Outsourcing for innovation takes on new meaning

Large pharmaceutical companies are moving quickly to outsource their drug discovery operations, predominantly to lower costs. This article argues that if outsourcing is done to capture value, ie developing and preserving intellectual property as a key competitive differentiation as well as increasing productivity, then costs will fall in line accordingly.

By Richard Boehner

Innovative drugs are the lifeblood of pharmaceutical companies, but the cost of developing them is rising to unsustainable levels. Pharma executives are already saying that as the economy falters, they foresee bleak prospects and mergers unless their companies get more innovative drugs into their pipelines. The clock is ticking on the race to increase productivity, as key patents worth a projected $30 billion in revenue will expire between 2010 and 2013, opening the floodgates to competition from generics, according to Barbara Ryan, an analyst at Deutsch Bank. This imperative is propelling increased outsourcing of R&D operations as companies trim overcapacity[1].

Meanwhile, certain other trends are inexorably converging to raise the stakes:

- **Costs keep going up.** A 2001 study by Joseph DiMasi and colleagues at the Tufts Center for Drug Development calculated the tab for developing a new drug at $802 million in capitalised costs, compared to $231 million in 1987. A follow-on report in 2003 pegged the cost at $897 million, noting that only 21.5% of the candidates that enter phase I trials are eventually approved by the FDA. DiMasi explains that more drugs are targeted at chronic conditions and degenerative diseases, requiring larger and more exhaustive clinical trials.
- **More money spent results in fewer new drugs.** A 2004 FDA paper noted that NIH investment in basic research, and pharmaceutical and biotech investment in applied research went up 250% between 1993 and 2003, but the number of new molecular entities (NMEs) approved declined. A pharma company executive estimated the industry is now spending about $60 billion on R&D[2]. But in 2007, only 17 NMEs were approved, the lowest number since 2003[3].
- **Insurers only pay for real innovation.** Healthcare insurers are balking at paying for new drugs that do not show a clear benefit over existing treatments.
- **Increased development time translates to regulatory risk.** A new chemical entity took about eight years in the 1960s to get to a NDA (new drug application) but can take between 12 to 15 years today as the FDA raised the safety bar for drugs targeting chronic conditions. Longer lead times mean increased vulnerability to competition and shortened time for pharmas to capitalise on their discovery efforts.

METRICS	MICROSCALE, PARALLEL R&D	TRADITIONAL R&D
Methods and human resources	Optimised, automated workflows with advanced informatics controlled by a single scientist	Largely manual, trial-and-error processes requiring a team of scientists
Amount of experimental material	Milligrammes (mg)	Grammes (g)
Data acquisition and analysis	Minutes or hours	Hours or days
Experimental results	Days	Weeks or months
Experiments per year	10,000 to 25,000	500 to 1,000
Cost per experiment	$25 to $100	$500 to $1,000

Compared to traditional preclinical R&D methods, microscale, parallel experimentation technology delivers significant productivity improvements and lower costs

In the search for increased productivity on a tighter budget, global pharmaceutical companies are increasingly behaving like thrifty biotechs and outsourcing non-core discovery, development and manufacturing activities. Outsourcing is a time-honoured strategy used in several different industries, but the catch is, outsourcing solely to cut costs, while an appealing transitional tactic to meet quarterly numbers, is not sustainable. Pharma companies today are reducing discovery risk by collaborating with biotechs to discover early stage compounds, as well as by sponsoring basic research at universities or licensing compounds. Pharmas are also reducing R&D labour costs by laying-off skilled scientists as programmes close, either outsourcing jobs abroad (off-shoring), or establishing wholly-owned divisions in other countries where they can get US trained scientists at lower cost. But this strategy only is sustainable if salaries remain low over the long term. Moreover, there are inevitably hidden costs involved in communication and language barriers, cultural issues, chain of custody issues, and the risk of losing control over IP, especially when off-shoring. To be sustainable over the long term, outsourcing has to increase value and competitiveness. The primary strategic issue for pharma is how to develop and preserve intellectual property as a key competitive differentiator and outsource to increase productivity, not just reduce costs. If outsourcing is done to capture value, costs will fall in line as well.

To understand why, take a look at the experience of some other industries.

Microscale, parallel experimentation combined with advanced informatics can deliver directional information in near real time so that scientists can visualise and analyse results immediately, determine which compounds hold promise, and avoid dead ends

The semiconductor industry goes fabless

Pare away extraneous functions but mind your core expertise

The semiconductor industry is extremely innovation driven, and business cycles are volatile. Labour costs are not significant, but R&D and capital equipment are expensive. Semiconductor companies have a shorter product lifecycle than pharma. For example, the time span between one generation of Pentium chip and the next is at most five years. Worldwide semiconductor outsourcing services revenue is estimated at $47.4 billion in 2008, a 10.8% increase from 2007 revenue of $42.8 billion, according to Gartner, an analyst group. Gartner forecasts the semiconductor outsourcing services market will reach $66.8 billion in 2012.

In the 1990s, the concept of outsourcing chip manufacturing to foundries abroad became popular. This did not occur in a vacuum. Manufacturers such as National Semiconductor built semiconductor fabrication plants or fabs in Taiwan, but divested them in the late 1980s. The Taiwanese Government offered subsidies to keep the factories afloat. Companies such as Hewlett

Packard, Texas Instruments and Motorola realised that if they went fabless they could slash overhead considerably, as building and maintaining a modern fab costs north of $4 billion. They outsourced their manufacturing to the foundries, but kept their core expertise in chip design as well as certain profitable niche businesses like image sensors and analogue devices, in-house.

At this point, semiconductor companies may outsource sections of specialised R&D projects, such as designing devices on a nanometer scale. But they jealously guard circuit design IP. For example, the only difference between the chips of Texas Instruments and those of its rivals is design, because chips are all manufactured in the same foundries using identical integration and design rules.

Outsourcing for value led to a new model of doing business and gave a huge boost to the industry. The semiconductor companies were able to take advantage of specialised equipment and expertise as needed, so they could focus on their core technology, reducing costs in the process. The industry effectively split into two entities, one dealing with chip design and the other on development, integration and manufacturing. This type of outsourcing also generated new types of companies that focused purely on design innovation. Companies such as Saifun, which proclaims its mission to be the leading provider of IP for the non-volatile memory market or Galileo Technology, which develops chips and networks for cable and satellite communications, sprang up once foundries were established.

The medical device industry outsources everything but the kitchen sink

Compress product development by outsourcing non-core IP

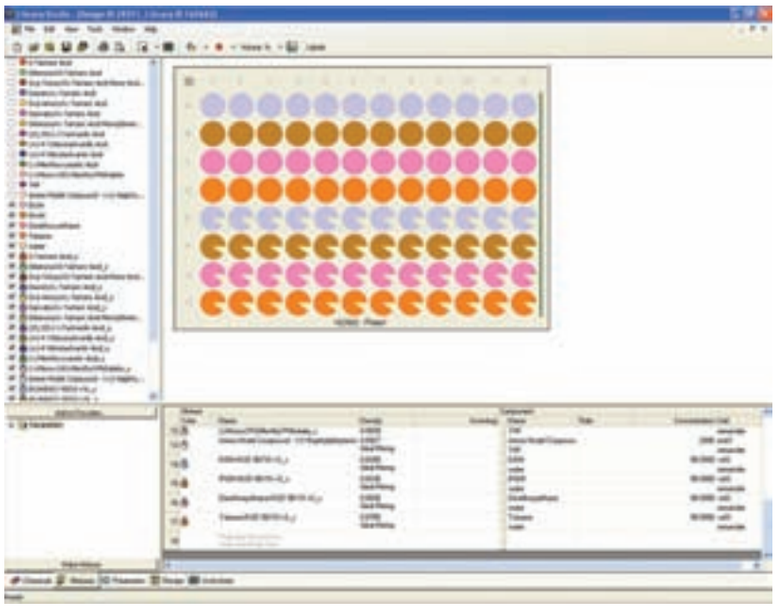
The medical device industry, on the other hand, comprises a few dozen large players and hundreds of smaller companies, and is valued globally at more than $300 billion. The top 25 companies generated $173.5 billion in product revenues in 2007[4].

Medical device manufacturers are innovation dependent, as product lifecycles are short. R&D is costly and advanced, incorporating complicated electronics, software and innovative materials. All materials and systems, while they need not be novel, have to be FDA compliant. Innovation is in the design and integration. Like the pharma industry, devices have a better chance of approval if

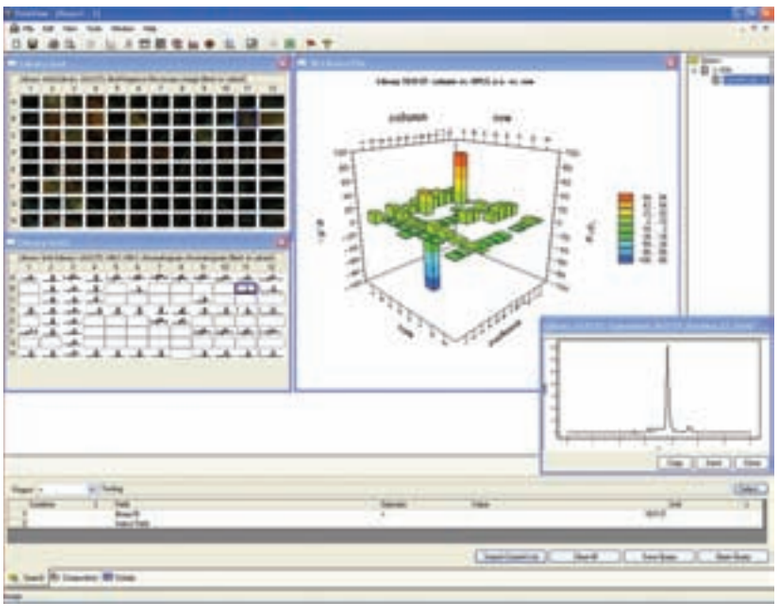
they offer significant or unique benefits over existing solutions.

Medical device manufacturers shorten the development cycle by outsourcing whatever they can, including prototyping, materials, electronics; virtually everything except for core IP. For example, a company such as Medtronic will not outsource the development of the algorithm that its pacemaker uses to monitor heart rhythm, but rather will set up a separate infrastructure for a one-time project that needs specialised expertise, or will contract with a CRO or a company such as DuPont to develop the biocompatible coating of a device. Medtronic might also outsource the prototyping or reliability testing according to given specs or enter a joint development project.

As regulatory approval and reimbursement by insurers is paramount, medical device companies tend to work backwards from what is needed for approval through stages of development. The pharma industry, however, doesn't have that option. Its level of uncertainty is even higher. For pharma, strategic outsourcing of early discovery work is the key to healthier pipelines.



Advanced informatics enable 1) fast and accurate statistical design of parallel experiments (top) and 2) comprehensive data-set analysis for directional information (bottom) in near real time



Back to pharma

Lesson: fail compounds early and often

In the pharma industry timing is everything. The later failures occur in the development process, the more costly they are. Half of compounds in development fail Phase III trials. In an average drug development cycle, according to Tufts, moving 5% of clinical failures from Phase III to Phase I cuts cost by $15-20 million.

Chorus, an experimental R&D venture established by Eli Lilly and Versant in 2001, is an interesting direction in strategy, operating on the assumption that only 10% of drug candidates make it to proof of concept. With the goal of managing early stage risk by shortening the time to decision points, Chorus attempts to fail drug candidates earlier in development, while agnostically generating more viable candidates. This autonomous group of a few dozen experts focuses on developing IP and outsources all experimentation possible. At this point, Chorus scientists assert that they can slice 12 to 18 months off the time estimated for certain drugs to reach proof of concept. But the jury is still out. Removing risk in the pipeline is correlated – but not directly linked to the endpoint of getting more candidates approved.

Outsourcing to increase productivity

Reuters Business Insights estimated that less than 15% of drug preclinical operations are outsourced. And most labs still operate manually and serially with a team of scientists using trial and error processes. Most CROs use the same manual, serial, trial and error approach, they just employ cheaper labour. The logical step forward in pharmaceutical outsourcing for preclinical R&D is to partner with contract research organisations that use microscale, parallel experimentation technology that combines automation with

Microscale, parallel experimentation technology enables a single scientist using milligrammes of expensive, early-development material to rapidly explore a broad experimental space and develop comprehensive data sets and direction information in days, rather than weeks or months

advanced informatics. The benefits and advantages of this approach, compared to traditional preclinical R&D techniques, are three-fold. 1) Automated parallel experimentation speeds preclinical research by integrating sample preparation, processing and analysis which enables a single scientist to deliver hundreds of experimental results in days, rather than weeks or months. 2) Advanced informatics enables predicting outcomes earlier and gives directional analysis to accelerate preclinical development. 3) Microscale experimentation uses much less (typically milligrammes versus grammes) expensive, early-development material, allowing more experiments earlier and at less cost.

Outsourcing using automation enables shortening the path to viable IP, because it is possible to explore different scenarios, running hundreds or even thousands of experiments in parallel, while receiving economies of scale on a per experiment basis. Automation can streamline a diverse array of workflow tasks, including solubility profiling, polymorph and salt selection, liquid formulations, forced degradation, excipient compatibility, biocatalysis and process optimisation.

New automation systems can improve experiment throughput 10 to 100-fold while eliminating costly, labour-intensive and rote work. Microscale, parallel experimentation technologies now make it possible to run up to 25,000 experiments a year, compared to a human scientist who can conduct about 500 experiments a year.

A system should also accommodate several different analysis methods as well as link to third party hardware. This enables the broadening of experiments without increasing cycle time. An automated system can improve safety as well, as it can precisely and accurately dispense powders and solids while protecting workers from exposure to biological and toxic chemical hazards.

It is not only what you know but how fast you know it

A critical business performance lever is the ability to acquire and manipulate information from data sets. Informatics can improve data visualisation and analysis as large sets of comprehensive data delivered in days, not weeks, can provide directional information and shorten the discovery path. Receiving real time directional information using multivariate data and integrating analysis into operations enables assessing which compounds hold promise, and which are dead ends. Flexibility

References

1 http://blogs.wsj.com/health/2008/11/25/the-clock-is-ticking-on-another-big-pharma-merger/trackback/. Note: the direct source is a report by Barbara Ryan, analyst at Deutsch Bank, released November 2008.

2 www.businessweek.com/magazine/content/08_45/b4107044232450.htm.

3 www.fiercebiotech.com/special-reports/2007-fda-approvals.

4 www.devicelink.com/mx/archive/08/05/news1.html.

Rules of engagement

Outsourcing for strategic advantage requires rigorous planning and partnership based on close communication and co-operation. To achieve the best results with a CRO:

- Be specific about goals, timelines, and responsibilities.
- Audit the CRO for qualifications, strengths, data and time management, and stability.
- Require case study references that demonstrate sustainable value through increased productivity and reduced costs.
- Look for experimental results that are delivered in near real-time as actionable, directional information so you can predict outcomes earlier and accelerate preclinical development.
- Set up framework for communication, as outsourcing adds a layer of steps. Assign a point person or team to work with the CRO. Have an expert retained in-house to supervise progress.
- Set up a legal framework for IP ownership and non-disclosure. Establish competitive nature of material up front; it is essential to sign contracts that explicitly protect IP.
- While core IP is held closely, a major worry with outsourcing is the chain of custody of sample data and results, there are ways to outsource sections out of context.

in prioritising experiments enables pursuing promising directions that may shift in importance. Moreover, it is easier to work with, analyse and share digital rather than handwritten data. A contract research organisation should collaborate to set standard protocols for investigating and transforming data, to incorporate data neutral formats into existing software systems, and standardise ontologies for characterising data.

Judging by current economic trends it is almost certain companies will be required to do more with less. It is a critical time for pharma, but outsourcing using new technologies offers the opportunity to reinvent the R&D process to make it more productive. Just as in the semiconductor and medical device industry, the next wave of outsourcing should be focused on freeing up internal resources to generate innovation. Microscale, parallel experimentation and sophisticated informatics enable better control over IP. Using technology to replace rote tasks and advanced bioinformatics to analyse data protects core technology development by keeping closer control and protecting IP confidentiality. At the end of the day, drug discovery remains a numbers game. But outsourcing to generate more viable preclinical compounds and receiving more directional information about them early on can shorten the path to a fuller, more promising pipeline. DDW

Richard Boehner is the President of Symyx Technologies High Productivity Research business unit. He joined Symyx in 2007 to lead the application of its microscale, parallel experimentation and advanced informatics technology for large and small molecule contract research services. Previously he served in corporate development and strategic planning roles at Sun Chemical Corporation, MacDermid Incorporated, Great Lakes Chemical and Allied Signal. Mr Boehner has a BS and an MBA from Colorado State University.