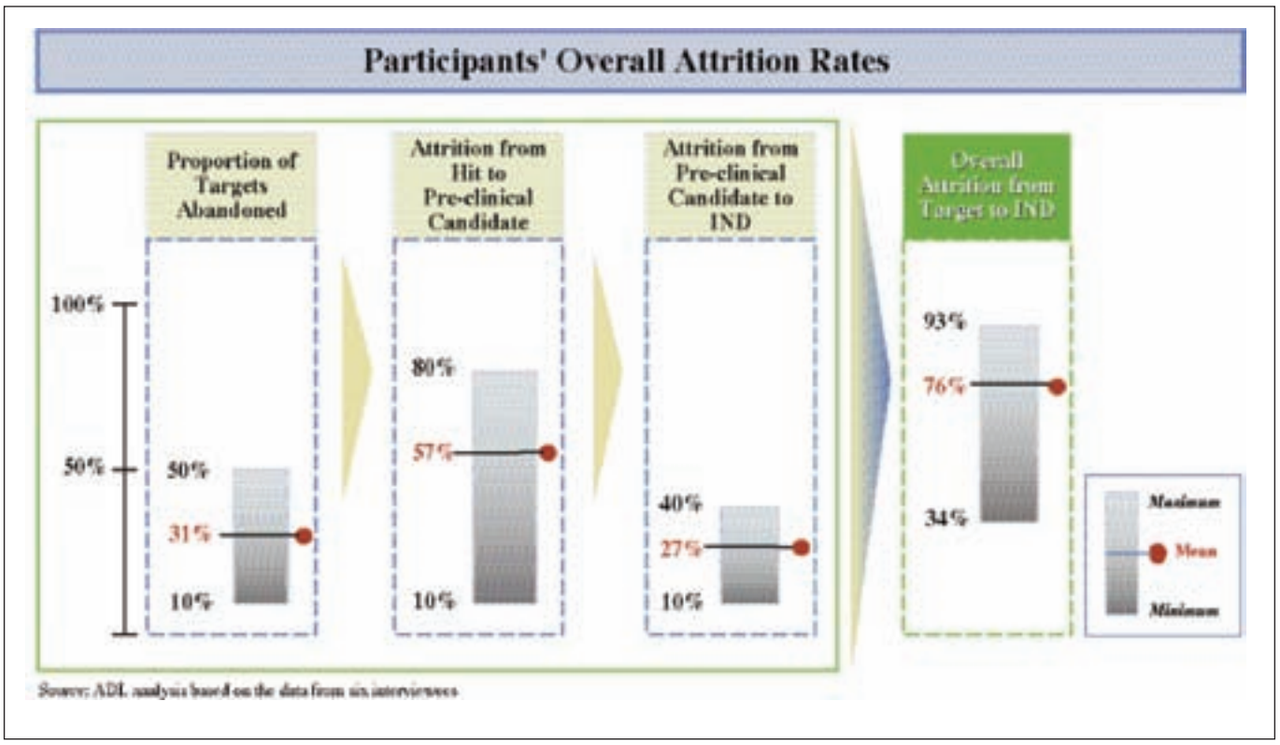


Figure 1

drug discovery companies during the late summer/fall of 2001. Participants included six of the top 10 US/European pharmaceutical companies, two of the top 10 Japanese pharmaceutical companies and one leading bio-pharmaceutical company.

We utilised a high performance business framework[3] to structure our benchmarking effort. Whether at the corporate, line-of-business, or business-function level, maximum productivity and performance are better achieved when critical business processes are designed to support the strategy, and when resources and organisation are effectively allocated and aligned.

Findings

Overall attrition rates for participants are shown in **Figure 1**. While the overall attrition rate from target to IND averaged 76%; the highest attrition rate was almost three times that of the lowest attrition rate. There was also notable variation around key milestones, with the widest variation in attrition occurring at the hit-to-preclinical candidate stage. This variation could be due to the differences in the criteria used to advance from one stage to another, as well as differences in business-model alignment. In fact, whether a high or low attrition rate is good or bad at this stage cannot be determined from the data collected in this study.

On average, 66% of the total leads generated were derived from combinatorial chemistry and high throughput screening (HTS), including traditional libraries, combined. As shown in **Figure 2**, combichem and HTS ranged from a low of 21% in the case of one company to a high of 100% for two other companies. On average, 9% of the leads were derived from external collaborations and only 4% from natural products – the main lead source throughout most of the twentieth century.

Strategies and tactics

When asked to identify their main tactics for improving lead finding and optimisation, the participating companies named early ADME/Tox studies[4], adoption of target family approaches and heavy emphasis on structural analyses. One respondent intended to "use IT tools, such as predictive models to incorporate ADME/Tox information early on". Another expressed a preference for a "chemicogenomics" approach as a pathway toward target families.

Most participants expect IT to improve productivity and have adopted an IT strategy that focuses on implementing portals with user-friendly interfaces to multiple databases. More than half the participating companies foresee important roles for computational chemistry/molecular modelling, virtual screening and predictive ADME/toxicology models. Seven of

the nine companies mentioned better IT tools as an important trend in medicinal chemistry.

No consensus was reached regarding the impact of genomics on drug discovery and the strategies adopted by participants to address the issue are notable in their differences. One group of respondents expects significant improvements to occur in target validation that will address the huge number of potential targets generated through genomics. Specifically, the respondents expected the pathway approach (eg, signal transduction pathway) and chemicogenomics to yield more high quality and 'tractable' targets. Other participants expect to rely more on external alliances to bring in series of lead compounds at the preclinical stage (ie, leads already optimised). All the participants agree that the challenges identified through genomics analyses should be addressed before lead optimisation. Of course, given that genomics is still in its early stages, its expected impact may not be realised for many years.

Processes

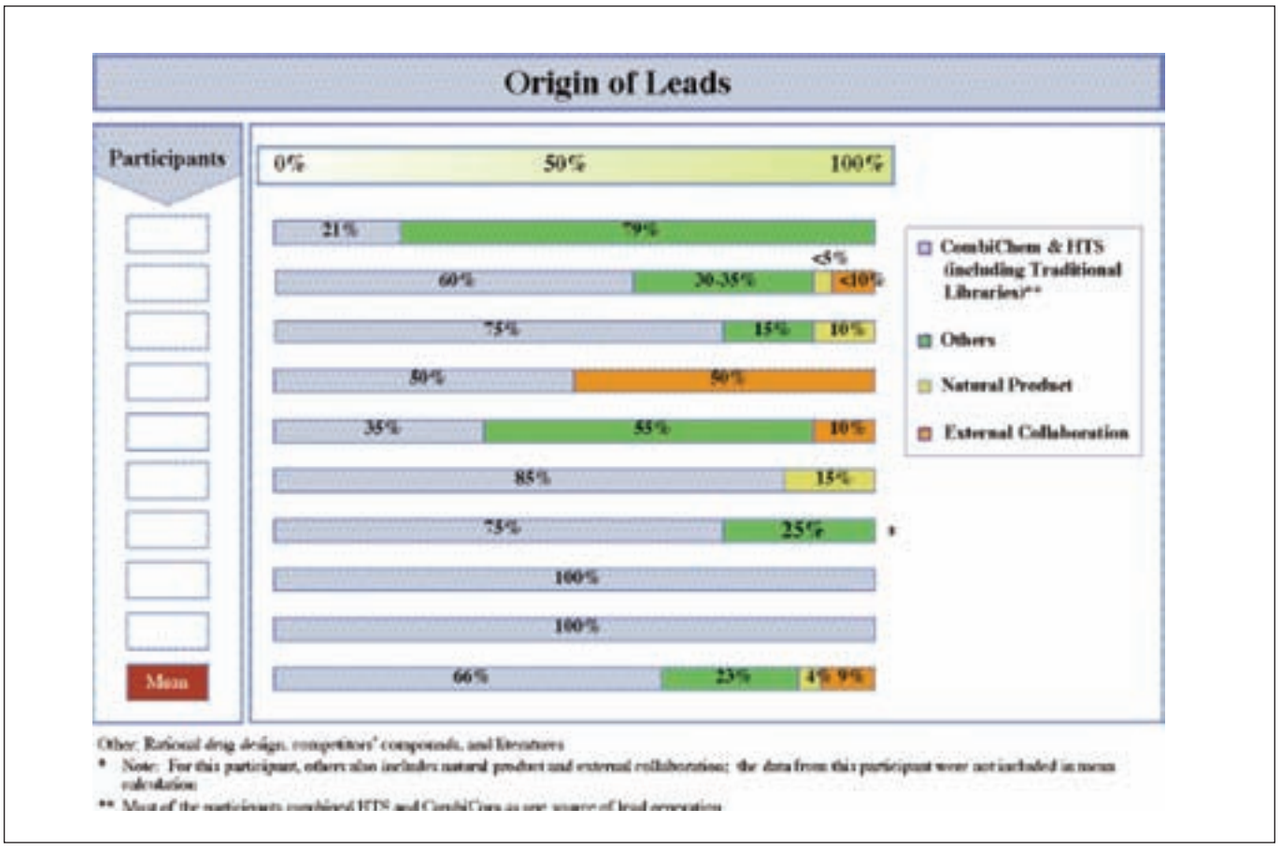
Most participants (seven out of nine) use the same milestones to identify the major steps in the R&D process. These milestones include: targets, hits, leads, preclinical candidates, IND/Phase I candidate, Phase II candidate, Phase III candidate and NDA. Two participants did not include 'hits' as a milestone in their processes.

The average cycle time for lead finding was 12 months; the average time for lead optimisation was 22 months. Only two participants use progress relative to elapsed time as a basis for stopping lead optimisation projects. More than half the companies noted lack of potency, ADME/Tox as criteria for terminating lead optimisation projects. Other commonly cited reasons for termination included: lack of progress, improper chemical and physical properties, invalid target and change in business or competitive environment. Most participants have cross-functional involvement in various discovery phases. To improve the quality of the early-stage compounds, most companies brought in medical and marketing groups to assess the compounds' economic impact and clinical relevance.

Resources

The average number of medicinal chemists per lead found is approximately three, while the average number for lead optimisation is approximately

Figure 2



Other: Rational drug design, competitors' compounds, and literatures

* Note: For this participant, others also includes natural product and external collaborations; the data from this participant were not included in mean calculation

** Most of the participants combined HTS and CombiChem as one source of lead generation

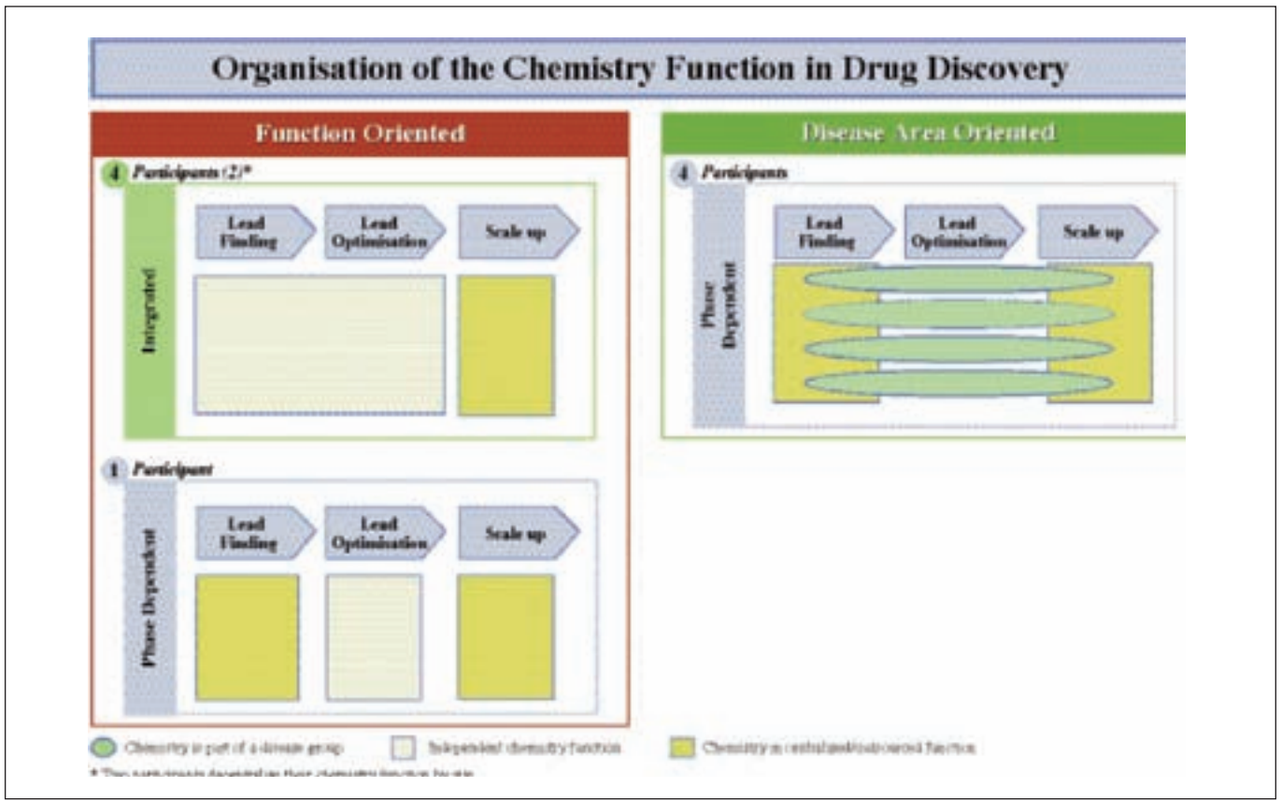


Figure 3

eight. Again, insufficient resources for ADME/Tox and lack of surrogate markers were cited as noteworthy bottlenecks in lead optimisation and selection of preclinical candidates.

All companies apply structural biology and computational chemistry capabilities to support hit/lead identification and lead optimisation. However, the companies differ in the degree of support provided by these capabilities. Two companies had notably higher support than the remaining seven. In describing the difficulty in measuring the impact of structural biology and combinatorial chemistry on lead optimisation, one respondent commented: "Both will have impact on lead optimisation… currently no methodology exists to measure the impact… but it may work by comparing average spans of lead optimisation projects."

Most companies acknowledged that predictive ADME/Tox is a key unmet need in medicinal chemistry. Toxicity and DMPK were noted as bottlenecks in lead optimisation and in the selection of compounds entering development. Lack of predictive toxicology is considered an obstacle to improving chemistry function productivity.

Three of the nine companies have kilogramme batch manufacturing capabilities within discovery. The other six maintain significantly smaller manufacturing capabilities within discovery and rely on manufacturing capabilities outside of discovery for batches greater than 100/150 grammes.

Organisation

Participants have adopted three kinds of organisational structures to conduct pharmaceutical research, as shown in **Figure 3**. Most have either a function-oriented or a disease area-oriented structure with scale-up usually performed in a separate organisation. Centralised lead finding groups are either accountable for generating hit/lead compounds or function as a service providers. All participants have centralised compound collections.

During the past 10 years, participants formed research alliances primarily in the areas of genomics, combichem and HTS. The principal strategic objectives of these alliances were to: enhance existing expertise, test new technologies, learn from partners as the technologies matured, fill internal gaps, bring new capabilities to the organisation and avoid the risks and high fixed costs associated with internal investments in unproven, novel technologies. Most companies employ a centralised group to organise and manage alliances. As expected, most companies

require different levels of management to approve the alliances, depending on the size of the investment.

Most companies have R&D sites with comprehensive capabilities and some specialised sites dedicated to key technologies, such as genomics. The participants have between three and 10 sites throughout the world. It is common for these companies to have two sites that are 16 time zones apart. The communication and work style/cultural challenges of working collaboratively across such large geographic areas are, of course, widely recognised.

The average ratio of PhDs to non-PhDs was 1:1.5 and the average PhD's experience was about 9.5 years. Most participants reported an average chemistry function staff turnover of 3.8% and have built, or are building, relationships with universities to enhance recruitment efforts and improve the retention of quality scientists.

The majority of study participants outsource activities equivalent to at least 5% and at most 25% of their chemistry budget. The highest levels of outsourcing are for items such as building blocks/chemical intermediates/bulk actives, for which six of the nine companies outsource 10% to 80% of their budgets. Six companies outsource libraries for lead identification, but only three of these use external sources for 20% or more of their chemistry budget. Six companies use external sources for chemical series for lead optimisation, with 20% being the highest level reported by any company. The level of outsourcing for libraries for lead identification and chemical series for lead optimisation is lower than for other functions in a pharmaceutical company. This suggests that these particular chemistry functions are considered core competencies and, therefore, internal to the organisation.

Discussion/Conclusions

Strategy & tactics: The jury is still out regarding the incremental value of genomics tools (as they currently exist) in the discovery process. There is clear agreement on the importance of IT to support discovery and manage data to improve the discovery process.

Processes: Cross-functional involvement is accepted as a way to improve outcomes. The companies that integrate chemistry across preclinical functions are more satisfied with the performance of discovery. Measures and milestones do differ among companies, as do the criteria used to terminate a project. The small sample size makes it difficult to draw conclusions about the relationship between these measures and performance.

Resources: There is agreement on some key technology bottlenecks. The lack of predictive ADME/toxicology technology and surrogate markers is both a barrier and a bottleneck to improving overall R&D productivity – a barrier because of the difficulty in predicting clinical relevance and a bottleneck because the high uncertainty may prevent projects from advancing more quickly. This investigation suggests that development of predictive toxicology screening methods (eg, assays to detect toxic responses) is likely to be readily adopted. Technologies that simulate biosystems *in silico* to enable predictive human ADME/Toxicology may be the 'silver bullets' in discovery, but are not likely to appear in the short term.

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