Faculty or Factory? Why Industrializing Drug Discovery Is Inevitable

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Preview

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INTRODUCTION

DURING THE PAST TWO DECADES, technological advances have revolutionized drug discovery. Automation, miniaturization, computerization, and giant leaps in biological know-how have spawned the development of high-throughput, parallel processes for synthesis and screening of compounds. Combinatorial chemistry is successfully addressing the scarcity of compound libraries. Large-scale, rapid sequencing methods and functional genomics are accelerating drug target identification and validation. HTS has emerged to wed the now plentiful compound collections and targets, ideally generating an abundance of "hits" and drug candidates, and giving birth to a renaissance in drug discovery and development.

However, this picturesque view of the drug discovery arena is lacking in both vision and depth and lacks an overall strategy to truly exploit the full potential of these technologies. The renaissance in drug discovery cannot occur until the whole—the product and the process—is complete and greater than the sum of its parts. This will require a restructuring of the process—an industrialization of drug discovery. It is necessary to change perspective, from the pursuit of intellectual endeavors, striving for ingenuity and innovation, to an emphasis on production and the supply of high-quality leads on a grand scale. A shift will be needed from the free-flowing, pioneering culture embodied in a research campus, to the highly structured and organizational culture of an industrial manufacturing facility.

This shift in focus from scientific insight to managerial foresight will ultimately set the stage for the creation of a "Drug Discovery Factory," a stand-alone facility that exemplifies the effective utilization of automation and the logistics-based mentality of a production-scale operation. The Drug Discovery Factory represents the inevitable "next step" in the implementation of high-throughput parallel processing in drug discovery.

Drug discovery has reached the point at which scientific breakthroughs, technological advances, and the automation of key processes are simply not enough to allow the pharmaceutical industry to accelerate the discovery of novel drug candidates. This goal demands a new paradigm, an integrated strategy that incorporates the broader principles of industrial automation and process engineering, plant-wide data management capabilities, and an organizational structure designed to maximize productivity while working hand-in-hand with the existing science base.

AUTOMATION AND BEYOND

Without question, automation and robotic technologies have dramatically changed the landscape of drug discovery, as they have revolutionized industrial development throughout much of the 20 century, from automobile manufacturing to silicon chip production. The same forces that drove these industries toward mass production and the creation of an assembly-line approach to product manufacturing are behind the implementation of automated systems in drug discovery: the demand for more and better quality products, increased throughput and consistency, wider user choice and flexibility and fewer product failures.

Automation has become essential for gaining and maintaining a competitive advantage; an advantage gauged more on the basis of product quality and innovation than simply on cost. In the pharmaceutical arena, that advantage translates into quickly bringing a drug to market that is either first-in-class or best-in-class. Pharmaceutical companies are under enormous stock market pressure to synthesize and screen novel synthetic and natural compounds at an ever-increasing pace, and to generate a steady stream of optimized hits and lead compounds that can flow into the company's preclinical and clinical development pipelines. A truly innovative and high-quality therapeutic compound can command a premium price and dominate the marketplace. As everyone knows, companies need to scale up their enterprise to produce new drugs faster.

As other industries have learned, scale-up is a linear phenomenon only to a certain point. At some point in the scale-up process, bigger (or smaller, if miniaturization is the goal) and faster no longer imply just "more of the same." Consider, for

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example, if you could trade in your family sedan for a Formula One racing car. Would you get to work any faster? Similarly, would installation of a high-speed modem into your computer necessarily increase your rate of data transmission? Not if the recipient of your transmission lacked at least the same sophistication in communications hardware and software. Unless the whole system can operate at the higher capacity, local speed gains are worthless.

At some point, the complexity of the entire process must increase to avoid simply shifting the bottleneck. The overall infrastructure must be optimized to allow the process and its components to achieve their full potential. Flexibility becomes increasingly important, because the system must be able to accommodate changes in the product or the process in response to technological advances, competitive pressures, or customer demand.

HTS is an excellent example of the way in which automation has advanced drug discovery, as well as of the inherent limitations of optimizing an individual component of a larger process. Take the automotive industry as an example once again, and look back to the 1930s when the introduction of the assembly line allowed Ford to scale-up production of its Model T. Over time, robots replaced human hands, and product volume, quality, and consistency increased. Automobile manufacturers and others poured billions of dollars into automation technology in order to gain a competitive edge. Quality, not cost, became the prime motivator. The competitive pressures became intense as new players, particularly the Japanese, demonstrated that manufacturing technology, combined with highly disciplined organizations, could provide low cost, high quality, and choice with frequent product upgrades.

But robotics alone is only a part of the solution, as the automotive industry came to realize. The initial design and engineering of the product and the process must also contribute to the flexibility, efficiency, and utility of the overall system. The system must be readily adaptable to manufacturing many different products, and to switching seamlessly from one production run to another. It must be able to accommodate continuous design and process changes.

The enormous growth in HTS has brought parallel processing and advanced automation technology to the pharmaceutical industry. Yet despite the widespread acceptance and apparent success of HTS technology, it alone cannot drive the scale-up of drug discovery. To realize its maximal capability, HTS has to be removed from the research setting and carried out instead in an industrial-scale manufacturing facility.

HTS has not yet demonstrated that it can reliably produce even a small proportion of the data flow and hits of which it is theoretically capable. That must change if pharmaceutical company executives are to justify to their shareholders the large capital outlays for HTS technology. The bottom line, and ultimate determinant of a pharmaceutical company's stock price, is the new product pipeline and the market revenues it can generate.

Discovery operations need to set and achieve ambitious goals: performing 100,000 assays per day, generating 1 million-compound libraries, and processing 4×10^9 cells/day, for example. They need to make the leap from a research-based entity governed by scientific dogma, to a production-scale plant that is managed by an omniscient, intrinsically logical, computerized control system. It is time to recognize that what works in the research setting might not be optimal in a production environment. At the projected levels of HTS process intensity, this is the only approach that can work.

Whereas innovation and scientific endeavor promote the use of cutting-edge technology, industrial practice often relies on the optimization and intensive use of proven technology. For example, although miniaturization has led to the development of microassays and high-density microplates, which saves money by reducing the volume of compounds and reagents, these are still often constrained by the logistics and surrounding infrastructure, so smaller doesn't necessarily equal quicker.

When viewed as an independent entity, a faster, higher capacity machine would no doubt be able to process more samples in less time. But it may offer little or no benefit to the productivity of the overall system. It will likely just shift the bottleneck to another part of the system, and have no impact on final yield. Furthermore, if the high-performance machine—which is likely replacing multiple, lower-capability units—is less reliable because of its increased complexity, the downtime for repairs will have greater financial consequences and could, at least temporarily, paralyze the entire system. Similarly, contamination or mishandling of a "batch" of assays has more serious implications as the batch size increases.

A realistic view of the potential impact of automating a process, such as drug discovery, must focus both on the real capability of each individual machine (versus its theoretical peak performance), and on the overall system capacity under real-world conditions. With respect to HTS, assay performance should be measured by the total time it takes to introduce and run a new assay and to generate and analyze the results, rather than by the potential throughput of the individual process modules. Put another way, it is the shortness of the iteration time in screening that is important, not the throughput.

THE DRUG DISCOVERY FACTORY

Automation should be viewed as much more than the implementation of robotics at the level of the process module. Automation of a process requires taking a global view of the process components, parameters, and desired outcomes, and integrating the hardware, software, and administrative functions at all levels of the process. This gives a strong emphasis to all the related people issues.

For drug discovery to reach the next performance level, each process module must be integrated into a factory-like setting in a facility that is both physically and philosophically separate from the research laboratory environment where computers design, simulate, monitor, and fine-tune the system, and technicians, not scientists, oversee the process; where the software synchronizes the entire process for maximum efficiency, performing inventory management and tracking functions, scheduling, data analysis, and management, and process and quality control operations. The facility needs to be functional, not fashionable.

The Drug Discovery Factory must shed and isolate itself from the unstructured, intellectually driven mentality of the research setting, and adopt the structured, logistics-based, and production-oriented culture of an industrial-scale operation. It should

be capable of performing any assay, new or old, on any target and compound at any time, with minimal downtime to change over to a new process or technology.

The function, performance, and reliability of the instrumentation should be predictable and unwavering. The machines must be capable of 24-h operation for weeks at a time, with planned offline time for maintenance and repairs.

The concept of a Drug Discovery Factory that is purposely isolated from scientific endeavors in no way demeans the research process. It is not antiscience. Rather it aims to optimize the intrinsic qualities and advantages of both the intellectual and the production elements of the drug discovery process. If this all seems a little too visionary and challenging, it is encouraging to report that a number of the industry HTS leaders have now independently reached the same conclusion. Construction and completion of these facilities is planned for 2000.

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