THE API SOLUTION PROVIDER

by G. Villax, Hovione SA

The Ford Motor Company used to ship coal to smelt steel for its own car production lines. The latest car factory, the Mercedes-Swatch plant near Lyon, was designed by its component suppliers. Less than 10 years ago IBM was the world's most valuable company, it did everything needed in the industry from designing its chips to distributing its computers: a paradigm of vertical integration. When IBM resorted to outsourcing for its Personal Computer project it created a new industry. Microsoft, making nothing but software, is now the most valuable company worldwide and a direct consequence of IBM's outsourcing policy.

Can there be lessons for the pharma industry? What impact does outsourcing of APIs[1] have on the shape of the pharma industry in 5-10 years?

The Hillary Clinton health reform package awoke the pharma industry from a long period of highly profitable lethargy. The "age of discovery"[2] when serendipity was golden and new products plentiful, was followed by one of "squeeze" and short term focus on the bottom-line. Fueled by the opportunity of merging or acquiring (lest you be acquired yourself), we entered the "age of efficiency"[2]. Downsizing, re-engineering, head-count reduction and outsourcing characterizes this time of incremental benefits.

Whilst the Large Pharma (the discovery based multi-billion multi-national companies) were hard at work transforming themselves into more competitive and more profitable corporations; a new company model was emerging: The Small Pharma[3].

The combination of venture capital, technology and outsourcing have spun off this new form of pharma company. The US Biotech sector[4] has a stock market capitalization of twice the value of Merck & Co, an R&D budget that is triple the value and has 220 compounds in advanced stages of development versus Merck's eight [5]. These companies may actually employ several hundred staff – but as virtual companies they will not own manufacturing facilities. Investment is reserved exclusively for those assets that serve discovery or are necessary for the key competencies of the company or its technology platform. The virtual company will own the invention and will manage the project, the rest is bought in. Without resorting to outsourcing, Small Pharma could not exist.

Small Pharma buys deliverables, not overheads

Outsourcing *per se* is not new in the pharmaceutical industry. Companies such as DuPont-Merck and Wyeth chose not to own synthesis plants and relied primarily on Lonza, the classic role model of the Custom Synthesis business. The real innovation that enables the Small Pharma is their unique approach to contracting out. They outsource not with a view to meeting peaks of demand or to compress costs but seeking to buy in complete solutions in fields/skills the company chooses not to be competent in. It buys deliverables, not overheads.

It is interesting to compare the different approaches taken by the Large and Small Pharma on APIs. The former used to do their chemistry 100% in-house and have now started to experiment with contracting out; but seem to have "fatherly frustrations and won't let go"… Relinquishing control of such activities seems "contra natura" in these organizations. Both Glaxo and SB have developed their own models for outsourcing; but essentially the aim is to buy capacity and look for a good balance between "risk/quality" and "$/kilo". Time is not the critical factor. The Large Pharma is also selling their plants to contractors and bundling the financial terms with a supply agreement to assure continued supply of products for the next few years[6]. This is very much part of the search for incremental benefits (less capital tied up in plant, variable instead of fixed costs), and the trend towards being a life-sciences company (leaving behind chemistry, its expensive plants and its not-so-green image).

For the Small Pharma it is not a question of mere "incremental benefits", these companies have no option but to outsource totally: from the first grams for early screening tests, to the DMF batches, through route selection and scale-up.

On reviewing this sector financial analysts conclude that "of more than 500 products in development […], 150 have moved to advanced stages of clinical trials"[7]. This begs the question as to who will synthesize the APIs, and with what level of success?

Growth is everywhere, and so are promises

The contracting out of APIs is not an easy skill. The pitfalls are considerable, and many managers have been bruised: labs that fail to deliver as promised, poorly written specifications that become time bombs, filed processes which cannot scale… So much so, that a whole industry of training courses and conferences has emerged, seeking to train managers on issues such as auditing suppliers, technology transfer, writing contracts, surviving an FDA inspection, etc…

On the other hand, many companies have sprung up claiming to be a "one-stop-shop" solving all problems under the sun: process chemistry, kilo-lab work, pilot-plant and commercial quantities' to your heart's content. One needs only to go to Informex[8] and be amazed: growth is everywhere, and so are promises.

On closer analysis, all capable suppliers are indeed growing, showing good profits and becoming short of capacity. There is considerable consolidation (the acquisitive Cambrex group; the merger of the two Dutch giants: DSM & Gist), and less-fine chemical companies are working hard to migrate to GMP API manufacture (e.g. Rhodia). Companies such as Zeneca LifeSciences Molecules have re-vamped older installations originally used for other purposes. Well-known traders are now turning themselves into producers and offer synthesis services. Others are on the fence looking to acquire plants, some buy for large amounts of money: see the recent Opos, Archimica and Hexachimie deals. The market should not be surprised if Ciba Speciality Chemicals were to join forces with Lonza. Oread in the USA advertises a structure modeled on the large pharma and aims to supply every service necessary to an NDA filing.

Where is the catch?

The first illusion is to think that all you need is hardware, and forget that the "soft" side of the business is just as critical and requires many years of focused work. Competence in chemistry and some vessels in a newly painted building will not make you an API manufacturer and will not give you a "pass" at an FDA inspection. The mistake is to contract out work without a sound understanding of the API business and without undertaking due diligence: meeting the people, auditing facilities and documentation, and checking references.
A gap analysis will show that because of the youth and fast growth of this business practice there is shortage of competencies and capacity. Both on the supply side, as well as on how to chart strategy and contracting for the outsourcing of APIs.

Many questions arise. Some are simple: what tests and limits to include in the specification, what stability studies are needed, at what step of the process is GMP required. Others are more complex: is the process industrial, how will it scale, how to deal with critical process changes, how to extend patent life with process or other patent.

Few companies offer a complete range of skills

The conferences exploit this lack of competence. Take for instance the recent focus on the issue of "technology transfer". This skill appears to be key because most Small Pharma companies rush to find the supplier for their next requirement but few take the trouble to look beyond the next quarter, on the other hand the services on offer are often deficient. It is not unusual to find a " merry-go-round" of contractors involved in a single project: a lab at the University of Iowa will make grams for screening; then another larger lab in Colorado will make kilos, process scale-up will be done again elsewhere. Analytical development is done in South Carolina. Then the first large quantities for validation will be done in the USA and this will be the object of a PAI[9]; but this supplier will soon run out of capacity. For larger quantities the client will invariably source the long-term business in Europe. (Europe today is still the work-horse of API synthesis. Over 90% of FDA foreign inspections are for bulk APIs, most of them are in Europe)[10].

The need to change suppliers, and therefore constantly go through a "tech transfer" exercise which is inevitably incomplete, expensive and time-consuming, results from the inability of most suppliers to offer a complete solution.

Clearly expertise in tech transfer is redundant if you have chosen the correct supplier of API. If your supplier can cover the full range of technologies, batch sizes and quantities and meet FDA requirements you will not need to waste time and expense transferring your process from site to site.

If the option of a "one-stop-shop" is a reality, then tech transfer is a remedial skill and not a key competence.

Though few, these companies exist and offer a complete range of services:

- Process chemistry (route development and scale-up; impurity synthesis)
- Analytical method development and validation
- Batch sizes from kilos to ton
- Quantities from tens of kilos to tens of tones
- Bulks with controlled particle size for oral or topical use, or sterile or injectable grade

with an ability to meet today the requirements of FDA, offer multiple site risk mitigation, whilst always being flexible, available and fast.

The current state of affairs with only a handful worldwide of such paradigmatic companies is negative

for the Small Pharma but suits the needs (or current practice) of the Large Pharma. The Pharma giants buy components not solutions. Their view of API outsoucring is limited to the buying of capacity for a well-defined (and-not-to-be-changed) process. Regulatory issues are perceived to be too serious and important to be outsourced; and the pre-approval inspection is left to the contractor only because FDA so imposes it… Large Pharma would not rely on an outsider to develop a synthesis route, scale-up, produce and handle regulatory filings.

Yet over time the landscape will change and more such "one-stop-shops" will appear on the map. Their number, track-record and breadth of competence will match the needs of the Small Pharma. These API solution providers will take the product from screening grams, to commercial launch through successful PAIs – and will do so with a speed criterion hitherto unknown. Because virtual companies are critically dependent on their suppliers, the level of comfort and trust that needs to develop between the most senior decisions-makers on both parts is considerable, and is more likely to be found in smaller companies.

Building a good name at FDA takes a lifetime; destroying it takes no time at all

Bringing more API solution providers on-stream will take time. Installing capacity takes a couple of years; building a 50 person strong process chemistry group probably more; writing, implementing and validating software to link up all GMP data at the API solution provider and enabling link-up via modem to the customer is still a far away dream for almost everyone[11]. Finally to build up a track record and a good name at FDA takes a lifetime; and destroying it takes no time at all as HMR's Italian subsidiary Biochimica Opos found out in late 1996[12].

Sen. Mikulski (D-Md.) has been pushing for increased scrutiny of foreign API manufacturers by FDA, and that vigorous action be taken over non-compliance[13]. It is likely that Forms 483 and warning letters will multiply significantly. Only the "fit" will survive. Does this raise a capacity issue ?

There are today new compounds developed by Small Pharma with annual sales in excess of $400million and exclusively produced by contractors. This is conclusive evidence of an emerging competence both in terms of what is being offered, and in terms of companies breaking new ground on how to source, contract and manage what amounts to an extensive and complex supply chain puzzle.

Could this signal that outsourcing of APIs is about to become a sellers' market ?

As the 150 products in advanced stages of clinical trials move forward and get approved there will be an increased demand for API production capacity. This, together with the absence of new GMP plants being built, means it is likely that in the next 5 years we will face a shortage of capacity. Lonza announced earlier this year that it had decided to charge reservation fees on production capacity[14] – could this signal that outsourcing of APIs by the competent few is about to become a sellers' market?

The imbalance between demand and supply of API synthesis capacity may come as a surprise to the Small Pharma sector. To date the limited demand for these services has meant that capacity has never been an issue; speed has been the critical factor. As more and more of the 150 compounds start demanding more bulk, the biotech sector might suddenly be faced with sourcing difficulties. Getting enough API, and getting through PAIs, might start causing delays to NDA filing time-lines. Soon venture capitalists shall learn the hard way not to overlook the supply side of the API: One might witness increased due diligence review by investors of the arrangements in place and on the reliability and track-record of the chosen API supplier.

The pharma landscape will change dramatically, in two aspects:

- Today, every year sees about 30-40 new products being launched, almost all from Large Pharma. In a few years Small Pharma will increase this by another 10 to 20 compounds per year.
- These new compounds will make shareholders very rich, but it is unlikely that they will lead the Small Pharma to start building plants. The future is for the highly focused specialist; demand for its competence and capacity will grow.

In the same way that Ford does not build ABS breaking systems, or Compaq does not make disk drives, tomorrow's pharma company will not need to know about large scale hydrogenation. The number of one-stop-shops for APIs will grow. On the list of API solution providers you will only find companies who are totally

committed to chemistry and to being ahead of the increasingly severe regulations. They will invest annually a large proportion (10-15%) of their sales in R&D and technology plus many, many millions in new plant, software and staff training.

The proposed efficiency "quantum leap" results from expertise, experience and specialization. The API solution provider will take over the responsibility to

solve the chemistry and regulatory problems of the API and will, in time, have the ability to deliver faster, at less cost and with more reliability than the Large Pharma.

Roche is worth looking at. This leading edge Swiss giant often displays a nimbleness that staggers. Not only does it appear to be amongst the first and cherry-pick on the latest additions to the biotech sector, they are also ahead in experimenting with Small Pharma models. Protodigm, headquartered in the UK, is a subsidiary without functional reporting of Roche. With Franz Humer on its Board, this PROTOtype of a new working paraDIGM is run as a virtual drug development company. A staff of 9 prepares business plans for the development of new NCEs or Biologicals, obtains funding on approval of the plan and then signs-up contractors responsible for the development up to NDA filing by using 100% outsourced services. They have selected API solution providers who must come up with all the answers for all the API problems and interface pro-actively with the other contractors (formulators, analytics, regulatory, etc...).

For more information please visit www.hovione.com

[1] API is the abreviation of " active pharmaceutical ingredient" ; the name given by FDA to describe the key pure chemical substance which when administered is responsible for the desired therapeutic effect.

[2] In Perspectives, ©1997 CSC Healthcare

[3] Giff Marzoni, Agouron Pharmaceutical Inc., IBC Conference London January 1998

[4] The Biotech Sector is a Wall Street term which groups the development stage pharma technology stocks; although it makes reference to biotech this is not meant as a limitation to the type of process technologies used; indeed in many cases it includes companies involved in small molecule products made with conventional chemical synthesis processes. Small Pharma may become a more widely adopted term.

[5] Fortune Magazine, 31st March 1997

[6] Although the assets sold are mostly formulation plants they have included some primary manufacture: eg the Catalytica acquisition of the Glaxo site in Greenville, South Carolina in 1997

[7] Goldman Sachs, US Research, Strategic Alliances in Biotechnology, March 1997

[8] Informex is SOCMA's annual trade show in New Orleans, the World's premier custom synthesis exhibition.

[9] PAI: Pre-Approval inspection – a physical verification by FDA of the API manufacturer which takes place after submission of the NDA but before approval. The investigator establishes whether cGMP and CFR requirements are complied with. A report [a form 483] results from this investigation; and the investigator's " recommendation to approve" is required for the NDA's approval. The Fisons debacle resulted from an un-succesful FDA inspection.

[10] New York Times May 3, 1998

[11] Hovione, an API solution provider, uses Migg software: Qstream® enables internet browsing of Hovione's DUNE® quality system data.

[12] The Gold Sheet, Vol. 32 No.1, January 1998

[13] The Pink Sheet May 18, 1998; page 21

[14] P. Pollak, Lonza Ltd, IBC Conference London January 1998