

# Executive Summary

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This report, *Medicinal Chemistry for Drug Discovery: Significance of Recent Trends*, aims to review the state of the art and determine the significance of technology and market trends in medicinal chemistry for advancing productivity in drug discovery. Although the fundamental task of medicinal chemists has not changed drastically over time, the chemical and computational tools and perspectives at their disposal have advanced significantly. Whereas each of these modalities has left its mark on medicinal chemistry, and several have become common practice, one in particular, fragment-based drug design, stands out as promising major improvements in research productivity. A popular trend of a different nature, outsourcing medicinal chemistry to companies with operations in countries with developing economies, has yet to play out in terms of contribution to the cost-benefit equation.

We examine these and other trends in depth via extensive literature survey, formal and informal discussions with industry players, and an opinion survey of personnel active in medicinal chemistry for drug discovery. Following an account of the history and evolution of medicinal chemistry, the report turns to a critical evaluation of chemical and computational technological modalities. The next chapter considers commercial manifestations of these modalities, and the following one deals with market dynamics with an emphasis on outsourcing and user views on the implications of current practices in drug discovery organizations. After a conclusions chapter, the report provides a collection of complete transcripts of seven interviews with experts in the field.

## Evolution of Organic and Medicinal Chemistry in Pharma

Although much of the work done by medicinal chemists has not changed much over the years, the strategies and tactics employed have evolved considerably, driven by major changes in pharma's overall approach to drug discovery. Origins of medicinal chemistry in the 19<sup>th</sup> and 20<sup>th</sup> century focused first on natural products, then on dyes, and later on synthetic elaborations of natural products. Major advances in biochemistry during the 1930s and 1940s began to shift medicinal chemistry away from empiricism toward a more target-based approach involving enzymes and, starting in the late 1940s, cell receptors. The prevailing paradigm through the 1960s entailed synthesis of relatively few compounds for phenotypic evaluation in animal models.

The use of animal models limited the scope of accessible therapeutic indications. During the late 1970s, the emergence of genetic engineering began to broaden the scope of purified targets available for *in vitro* screening of drug candidates. The growth of high-throughput screening (HTS) fueled a new phase, which has been called the industrialization or commoditization of drug discovery. Capacity for increased throughput stimulated the need for larger compound libraries and the concomitant growth of combinatorial chemistry. Although combinatorial methodologies and early attempts at quantitative structure-activity relationships (QSAR) failed to yield the hoped-for revolution, they did stimulate new thinking, one of the fruits of which was the highly useful Lipinski Rule of Five describing the physicochemical characteristics of drug-likeness. This seminal observation placed the evolution of medicinal chemistry on a new track, which led to some cul-de-sacs along the way, but appears now to have generated a more productive paradigm.

## Organic and Medicinal Chemistry Technologies for Drug Discovery

Key topics considered include structure-based drug design, fragment-based drug design, natural products-based drug design, diversity-oriented synthesis, and chemogenomics. Medicinal chemistry has come to rely increasingly on support from various flavors of computer-aided drug design aided by rapid growth in the number and diversity of 3D target structures. Virtual screening as an aid to selecting compounds for screening campaigns is pervasive, if not universal. Structure-based drug design stemming from known 3D structures of targets, endogenous ligands, or both is becoming increasingly helpful, although they usually play supportive rather than decisive roles.

Fragment-based drug design appears to have great promise for improved productivity in drug discovery. During the past decade, the notion of screening smaller molecules than previously used started to evolve. The concept was slow to catch hold largely because these small, relatively featureless compounds tend to have low affinity for targets, often in the millimolar range, which brings into question the meaning of such results and highlights the difficulties in making measurements. Nonetheless, crystallographic and nuclear magnetic resonance (NMR) modalities have been shown to generate meaningful results, and as enthusiasm grew, so has the number of technologies applicable to fragment screening. A major advantage of fragment-based drug design is that much smaller libraries, often in the hundreds or low thousands, represent large scaffold diversity and can open the door to exploration of much larger segments of chemical space than can the massive compound libraries typically applied in HTS.

Several other modalities and approaches deriving from academia have so far proved more useful in a philosophical than a practical sense. One of these, diversity-oriented synthesis, uses sophisticated synthetic approaches to generating major scaffold diversity from relatively few starting materials. Its chemistry-related complexities would have justified greater emphasis on the approach if early attempts at it had generated any notable success stories. The difficulty appears to involve finding overlaps among islands in chemical space occupied by molecules synthetically accessible by diversity-oriented synthesis and other islands with sufficient lead-likeness to justify the effort.

Basic research efforts are moving in the direction of generating diversity libraries inspired by natural product structures, which are programmed by evolutionary forces for interaction with biological macromolecules. Pharmaceutical companies have recently tended to reduce or eliminate their natural products programs, leaving such research to a relatively few small commercial ventures. Despite their apparent advantages, natural products per se are difficult subjects for synthetic modification and interesting new leads tend to come infrequently. However, attempts are actively underway in pharma to consider natural products-likeness in drug design, and in academia to replace diversity-oriented synthesis with BIOS (biology-oriented synthesis).

Chemogenomics has entered the medicinal chemistry realm in an attempt to annotate chemical libraries with diverse information, notably on the interaction of compounds with diverse targets in various

biochemical and biological screening modalities. These efforts, while high in potential, are still in the formative stage and have yet to make a large perceived impact on the practice of medicinal chemistry.

### **Applications of Organic and Medicinal Chemistry in Drug Discovery**

Each of the aforementioned technological modalities is viewed in terms of practical examples and commercial activity. Outsourcing arises as a prominent theme in the applications realm, with special emphasis on companies with primary operations in countries with developing economies, notably China, India, and Russia. Among 32 companies considered, structure-based drug design is the most prevalent activity with most players emphasizing the fragment-based variation. Virtual screening is the second-most prevalent modality, whereas natural products, diversity-oriented synthesis, and chemogenomics appear in only a small minority of cases.

Outsourcing vendors are viewed according to participation in hit discovery, hit-to-lead synthesis, lead optimization, library synthesis, in-house drug discovery, and virtual drug design. More than one-third of the companies considered have operations primarily located in countries with emerging economies. A large majority of companies offer computer-based services, hit-to-lead, lead optimization, and library synthesis. Fewer engage in hit discovery, and a small minority do their own drug discovery.

### **Market Dynamics**

The report next examines deal activity and the influence of outsourcing on research productivity. Results from a survey of managers and researchers active in the field provide a multifaceted picture of practices and attitudes prevalent in drug discovery organizations today.

Intensification of efforts by drug discovery organizations in developed countries to lower research costs has led in recent years to a dramatic upsurge in outsourcing of medicinal chemistry activities, especially to India, China, and Russia. These countries not only offer cost savings, but the chemists involved are considered on average to be highly skilled and motivated. Of 27 outsourcing deals considered, more than half involve organizations with operations located primarily in nations with developing economies.

During the 1990s, much of the outsourcing activity practiced centered on compound synthesis. More recently, entire drug discovery programs are being outsourced to vendors contracted to deliver lead compounds for preclinical evaluation. Indeed, some deals move things even further down the pipeline. However, a significant minority of recent deals cover earlier-stage activities or are limited to lead optimization. Deal terms often moved well beyond classical fee-for-service models, with milestone payments and royalties appearing in a surprisingly significant minority of arrangements. Concerning the risks versus benefits of outsourcing to India and China, interviewees generally recognized the high quality of skills available, but cautioned that logistical and organizational issues may well circumvent some of the advantage.

Conclusions from the aforementioned survey of individuals active in medicinal chemistry for drug discovery include:

- Computer-aided drug design is rather firmly established as a useful modality with emphasis on structure-based design.
- Fragment-based drug design has yet to make a major impact on drug discovery, but expectations for the near-term future are quite positive. The modality has already played a significant role in getting compounds into preclinical development, but it is too early to judge the impact on getting them beyond Phase I clinical trials.
- Surprisingly, chemogenomics, which has minimal current influence on medicinal chemistry, is also viewed as having high potential for the medium-term future.
- Participants view the potential contributions of current technology trends as modestly evolutionary for medicinal chemistry productivity rather than revolutionary.
- Concerning medicinal chemistry budget outlays, respondents mainly reported stagnation or modest reductions for 2009, with a bit more optimism looking several years down the road.

