Biotechs as integrated drug R&D factories

'Large pharmaceutical companies like to work with one interface in drug discovery and development outsourcing models.'

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The year 2002 was another consecutive year of falling numbers of investigational new drug (IND) filings and new molecular entities (NMEs) approved by the Food and Drug Administration (FDA). NME approvals were down to 16 in 2002 from 24 in 2001 and 2000, and 35 in 1999 (see http://www.fda.gov). This seems surprising, in light of the flood of target candidates that have resulted from efforts in sequencing the human genome, functional genomics and improving the understanding of disease mechanisms, as well as the growing amount of money spent. Several reasons seem to negatively influence the industry's output. These include:

- The lack of proper target validation and functional understanding of the link between a target and a disease phenotype
- The ever-growing demand for drug efficiency, safety and lack of side effects
- The continuous restructuring within big pharma's research subsequent to mergers
- An ever-growing difficulty in managing and coordinating an R&D process that involves a large variety of out-sourcing or in-licensing partners
- The movement away from conventional pharmacological approaches to drug discovery.

To fulfil the expectations of the financial markets and the demand for ethical products for unmet medical needs, the industry certainly feels an urgent pressure to fill its pipelines with promising clinical candidates of relevant market potential. This process requires the help of outside partners with proven capabilities in drug discovery and a high probability of producing a deliverable in a currency the industry can use, for example, proprietary compounds with a proven concept of pharmacological action. Proof-of-concept might be attained using sophisticated biological model systems or, ultimately, by proving efficacy in humans in limited Phase IIa trials. The mere biotech specialist is definitely not equipped to cope with all of today's industry needs, even though such a company might offer a brilliant single piece of technology such as ultra HTS, a set of novel chemical structures, a specific animal model system or a certain target candidate.

Accordingly, the pharmaceutical industry is seeking ever more partnerships with biotech companies, which promise to deliver compounds on the basis of a well-organized and integrated drug discovery and development process. Although impressive in overall size, the financial structure of such deals has a back-loaded characteristic. Only those biotech partners in a position to manage the risk of failure and to reduce the attrition in the multi-step R&D process will be in a position to enhance the value of the biotech partnership without creating unacceptable risk for their shareholders.

If the currency that the industry accepts in the future were to be mere clinical candidates with 'pharmaceutical proof-of-concept', what would be the crucial building blocks that biotech would need to manage an industrialized discovery and development process? Looking from Evotec OAI's (http://www.evotecoai.com) point of view, the most probable factors of future success, in terms of interdisciplinary components at the interface of biology, chemistry and handling technology, process management and quality control, are pretty clear. Just a few powerful, energetic and innovative discovery companies that can provide service alliances and intermediary products will be able to fill pharma's pipelines and to support their growth according to their needs for output and speed. Some 'hardware' and 'software' elements with the required technical performance, speed and quality are already in place. These include libraries of synthetic or naturally occurring drug-like compounds, fully automated uHTS machines, high-capacity machinery for medicinal chemistry, assay technologies, cellular and animal test systems with conditionally activated genes, and the power of rapid good manufacturing practice (GMP) production of chemical candidates. Several supportive ADME–Tox technologies are being used not just to select and improve compounds for efficacy but also to identify negative side effects at an early stage of development.

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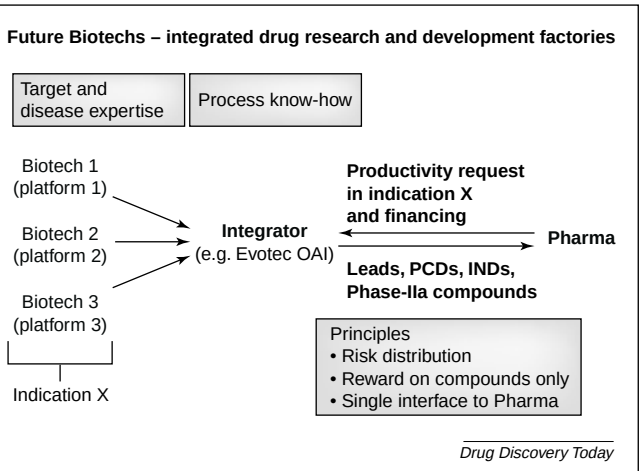

Figure 1. Future biotechs – integrated drug research and development factories.

Most importantly, the biotech company needs to form alliances with appropriate medical centers who work closely with patients – the final client. Integrating the patient as a partner from the beginning of the drug discovery process will provide essential data on the disease and thus facilitate drug R&D. We expect the early integration of multiple samples of patients of multi-ethnic origins to identify generic principles for drug action. This will contribute considerably towards avoiding cost-intensive personalized medicine and, hence, will enlarge the market for the resulting drugs.

Integrated drug discovery alliances involving target providers and drug discovery companies boil down the process of drug development from an industrialized approach with a lot of generality to an approach involving an in-depth understanding of disease mechanisms and the pharmacological actions of novel therapeutic compounds in humans. Obviously, big pharma needs a second interface in the alliance, the interface at which 'target-to-IND' process companies have appropriate access to patients, tissues and disease models for in-depth validation of target candidates as a basis to generate a drug. A fourth party could be the hospitals and Disease Centers of Excellence, which as public entities in Europe have political responsibilities for public health.

In recent years, innovative and hungry scientists and entrepreneurs have created hundreds of rapidly expanding companies focussing on a wealth of new targets – receptors or pathways – that are instrumental in disease treatment or pathogenesis. Rather than spending limited cash resources on building an expensive discovery infrastructure themselves, they need to team up with 'target-to-IND' process-oriented companies (see Fig. 1). All four parties in integrated drug R&D (i.e. big pharma, target providers, drug discovery company and Disease Centers of Excellence) are beginning to appreciate that speed to market, based on high-quality compounds and results, is the final value driver for all of them to realize market success under product protection.

The leaders in the market of strategic outsourcing seem to focus on three business opportunities:

(1) Driven by pharma companies' need to leverage their own research, pharma customer contracts continue to expand into integrated services from 'target-to-IND'. This trend leads to changing risk profiles with pharma deals becoming more results oriented. This evolution favors companies with the right critical mass. I expect pharma companies to focus on fewer biotech partners with whom they forge longer and bigger relationships, thus effectively establishing a first tier of suppliers.

(2) Many target discovery companies are unable to sustain their 'do-it-alone' model. They have forged important relationships with biotech companies, sometimes supported by venture capitalists who discourage their portfolio companies from spending their cash on building infrastructure that already exists elsewhere. There is also an opportunity to integrate targets from biotech companies into joint partnering programs with big pharma.

(3) The continuing short-term need for specialist assay development and high-quality medicinal chemistry services will continue to spur growth in out-sourcing services.

The biotech companies that will be among the best partners for strategic out-sourcing will be those that are based on a fully integrated and universal platform, have world-class scientists, critical mass, access to patients and the broadest portfolio of clients. These are the assets that will enable a company to continue on the track to success.

Finally, the few biotech companies and biotech alliances among the final winners will be those that:

- Can manage drug discovery and development as an industrialized process
- Spend a minimum of financial resources and time
- Integrate the patient, and his associated disease pattern, during all stages of development to control the risk of attrition maximally.

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