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# Widening bottlenecks in drug discovery: glimpses from Drug Discovery Technology Europe 2005

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The meeting was held 14–17 March in London and for the first time the *Drug Discovery Technology* conference was combined with the *InfoTech Pharma 2005* meeting, which emphasizes the overlap between the disciplines and the increased need for informatics and data management in the discovery phase.

**The changing face of drug discovery**

Phil McHale, Elsevier MDL, chairman for the first keynote lectures, gave an interesting perspective on how the focus of the DDT meetings has changed over time, moving from more general topics on discovery, technology and targets towards more applied subjects covering processes and applications. Newer topics, such as systems biology and biologics, are also emerging. Although new technologies have been introduced over the years to improve drug discovery processes, many of these are not living up to expectations. Alternatively, the solution of one problem introduces another bottleneck into the process. For example, the quality of chemical libraries, optimization of ultra-HTS assays, purification and analysis of high-throughput-synthesized libraries and ADMET predictions need to be improved – topics that were also addressed during the conference.

**Turning the declining productivity**

Keynote presentations by representatives from the regulatory field (Lumpkin) and industry (Ruffolo and Dolsten) posed a good frame for the meeting and tackled the decline in productivity in industry from slightly different angles. The total number of New Molecular Entities (NMEs) has declined despite increased R&D spending. Murray Lumpkin, Deputy Commissioner for International and Special Programmes at the FDA, discussed what regulatory agencies can do to assist the publicly perceived decreased innovativeness in industry. Lumpkin pointed out that the decline in productivity in industry is not due to either a lack of inventiveness or money, as an increasing number of sophisticated tools have been and are being developed. Rather, the failure to predict efficacy and safety is underpinning the depressing figure that only 20% of candidate drugs are entering clinical trials and of those in Phase III trials, only 50% make it to the market. The regulatory agencies are in a unique position of collecting knowledge from failures – information that rarely reaches the public domain. The aim of a recent FDA initiative called 'Critical Path' is to develop validated tools for efficacy, safety and quality to make product development more predictable and less costly – an area that has been outside the scope of academic research and funding. The initiative has been put down in a White paper and a Critical Path Opportunities List to outline the task more firmly is presently being finalized (http://www.fda.gov/oc/initiatives/criticalpath/whitepaper.html).

Robert R. Ruffolo, President R&D, Wyeth Pharmaceuticals, agreed with all statements made by Lumpkin and analyzed why industry is now perceived in a bad light by the public, despite enormous efforts in complying with regulatory requirements and providing improved therapies. However, the public debate is mainly discussing risk, without reflecting on the benefit side. Notably, drugs only contribute to about a tenth of the health care cost in the USA and 1–2% of Gross Domestic Product in OECD countries, so the negative image of the pharmaceutical industry is not really justified. The International Conference on Harmonization (ICH) efforts initiated several years ago have still not resulted in common international standards, which in combination with prolonged review times have increased the cost and delayed the delivery of new effective medicines to patients. Ruffolo argued that the loss in productivity is, to a large extent, driven by the numerous mergers and acquisitions (M&A), which have drained the combined pipelines considerably. Also, the success rates in all phases have declined, which to some extent is related to the research on more innovative targets associated with greater uncertainties [1]. Ruffolo went on to describe how Wyeth, to reverse this trend, sought inspiration from the business models of non-pharma companies,


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such as IBM. Consequently, Wyeth implemented considerable changes to accelerate the R&D programs. The target has been set to annually enter 12 compounds into early development (Phase 0), which, ultimately, should result in submission of two New Drug Applications (NDA) on new entities every year. A dramatic increase in productivity has, in fact, been gained by implementing performance management, and the target of 12 development candidates has been realized since 2001.

Mikael Dolsten, Head of Corporate Research, Boehringer Ingelheim, corroborated the comments on low success rates and long R&D timelines despite enormous scientific advancements. The observed shift in focus from classical compounds to biologics, such as recombinant therapeutic proteins, has been driven by the prospect of improved success rates in earlier phases due to the more generic nature of the products. However, the risk of failure of biologics in Phase III is higher, which is reflected by the uncertainty in target-related efficacy. Another point of reflection for out-licensing strategies for biotechs was the considerably higher incidence of late-stage failures in the areas of oncology and CNS. Dolsten argued for the use of parallel and target-oriented approaches to improve effectiveness compared to the traditional serial processes. He predicted that some of the technological advancements will probably only lead to incremental improvements, whereas other approaches, such as humanized animal models, high-throughput *in vivo* phenotyping, virtual screening of novel chemical space, therapeutic small interfering RNA (siRNA), predictive toxico-omics and oral delivery of biologics, would lead to radical improvements. Notably, Dolsten and Ruffolo could be seen as representatives of mid-sized 'big pharma' organisations, which might be argued to have the 'right' size to conduct effective research utilizing collaborations with external biotech partners to fill pipeline-gaps and access new technologies.

## Improving the tool box

High-density screening formats, such as1536- and 2080-well plates, demand significantly improved assay optimization protocols if advantages afforded by miniaturization are to be capitalized on. Lorenz Mayr from Novartis Pharmaceuticals presented an impressive platform of automated assay development using experimental design to reduce the number of experiments needed to explore the different conditions. This, in combination with robotics, allowed assays to be developed during the impressive timeframe of three days. Another innovative concept to filter out unspecific compounds in uHTS (1536-well format) was presented by Eckhard Bender from Bayer Healthcare. A target G-protein coupled receptor (GPCR) was expressed in a cell-line containing the endogenous P2Y2 receptor, which enabled the recording of the target response directly followed by measuring selectivity response using ATP stimuli. The solution for widening another bottleneck was given by Marcus Koppitz from Schering who indicated that the increased productivity in library synthesis, resulting in the production of >20,000 compounds annually, has triggered the need for fully automated purification and analysis processes to cope with over100 and 200 compounds per day, respectively.

The GPCRs or 7-transmembrane (7TM) receptors represent the largest family of drug targets, which justifies the continued interest to develop novel approaches to identify ligands. Applications of *in silico* approaches in the selection of libraries targeting GPCRs were outlined by several speakers. Modest von Korff, Actelion Pharmaceuticals, presented a successful classification of GPCR and non-GPCR ligands using fingerprints on carefully selected test sets of compounds. Self-organizing maps were used to provide effective illustrations of the distribution of compounds from commercial vendors and the in-house library to support the acquisition of the appropriate compounds. This led to significantly improved hit rates in the subsequent screening campaigns. A different angle was provided by Thomas Högberg from 7TM Pharma, who described the use of pharmacophore queries to extract small libraries targeting a specific GPCR receptor. These libraries have been used to generate novel chemotypes for several types of receptors. John Steele from AstraZeneca described the use of GPCR clustering in library design. He also outlined the enormous work that has been ongoing to transform the original HTS library to a library containing the desired starting points with minimal ADMET liabilities and suitable molecular properties. Enhancing the quality of internal libraries seems to be conducted at most companies after disappointing outcomes of many HTS campaigns. The jury is still out to see if the large libraries used for uHTS can be challenged with considerably smaller libraries biased for specific target classes or even specific targets. Obviously, the majority of the post-processing work after the screening campaigns can be avoided by improving the quality of the libraries in general and creating targeted libraries of smaller size. Another notable remark made by many big pharma representatives was the current drive towards incorporating more proprietary compounds in the libraries, which would, hopefully, avoid competitors identifying the same chemistries.

To provide chemical starting points that can be expanded in size and complexity easily, attention will most certainly be shifted to fragment-based approaches. Philip Dean, *de novo* Pharmaceuticals, outlined different *in silico* strategies for growth from seed fragments to explore structural alternatives. Harren Jhoti (Astex Technology) described the effective utilization of high-throughput X-ray crystallography that triggered their modification of the Lipinski 'rule of 5' into a rule of 3 (i.e. MW<300, HBD 3, HBA 3 and clogP 3) for attractive fragments [2]. This philosophy is in line with the ligand efficiency introduced by Kuntz [3], and extensively used by Pfizer, to ascertain that the chemical starting points allow for addition of chemical groups during optimization [4].

## Conclusion

Not only did the meeting provide concrete examples of how drug discovery processes have been improved to cope with current limitations, strategic and philosophical considerations were also discussed. With respect to novel technologies and concepts, it might still be worthwhile to reflect upon the track record of previous ones of which many were regarded as ultimate solutions when they were introduced, but reality often indicated a more modest benefit. It will be interesting to follow future topics on the meeting series to see when the predictions

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made by Dolsten concerning high impact technologies appear on the agenda. The productivity in pharmaceutical R&D clearly needs to be improved, without further increase in spending, so the mutual recognition of the problem by regulatory agencies and pharmaceutical industry lends some hope for the future.

**References**

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