Fine Chemicals Revisited

Despite enormous changes that have taken place during the past few years, finding a supplier who is committed to the pharmaceutical industry is more important than ever.

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THE WOES of the fine chemicals industry can be traced to 1999 when Deutsche Bank Alex. Brown issued a report entitled "Pharmaceutical Contract Manufacturing." The document was the catalyst that caused the pharma fine chemicals sector to take a view that they were part and parcel of the irrational exuberance of that time. Within months, the kind of prices public companies were paying for acquisitions made seasoned observers wonder if the acquirers lived on a different planet!

A year later I made a presentation to financial analysts at a UBS Warburg's Life Sciences Conference. At the time, two suppliers had recently made key decisions regarding their pharmaceutical businesses that completely opposed each other. While one was expanding its presence in contract research and manufacturing via a $545 million acquisition, the other was exiting the pharma fine chemicals business, insisting that pharmaceutical chemical manufacturing is "a highly capital-intensive business plagued by over-capacity, clinical trial failures, limited new drug approvals, new drug marketing disappointments and price wars..."

The presentation proceeded to show that public companies were at a special disadvantage in our segment because shareholders who were unaware and uncommitted to the sector would not have the patience to wait for results. Five years later is a good time to take stock of all that has occurred and to see if the market gives us insights.

Misinterpreting the Market?

Unlike other sectors, the chemical industry is able to manufacture a very wide range of products. Faced with this amazing power, business people need an extra dose of humility when they put shareholders' money into making chemicals because business mistakes can be awesome. Fine chemicals firms tend to specialize. Often, their DNA—i.e., their past, the products they manufacture, the customers that know the firms, the technologies they have demonstrated competences in and the regulations they are able to comply with—define their market. Although strategic changes do happen, it is usually a slow evolution, hardly ever a revolution. What happened to the fine chemicals' bubble in 2000 was that companies new to the sector insisted that their knowledge of chemistry and of the chemical industry made them uniquely qualified to move in and take over the growing pharmaceutical outsourcing market.

Fueled by statements such as "by our estimates, the fine chemical/pharmaceutical contract manufacturing organization (CMO) industry will grow in excess of 15% per year over the next five years," it became common to hear the new entrants touting "we have aggressive goals [to build a] $500 million division within 3-5 years."

In fact, from 2002 to 2004, the combined pharma sales of seven significant fine chemical giants averaged a 14% decline. Even very successful firms faced an interruption in their usual stellar performance with declining sales from withdrawn products, slashed contracts and reversals of outsourcing strategies. Yet one segment of the outsourcing business did grow. Despite the front-page stories of insourcing by Big Pharma, the shortage of new approvals, etc., some firms did expand their offering to include an outsourcing business.

The surprise is that those that made big bets on that growth did not get business anywhere in proportion with their investments. Traditional small API companies did get the business because they had:

- Track records in the sector;
- Available capacity;
- Demonstrated competencies; and
- Management that focused on serving customers well.

The beneficiaries of the outsourcing business were mostly private and European companies with a tradition in pharma chemicals and having FDA compliance expertise built upon decades of making generic APIs for the U.S. market. These were European companies who were pushed into the outsourcing business in the late 1990s by a number of factors, including:

- The Asian threat was becoming tough in the commodity-like generic APIs;
- The service intensive outsourcing business was growing; and
- European legislation (such as the SPC) was killing all avenues of product development for French and Italian generic API firms.

The European independents realized that innovation was shifting to the biotech sector, and that this represented an interesting market opportunity they could easily enter. They were ready to take a risk (something they learned in the generic business); they were also flexible and service-oriented. Traditional CMOs did not consider this a winning formula.

The established players were too well entrenched in Big Pharma's "preferred suppliers list" to be dislodged and replaced. They showed little interest in the small development stage company that seemed a comparatively risky proposition.

Traditional CMOs also demonstrated a disconnect with the biotech sector because they had little experience with APIs. Big Pharma's manufacturing strategy is set on fiscally efficient manufacturing strategies, which drives an outsourcing strategy almost always focused on tolling intermediates.

The small molecule biotech sector needed to outsource its APIs to experts, to firms with a demonstrated track record at the FDA and they found them in Europe. The chemical giants may have on occasion purchased the right factories, but they also bought old and under-invested factories or factories never designed to be multi-purpose, flexible or lean.

The independent CMO must build for an uncertain product portfolio, which explains why they have no option but to excel in speed, flexibility, lean manufacturing and efficiency. The chemical giant did not always pick the right asset and usually paid too much for it. When the downturn came, it took many decisions that further handicapped the outcome of the CMO strategy:

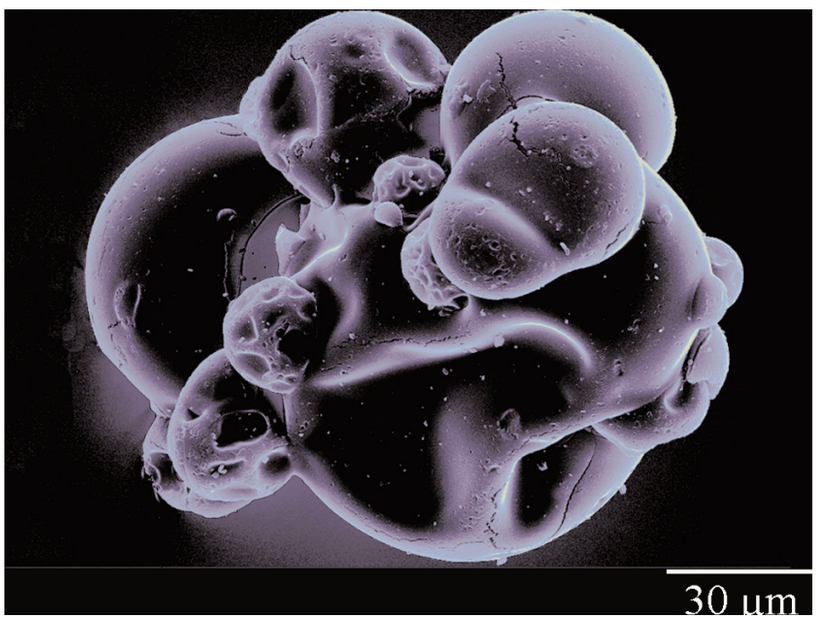
- It focused on manufacturing and ignored the service component;
- It imposed unrealistic sales budgets, cut head count and stopped investing.

When the sales quota becomes too tough, plants become occupied with the wrong projects. When headcount reduction measures are taken, often some of the first to go are maintenance, quality and compliance personnel. When you combine reduced quality resources with an investment freeze, you will soon be out of compliance.

When goodwill started to be written off and the red ink appeared, the future and long-term commitment of the new entrants to pharmaceutical active ingredients became a risk factor. Are Big Pharma companies going to give business to firms with a junk-bond rating? In fact, many purchasing agents from Big Pharma did take advantage of the very aggressive pricing big chemical firms were offering to stem the red numbers. Unfortunately, they only got the uninteresting, one-off business, which had no likelihood of continuity.

The real opportunities, the promising Phase II compounds, went to those companies with an unquestioned commitment to pharma fine chemicals. They will still be around in the next 10 years, just as committed as they have been in the past 20 or even 40 years. The consequences of the "perfect storm" in the pharmaceutical fine chemicals market are not limited to the destruction of shareholder value. This is an industry that, rather than getting itself ready and fit for globalization, chose to weaken itself by making billion-dollar mistakes. It is sad to see great brands and great plants, built by some great people, slowly disappear. Raylo, Torcan, Hexachimie, Finorga,

A large agglomerate obtained via spray-drying.



Making APIs, supporting development and addressing commercialization surprises is for committed firms.

Laporte, Hickson and Gist-Brocades are some of the names fondly remembered.

Where Are We Now?

Where are we now in terms of opportunities for the pharmaceutical CMO? The number of drugs under development has never been greater, and the amount of development funding is at an all-time high. Much of the growth is coming from the biotech sector and may, in part, be based on compounds that Big Pharma would have "terminated" earlier. Is there a historical downward trend of weakening of R&D productivity? Are marketing departments so addicted to blockbusters that good compounds get cancelled for no good clinical reason? Or are we in the down phase of a cycle triggered by too many distracting events such as mergers or Hillary Clinton-type health reform.

Although the answers are not clear, the opportunities are evident: Big Pharma has probably by now realized they would rather "buy than make" for a number of reasons:

• First, they have great difficulty building plants that are low cost, efficient, lean, flexible and compliant-like specialists do–because the project manager usually needs to satisfy five or six different vice presidents that all want their different requirements met. The rule becomes the highest common denominator, so one often hears of plants being described as "gold-plated" because nobody wanted to take a risk or had the power to say "enough."

• They won't take a risk to invest in capital items before the drug is approved, as the risk is too high. However when the drug is approved, it is probably too late to start building.

• Few, if any, have the product flow to level the peaks and troughs of capacity utilization at pilot and manufacturing scale. Having said that, unless the CMO can provide a manufacturing location that is tax efficient, the tax savings that Big Pharma obtains through the use of Singapore, Ireland or Puerto Rico are so significant that the CMOs' added production efficiencies are immaterial.

About the Author

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Highly Sophisticated Products

However, what will probably drive Big Pharma to outsourcing is the challenge and liability that API operations themselves represent. In the past five years there has been a significant increase in the complexity and sophistication along two key areas: compliance and technology.

For example, regarding regulatory compliance, there has been a long list of seizures, consent decrees and some surprisingly heavy sanctions, including fines of $500 million and lost business in the billions. In many instances the problems have been brewing for years, and the only justification for not addressing them can be linked to "the numbers game;" i.e., the pressure to reduce headcount, the importance of good quarterly numbers, the drive to improve performance indicators and even to meet bonus criteria.

Failure to comply can lead to very large fines, production stoppages and product recalls. Health, safety and environment concerns reveal potential liabilities that correlate unfavorably with the high margin and the very high public profiles that Big Pharma has with consumers. This is a good reason why chemistry should not be on the books of pharma companies.

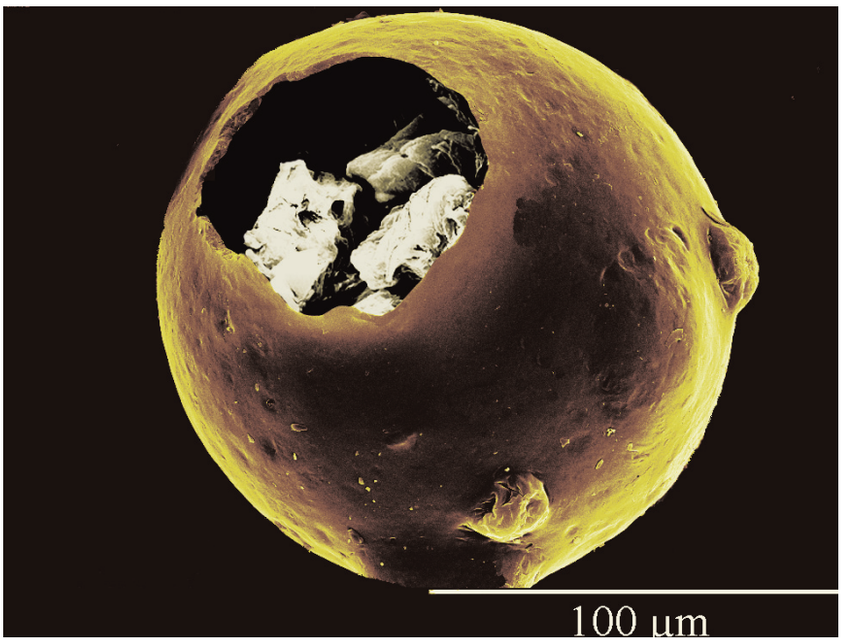
In addition, very often new compounds have unforgiving chemistries. Executing these sensitive processes require a depth of skill and plant sophistication not widely available. This requires expertise in preparing and executing proven acceptable-range studies. And, when the tight safe parameter ranges are defined, executing large-scale batches demands powerful engineering solutions supported by validated automation.

Furthermore, process technologies demand a multi-disciplinary approach. New APIs often require an array of capabilities often not found on a single campus. Increased technical complexity along several dimensions is a major challenge when success demands solving a tough scientific assignment quickly, reliably and in compliance. Inter-disciplinary teamwork is better achieved in small, focused organizations.

FDA expects control to be on-line and to rely increasingly on Process Analytical Technologies (PAT). This has seen much success in the formulation world, and we have seen excellent results in its use to control synthetic chemistry processes. This is a disruptive technology to be used in an environment that must meet the scruti-

ny of regulators. Large organizations will have a tough time making it happen. Specialists can see the benefit and they will know how to implement the changes, meet the criteria and reap the benefits more quickly.

The few examples provided here are not very different from the arguments put forward in the 1999 Deutsche Bank report. The case for the pharmaceutical CMO remains—current needs must be filled by the European independents from Phase II to commercial phase. The pre-Phase II needs have caused the emergence in the continental U.S. of a large number of operators that benefit from the proximity and culture factor. Will this trend continue? It all depends on the ability of the successful companies to listen to the market and to constantly re-invent themselves.



A microencapsulated API obtained by spray-drying.

Asia: Threat and Opportunity

Asia is a serious competitor, and worse than ignoring it is to continue to make sweeping generalizations about the Indians and Chinese. The successful European companies understand that they must be in the continental U.S. to be close to the client, the science and FDA. Furthermore, they have developed an intimate understanding of China and India and have integrated these low-cost producers into their value proposition—far from dismissing them as low quality.

It takes years to get on anyone's "preferred supplier list." You only get on because of a one-time event (such as a new technology or a competitor messed up) or growth (more products, more demand). Price plays a role, but in view of the small percentage that the API represents in the direct costs of the drug product, comfort and peace of mind are important drivers in the supply-chain decision. Locating production in a newly-developed country opens up liability concerns, not necessarily as a result of an individual plant being out of compliance or pollution issues, but because of proximity to chemical companies that have lower standards. Since Bhopal, the world has changed considerably and today, more than ever, large pharmaceutical companies are acutely concerned with their public image. An isocyanate leak will cause major PR damage, hurt share price and trigger lawsuits. Large pharmaceutical companies want to benefit from low-cost production but will insist that such advantages be ring-fenced by other credible and deep-pocketed firms acting as master contractors with multi-level HSE audits and continuous improvement programs. It is up to the incumbents to take up the challenge.

The EU Commission continues to handcuff the European fine chemicals industry with regulations, so business reacts by de-localizing. As the fine chemicals industry booms in China and India, accidents happen: In Europe compliant firms lie idle but in Asia, those with poor standards succeed. *The New York Times* published an article on Nov. 5, 2003 that has surely circulated in many U.S. boardroom (*you can also find it on www.gmpapi.migg.com)*.

It pointed out how a U.S. multinational and many generic firms used API products made at a Chinese manufacturer (that had multiple FDA DMFs and dozens of certificates of suitability issued by a European agency), a plant where fatalities seem to occur routinely. The outlook for the European fine chemical producers is therefore looking more favorable. The recent slump has led the listed companies to cut investment, curtail headcount and focus only on the closing quarter's results. The committed independents will come out ahead for a variety of reasons, especially because they have no alternatives to invest in or other businesses to run.

During the past few years it has become clear that making APIs, reliably supporting the drug development process and successfully addressing commercialization surprises is a job for the committed, focused specialist firm. Freedom from short-term pressures, commitment to drug approval success and dedication to service are the hallmarks of the European independents that for more than half a century have provided the API for most of the medicines found in U.S. pharmacies. ■