Learning from History: For CMOs the cycle is back

What is happening to the CMO industry (particularly the pharmaceutical fine chemical industry) looks pretty similar to what it did almost 20 years ago. The attached 13 articles written between 1998 and 2005 -half of which were written by me- recount a well-known story: exuberance and over-investment results in write-offs and losses. What happened then was crystal clear to me when in 1998 someone came with a large cheque book convinced that a $500m API business could be built in 3-5 years. Shortly thereafter a well-known Deutsche Bank analyst's report made sure the herd mentality took over. By 2005 most of the $15bn or so spent in M&A deals were mostly written off and a number of wonderful brands and several major companies had vanished.

It is interesting to note that at the time that some entered the CMO business Honeywell was exiting and said: "..pharmaceutical chemical manufacture is a highly capital intensive business plagued by over-capacity, clinical trial failures, limited new drug approvals, new drug marketing disappointments, and price wars…"

Maybe there is an opportunity to learn from history. The challenge today is to check whether what looks the same is indeed the same, and whether what is really different can contribute to a different outcome. What remains to be seen is whether outsiders understand what they are getting into, and one thing is certain: when the dust settles you will have the usual suspects picking up the pieces.

If anything we should be concerned because as of today over $33bn have already been spent in CMO related M&A activity in the last 4 years – in exactly the same pattern as in 1995-7, 1998-2000.

Yours,
Guy

Guy Villax
Hovione
gvillax@hovione.com

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

Pharmaceutical Intermediates

Custom Manufacturing for the
Pharmaceutical Industry

What are we trying to do?

Establish a leading and high margin contract manufacturing \ pharmaceutical intermediates business supporting ethical pharmaceuticals based on long-term supply agreements.

SOLUTIA™

We Have Agressive Goals

- $500 million division within 3 - 5 years
- Gross Profit > 40%
- Expertise in at least two fields of chemistry
- Strong drug development alliances with key pharmaceutical companies.
  - Target is at least 2 new chemical entity's in phase II/yr. (110 last year)
- 3 - 5 contracts with the top 20 Pharma Companies
- Global (N.A and Europe)
- Multiple acquisitions
- Foundation for growth and P/E multiplier

SOLUTIA™

Why Contract Manufacturing of Pharma Intermediates is attractive:

- Strong growth rates (c.15%) in ethical pharma and outsourcing.
  - *Pharma Intermediates sales growing at 12-15% cagr over 3 years.*
  - *Ethical pharmaceuticals sales growing 7-8% cagr over 10 years.*
- Reduced exposure to economic cycles:
  - *10 year cagr of 7% for pharma.*
- High gross margin potential:
  - *40-75% at full scale production of intermediates.*
  - *EBIT margins of 25-35% normal*
- High technical service component.
  - *Excellent fit with "Applied Chemistry, Creative Solutions"*
  - *Strategic Fit for Specialty Chemicals aspirations*

SOLUTIA™

Investment Thesis: Positioning for Growth

- **Our research suggests that the fine chemicals/ pharmaceutical contract manufacturing segment of the specialty chemical industry will experience growth rates well in excess of industry average over at least the next two to five years.** We expect the fine chemical/pharmaceutical contract manufacturing industry to generate growth in excess of 15% per year as strong end-market growth combined with increasing utilization of contract manufacturers will drive this strong industry growth.
- **The fine chemical industry is expected to undergo massive structural change over the next two to five years as industry participants strive to achieve key success factors, including critical mass. We have identified several critical success factors that we believe will define the evolution of the industry.** We expect competitors to build expertise in these critical areas over the next several years in order to position themselves for growth. Today, the fine chemical industry is highly fragmented with no single competitor having greater than a 5% market share. Given the customer push for broader supplier capabilities both on a technology front and geographically, we believe consolidation is necessary and, consequently, inevitable.
- **We believe that two categories of "winners" will emerge in this industry: 1) those companies that are the most aggressive acquirers, achieving critical mass and industry leadership as rapidly as possible; and 2) those that are acquired.** Our research reveals that no clear industry leader has emerged. Based upon a number of factors described at length in this report, we believe seven to 10 major fine chemical manufacturers will materialize over the next two to five years.
- **Initiating coverage with STRONG BUY Ratings.** We believe both Catalytica Inc. (Nasdaq-CTAL-$15 5/16) and Cambrex Corp. (NYSE-CBM-$27) will either become successful industry consolidators or be consolidated themselves. In addition, we believe both of these companies are currently well-positioned to take advantage of the strong industry growth. Furthermore, we believe the management teams of both companies are extremely shareholder oriented. Therefore we initiated coverage of these companies with STRONG BUY ratings.

Executive Summary

Based upon our extensive research, we believe one of the fastest growing segments of the chemical/specialty chemical industry over the next five years will be fine chemicals/pharmaceutical contract manufacturing. By our estimates, the fine chemical/pharmaceutical contract manufacturing (CMO) industry will grow in excess of 15% per year over the next five years. By way of comparison, the overall specialty chemical industry is expected to grow 4% per year over that same time frame. This growth, coupled with what we believe will be MASSIVE structural changes in the industry over the short to intermediate term, will create rare opportunities for investors to generate substantial returns over the next five years.

We believe secular trends in the pharmaceutical and biotech industries will drive 15%-plus growth in the fine chemicals/CMO industry. In particular, we believe refined management focus in the pharmaceutical industry is driving increased utilization of outsourcing services across the industry in an effort to improve ROIC, reduce risk, and focus on core value drivers. In addition, we expect that pharmaceutical/biotech end-market growth will remain robust for the next several years. As a result, we estimate that these factors will drive growth in excess of 15% in the CMO industry over the next three to five years. In particular, we believe growth will be driven by:

- Strong market growth in both the pharmaceutical and biotechnology industries. IMS Health estimates that the global pharmaceutical industry will grow at nearly 8% compounded through 2002. Today the global pharmaceutical industry is roughly $300 billion in size; IMS expects the size of the industry to grow to more than $400 billion by 2002. IMS expects the North American pharmaceutical industry to grow at nearly 10% through 2002 to roughly $170 billion.
- Increased penetration at the customer base. We anticipate that pharmaceutical manufacturers will increasingly utilize contract manufacturing. We believe that the following factors are driving increased utilization of outsourcing by the pharmaceutical industry:

  1) The pharmaceutical industry is focusing on the highest value-creating portion of its business: drug development and marketing. Manufacturing is becoming increasingly "noncore." We believe that refined management focus in the pharmaceutical industry is driving increased utilization of outsourcing services across the industry.

  2) Need to shorten the drug development cycle: The industry is increasingly utilizing contract manufacturers in early-stage drug manufacturing to speed time-to-market of new compounds.

  3) Reduce the costs of developing record number of drug candidates: Through utilization of contract manufacturers, pharmaceutical companies do not need to invest capital in new production capacity to develop new drug candidates.

  4) Increased focus on improving return metrics: ROIC, ROA. Increasing utilization of return-based management philosophies, such as ROIC, EVA, etc., is driving decision making across the pharmaceutical

industry. The use of contract manufacturers enables pharmaceutical customers to maximize their returns.

5) Increased complexity of molecules: The manufacture of increasingly complex molecules requires greater focus. Contract manufacturers who focus on complex routes to molecules are generally able to manufacture these more efficiently and master unique niche technologies.

6) M&A activity in the pharmaceutical industry is driving asset sales: We expect that M&A activity in the pharmaceutical industry will result in increased asset sales to contract manufacturers.

7) Emergence of virtual pharmaceutical companies. Virtual pharmaceutical companies rely completely on outsourced manufacturing for production. The growth of this subindustry could provide an additional avenue of growth for contract manufacturers.

Massive Structural Changes in the Industry Are Likely to Occur Over the Short to Intermediate Term as Companies Strive to Build Critical Success Factors

We have identified several critical success factors for industry participants. In general, we believe that the CMO companies that will capitalize on this tremendous growth opportunity will be those that directly align their business model with the goals of their customer base: pharmaceutical, virtual pharmaceutical and biotech customers. In addition, we believe that the formation of long-term strategic relationships with pharmaceutical customers is becoming increasingly critical.

Customer Relationships at R&D/Drug Development Levels: Our research suggests that long-term strategic partnerships beginning at the R&D level during the early stages of the drug development process are key to success. We believe that those companies that are tied to products during the early stages of development are well-positioned to capture manufacturing contracts upon commercialization of new drug candidates.

Technology as a Key Differentiator: Our research suggests that those suppliers who have "multitechnology" capabilities are better positioned than others to win "supplier of choice" or favored-status position with potential customers.

Manufacturing Capability: We believe that offering a broad base of manufacturing technologies and available current Good Manufacturing Practices (cGMP) capacity for manufacture provides industry participants with a competitive advantage in winning new contracts.

Demonstrated "Soft" Capabilities: Due to the nature of the pharmaceutical industry, we believe the possession of several intangible qualities is extremely important to generating contract wins. In particular, we believe that flexibility, scalability, adaptability, reliability and quality are extremely important to the pharmaceutical/biotech customer base. The CMO's knowledge of and skill in meeting regulatory approvals are included in this area.

Strategic Customer Relationships: We believe that those CMOs that form strategic relationships with key pharmaceutical customers are well-positioned to generate additional new business from these customers. Our research indicates that pharmaceutical companies would ideally like to limit their number of suppliers to reduce complexity.

Critical Mass: We believe scale is required to support the broad range of capabilities necessary for success.

Today, our research suggests that *no* single company has achieved all of the critical success factors described previously. As a result, we believe major business consolidations and joint ventures will occur over the short to intermediate term as competitors build strengths in these key areas.

We believe the "winners" in this industry will be those companies that are the most aggressive acquirers of the critical success factors. We expect this industry to undergo extensive structural reconfiguration over the next three to five years as companies build capabilities in the areas outlined previously. We believe that the long-term winners in the industry will be those that build competitive strengths in the areas outlined previously the fastest. Due to the long-term nature of customer-supplier relationships in this area, we believe early establishment of a relationship with the customer is critical. The earlier a broad competence is achieved, the better positioned the supplier should be over the long term. As such, we believe early, aggressive consolidators in this industry will ultimately be best-positioned.

We believe several companies are best-positioned today to become "winners" over the next few years—Lonza, DSM, Catalytica, Cambrex and Sigma Aldrich Corp. (Nasdaq-SIAL-$32 3/4) appear to be forming an early lead. We believe these companies are currently well-positioned to take advantage of the growth in contract manufacturing; however, this industry is still relatively young and dramatic changes in competitive positioning can occur overnight. In addition, several industry participants have vast financial resources from which to draw on and are aggressively building competence in this area. (e.g., Bayer, AlliedSignal Inc. [NYSE-ALD-$65], Dow Chemical Co. [NYSE-DOW-$114 5/16], Eastman Chemical Co. [NYSE-EMN-$46 ½] and others). Furthermore, the structural changes in the industry that we expect to occur over the next several years will likely leave the industry completely reconfigured. For U.S.-based investors, we believe that the best way to "play" this growth is through owning Cambrex and Catalytica.

Recommend Investors Purchase Cambrex and Catalytica to Play in This Space

We believe that the best way to play the opportunity emerging in this area is to own Catalytica and Cambrex. As a result, we initiated coverage of Catalytica with a STRONG BUY Rating. We established earnings estimates for Catalytica of $0.43, $0.52 and $0.65, for FY99, FY00, and FY01 for Catalytica, respectively. We also initiated coverage of Cambrex with a STRONG BUY rating and established earnings estimates of $1.70, $2.00 and $2.30 for FY99, FY00 and FY01, respectively for Cambrex.

Article / Oct 09, 2001

Article published in the CPhI Show Daily Newsletter

Show Daily CPhI, 9 October 2001

Dear Friends,

When the organisers of CPhI asked us to write an article about Hovione for the CPhI Show Daily, we accepted but the words that follow are probably not what they expected.

Last year we were basking in the sun-shine, it had been a golden time for the fine chemicals industry. The El-dorado was nigh, everyone was investing, the brave ones were buying plants, and some, driven by consultants were spending hundreds of millions of dollars on merging and acquiring other companies. The folly of the stock-market still had everyone in a frenzy. Life seemed sweet, easy and money was plentiful. The bankers in their excitement even decided that those making fine chemicals for the Pharma industry deserved some attention, they organised conferences and issued reports.

What a difference 12 months make. We are now in a recession, and the atrocities of September 11th are fresh in our minds. Everywhere one looks, it seems the colours have gone and the World is now in black and white. The articles one reads in the industry magazines talk of over-capacity, slowing growth, withdrawn drugs, unapprovable letters, cancelled projects. In some cases, the extent of the excess-enthusiasm was even given a number: a CHF1.3 billion goodwill charge on acquisition. The fascination with our business will now wane and the wave of interest will go elsewhere.

Quite a few of us will remain behind to pick the pieces left behind by this storm, tidy up the house and get it to move forwards. It will take a couple of years to get things back into balance, for the new-comers to find their direction, to establish with clarity who is a quality competitor and who has remained a trusted supplier. Those that expected to grow an API business in 4 or 5 years to $500 million in annual sales will be disappointed; those that have been at it for decades, focusing on compliance and excellence will continue to deliver work that satisfies customers. It is the repeat customer that drives growth; track record is not just the absence of recalls and warning letters, it is also the ability to consistently find solutions for customer problems - and in drug development there are plenty of tough surprises to solve.

Being in compliant manufacture is not just a question of dollars; being "cGMP" is not just a question of investment in new facilities. It needs time more than money, it requires having a team of dedicated technical people with many years of accumulated training. You do not "go fast" because of more resources or tougher deadlines; projects move fast well because your technical groups are trained and have done it together many times before, your people are aligned, and the range of skills is well covered and well balanced. Can a confederation of a dozen plants acquired through multiple mergers ever have a common culture, a same view of safety, let alone of quality? How do you manage all the site managers competing for the new project? Being successful in compliant manufacture is tough, it comes with years of nurturing and focus. Is it a surprise that the smaller independent companies do it better than the large giants ?

The divide is often the time-scale - some squeeze their people and business partners for their quarterly results, the annual budget takes precedence over customer satisfaction, available capacity is a dreaded cost - others look at available capacity as a positive thing enabling prompt service, and focus on what is in their control: sales in 2003 and 2004 (indeed the sales for the next 2 years were decided some time ago...).

The divide is often the choice of target: large companies look at sales and profits, they look at the share price and at how to cut costs, performance is judged on dividends. This is not so for all: some of us are motivated by customers that say thank you, some even compete for, and win, environment awards, but those that succeed, work as partners with their customers to develop new drugs; if they were lucky they started working together 5 year ago for the first 10 kilos; if they are statistically normal, they will have worked together on two failed projects well before they can claim to have put a new drug on the market.

Our industry is about saving lives. Though on occasion we are seen as polluters carrying out unsafe operations, and sadly accidents do occur, as in Toulouse only last week. Odd how energetic reactions, deadly reactants, explosives, corrosives and flammables all come together to make pills that cure disease, kill bacteria and destroy viruses. Safety First is not a negotiable item, chemistry and its engineering need competence and have priorities that business pressures must not be allowed to interfere with. Success in this business needs great leadership, the decisions are not easy - Bayer reminded us all how tough it can get.

At Hovione we did not participate in the Technicolor storm of the past few years. We had approved a medium term plan in 1994 and executed it with success; in 2000 we approved another medium term plan and we are taking it forward unchanged. It involved buying a field near Princeton to build a kilo lab and pilot plant to support early phase customers in the USA and to assist in the technology transfer to our larger plants when the projects so warrant it. The plan also aims to build additional capacity in our areas of strength: process chemistry, GMP manufacture, injectable grade APIs and corticosteroids. Some of this expansion is taking place in our plant in the Far East which is not encumbered with EINECS costs and speed limitations that slow the pace of drug discovery.

The companies that meet at CPhI play a critical role in the world economy. We are a key link in the worldwide health care system - without us the pharmacies would be empty. Ours is an important job, one we can be proud of. It is important that we should move ahead and get on with our business with professionalism, and keep distractions to a minimum.

Guy Villax
Chief Executive - Hovione

Article / Feb 27, 2002

Pharma Fine Chemicals - Nothing's changed!

Informex Show Times Newsletter, 27 February 2002

Article published in the Informex Show Times Newsletter

Pharma Fine Chemicals - Nothing's changed!

Since the summer there has been an avalanche of gloom in the industry magazines. Many articles reporting how much everything had changed since the last year; how fine chemicals are suffering by over-investment, by over-capacity, by a downturn in the cycle etc.. etc.. The reality is many companies made bets that the market perceived then as being excellent ones, but hindsight now tells us that too much optimism about the fine chemicals sector drove acquisitions and investment in plant expansion by companies inexperienced in the sector.

The tough part is, though many are now hurting, the misunderstandings seem to persist:

1. "We are in a down-turn in the cycle". In pharma API there is no cycle - indeed some trends are up (more projects are coming out of the Biotech sector) others are down (more advanced stage projects are cancelled, more drugs have been withdrawn, pressures for better plant utilization at the merged large pharma drives less outsourcing)) but overall they probably cancel each other out - the amount of work out there is still increasing and is finding outsourcing homes. It is probably now in smaller parcels, bought by more experienced decision-makers and there is certainly more competition. The only cycle at Hovione is the winter when more antibiotics are sold because of the US flu season.

2. "The complete tool box". Every company out there seems to agonize about the technologies they do not have. In making APIs you do not need to be a cost leader and a specialist in everything, you need to be a sound generalist able to address all the technologies, whether chemistry, engineering, analytical, etc... Technologies are therefore not a differentiator; if you are not a generalist, you are out of pharma APIs anyway. In the past 40 years Hovione has addressed every chemical reaction that has come its way, successfully. We have however some policy decisions such as: We do not use cyanides or other dangerous poisons and do not work with betalactams, penicilins or cephalosporins.

3. "Building a $500m business in 5 years". The wishful thinkers blame the failure of their plans on market changes. In fact nothing has changed: the $300b Pharma sales worldwide are still made up by about 4000 different APIs, 95% of the medicines in the pharmacy have sales of <$95m - in terms of API sales this equates to $5m or less per API. So building a $100m business takes, with luck, maybe no more than 20 different APIs at commercial phase. Fast growth or very large products means more risk - this business has already plenty of risk, you should not push your luck.

4. "Investment in plant and equipment". In the last 3 years some of our competitors even carried out head-count reductions. The most critical aspect of Pharma API development and manufacture is people: technical expertise, compliance, project management, solving problems, communicating. People take forever to train, a research group needs so much time to learn to work well together, scaling up and optimizing quickly requires full collaboration between production, pilot and lab people; compliance is a people issue; - none of the articles ever mentioned people, and the need to have depth in, and a balance across, a complete rage of skills. A passion for a job well done and customers that show appreciation for your efforts and commitment is what makes the difference.

5. "Time is money". Managers faced with the stock market need to show increased profits at quarterly intervals. Drug development reality is more like 5 years before an API producer can have commercial phase invoices. CFOs of pharma fine chemicals need lots of patience, but for the technical people there never seems to be any time. Pharma APIs is not for investors in a rush. At Hovione we take the time to make sure we get it "right-first-time" every time.

Hovione's strategy remains unchanged for 40 years: APIs. It is all about doing well things that are difficult, giving customer what they cannot find elsewhere. We focus on our people and encourage them to find solutions for our customers and to anticipate problems and avoid surprises.

Later this year we will open our Technology Transfer Centre located in New Jersey. This facility has a kilo-lab and a pilot-plant designed to supply 1-50Kg of API very quickly and to act as a bridge between our US customers and our plants in Europe and the Far East. Where a year ago corn was growing, we now have a beautifully architectured state-of-the-art facility sprouting with designed-in compliance. Everyone at the TTC has already worked at other Hovione facilities; all SOPs, specifications, methods and IT systems are the same as those adopted in our plants: a pre-condition for seamless transfers.

We grow on our own, never buying other companies, hiring talents straight out of university, developing our own engineering, chemistry and IT systems. We grow slowly, patiently, and nurture a solid, well diversified, portfolio of excellent customers with great compounds. With us Clients fly first class, there are always seats, we never over-book and we arrive on time.

Guy Villax
Chief Executive - Hovione

Outsourcing: The Dust Has Now Settled

By Guy Villax, CEO, Hovione

The dust has now settled after the exciting but turbulent times two years ago that saw the chemical giants snapping up pharmaceutical Fine Chemical specialists for hundreds of millions. Almost $3 billion were invested in three deals alone.

The drivers for outsourcing of APIs remain unchanged, yet the business model adopted by the various players seems to fall clearly into two very different types, with different offerings and different strategies. Yet for all exclusive manufacturing of NCE APIs remains a roller coaster: Approvals carry high rewards; product cancellations and withdrawals mean significant disappointments.

The notable new entrants are the integrated chemical giants that have acquired or invested in GMP businesses (some of the businesses that got acquired were great brands: Archimica, Carbogen, Chirex, Finorga, Raylo, Torcan…). Their original strategy was to bet on size and enter a high-margin, non-cyclical business that had synergies with their existing businesses. Some articles emphasized that the acquisition of API capabilities was strategically aimed at giving them total control over the key building blocks, which could be sourced internally.

On the other hand, the traditional players have remained independent and have taken no part in the M&A frenzy (FIS, Hovione, Lonza, Omnichem, Orgamol, Siegfried). In fact, they all probably see M&A as a strength-diluting exercise, as it debilitates one of their strongest assets; namely, their company culture. Their growth, which has been consistently in double digits for the past 10 years, remains purely organic.

The Independents strongly disagree with the assumptions that formed the strategies of the new entrants:

- Why should size matter?
  - when most APIs are only a few tens of tons
  - when there is a trend to more highly-active compounds
  - when an API producer should be a generalist—able to do all technologies—and not the lowest-cost technology specialist
  - when the early phase clinical materials require service, service, and more service, which traditionally is not a characteristic of large, multi-site companies
- Backward integrating only adds to an already risky business, whereas the Independents have the whole world—including India and China—to source low cost raw materials.
- Buying sites from large Pharma with supply agreements often resulted in:
  - a low-margin business,
  - a single-customer dependence,
  - an old plant, which was often not multi-purpose and certainly not designed for quick change-over and evolving compliance standards.

Furthermore, with their expansion into the API business, the chemical giants risk antagonizing their traditional customers who now could perceive them as competitors and no longer as supplier/partners. As an example, Hovione would prefer to discuss its new catalyst needs with Engelhard rather than Degussa or Johnson Matthey, who are now perceived to be competitors.

Neither the analysts, the board members, nor the shareholders considered any of these matters, but management thought they saw opportunities for making a difference in their shareholder value and the stock market supported them wholeheartedly.

In our view, the winning model appears to be a company big enough to:

- have the critical mass that will support the diversified portfolio necessary to mitigate risk
- support a large process chemistry group able to develop several dozen simultaneous projects
- have the depth and breadth of know-how and technology that is necessary to support multiple process validation campaigns per year
- assure long-term capacity.

and yet small enough to:

- take decisions and communicate them quickly
- provide extreme levels of service, flexibility and transparency

We believe the entrepreneurial, single-minded company without share-price concerns or peripheral activities to serve as distractions is likely to be a step ahead of the competition.

The constant need for large amounts of capital investment, the many years that projects take to mature from development phase to commercial scale, and the inherent risk of each project make our business unfriendly to the stock market. Therefore, it should be no surprise that the key players have a reference shareholder able to look at the longer-term: whether it be Ajinomoto, a family, or a foundation.

Over the last 12 months Hovione's normal growth has been further enhanced by:

- Satisfied customers who bring us repeat business
- Projects that have moved beyond validation to commercial phase

See **Hovione** *page 7*

Sumitomo Chemical Catalysts Improve Yield, Regiospecificity

Sumitomo Chemical's novel proprietary catalyst technology is in the forefront of novel synthesis of customized racemic and chiral Cyclopropane carboxylates. Employing proprietary novel catalysts, Sumitomo Chemical has simultaneously achieved significant yield improvements and enhanced regiospecificity in the synthesis of Cyclopropane carboxylates.

Chrysanthemic acid is a well-known cyclopropane carboxylic acid derivative occurring in natural pyrethroids such as Allethrin. Such intermediates are important in the Life Science industry in the synthesis of drugs as well as crop science chemicals.

Industrial synthesis is conducted by either the addition of a copper carbenoid species, prepared from a diazoacetate, to an alkene, or by addition of an alpha-halo ester to an alkene. Other synthetic approaches have involved the employment of Dimeric rhodium carboxylates such as rhodium acetate ($Rh_2(OAc)_4$) , which have been extensively used as extremely mild catalysts for decomposition of diazo compounds but are known to have limitations in the synthesis of cyclopropane carboxylic acids.

In the course of Sumitomo Chemical's research to find more effective catalysts, a new Rhodium catalyst, Dimeric Rhodium triphenylacetate, ($Rh_2(OCOCPh)$), has been discovered, which has a very high reactivity, and gives higher yields of cyclopropane carboxylic acids compared with rhodium acetate catalysts. This catalyst enables higher yield attainment for products than is achieved with conventional catalysts, even when high yields have been difficult to achieve with substrates such as mono substituted alkenes. The addition of diazoacetates to alkenes goes smoothly when employing alpha, beta unsaturated esters. Good results have never so far been reported in the reaction of such substrates with copper or rhodium carbenoids.

Despite a history of successful asymmetric synthesis of cyclopropane derivatives by chemocatalysis, where Sumitomo Chemical has itself been to the forefront of such technology, the company has now developed novel procedures employing optical resolution and biocatalysis for the economic synthesis of cyclopropane carboxylates. This has involved the use of proprietary enzymes and optical resolving agents (chiral acids & amines), supported by robotics and analytical science to rapidly identify the most economic catalyst system.

Industrial activity ranges from Kilo Laboratory, through pilot to commercial manufacturing scale. The core of such processes is novelty in catalyst design. ❊

From **Hovione** *page 5*

- Customers with projects in Phase III who are looking for a more reliable long-term supplier

Our experience indicates that Phase III projects change suppliers because:

- They want a stable supplier for the long term, "one that does not shop itself around constantly"
- They want assurance of capacity and of compliance and are fed up with "getting a different color batch every time"
- They want to be in-the-loop and not be the last ones to know of problems or of process changes

The key buying factors for our customers seem to include: a company capable of developing robust processes based on sound science that delivers "right-first time, every time"—shareholders who are committed for the long-term, and a track-record of rock-solid delivery as well as open and honest communications.

Some European companies have continued to invest at a time when others are trying to sell. Orgamol is building a new pilot plant and synthesis unit in Switzerland; Siegfried has innovated dramatically in the GMP design of its own new facility; Rohner has started up a new cGMP multipurpose plant.

Hovione has just commissioned its new Technology Transfer Center in New Jersey (USA). This is an investment in a green-field site with kilo-lab and pilot-plant facilities within a short drive of the largest cluster of API customers in the World.

In the past few years exclusive manufacturing as an industry has been the object of far too much interest, and too many bets were placed with exaggerated expectations—and most are not pleased with their investments. The business, however, exists, and the market continues to grow; but it is just not as simple as many companies expected it to be. Fines for non-compliance of GMP that have reached a record half billion dollars, and FDA's most recent initiative, "Pharmaceutical cGMPs for the 21st Century," are but two indications that the scope for differentiation has increased yet again; and that the role of a professional independent manufacturer of APIs has never been more relevant. ❊

c&en

Volume 83 Issue 3 | pp. 58-61
Issue Date: January 17, 2005

COVER STORIES: CUSTOM CHEMICALS

EUROPEAN PRODUCERS FACE UNIQUE ISSUES

The dollar and other obstacles snarl the path to success of custom synthesis providers in Europe

*By **A. MAUREEN ROUHI, C&EN WASHINGTON***

Over and above the business outlook that offers only cautious optimism for 2005, European producers must contend with other problems. The diminishing dollar is wreaking havoc. A discrepancy in regulatory requirements for suppliers of active pharmaceutical ingredients (APIs) based outside Europe is undermining the competitiveness of those manufacturing in Europe. Industry insiders are concerned that not enough people skilled in science and engineering are entering the workforce.

The plunging value of the dollar is a "nightmare," says Guy Villax, chief executive officer of Hovione. "With 70% of our invoices billed in U.S. dollars, every five cents of change in the euro/dollar exchange rate wipes out $1 million of the bottom line." Only businesses that are well managed and that have highly competitive cost bases can meet such rising costs without drowning in red ink, he adds.

The problem is mitigated by global production facilities. "If you have sites in the U.S., India, or China, where costs are based in dollars, you produce there, you pay your costs in dollars, and you sell in dollars," according to Ralf Pfirmann, senior vice president and global business director for Clariant's pharmaceuticals business unit. "We are lucky that we have dollar-based sites," he adds, pointing to Clariant production facilities in Florida, South Carolina, and

ENGAGING YOUTH
In the U.K., the chemical industry hopes to attract young people through programs like

Missouri. "But still we have a large footprint in Europe-based production."

Children Challenging Industry, in which companies such as Avecia host science open houses for children (top), and through the example of young chemists in industry, such as Solvay's Harper (below), the industry's young ambassador for 2004.

Credit: PHOTO BY MAUREEN ROUHI

Credit: AVECIA PHOTO

European producers really can't do much about the weak dollar, but they are taking the bull by the horns with the other challenges. For example, to eliminate the discrepancy in regulatory requirements for API manufacturers outside Europe, European producers are demanding inspection of all manufacturers that supply APIs for drugs produced in Europe.

In the U.S., the Food & Drug Administration inspects all API manufacturing facilities to ensure compliance with current Good Manufacturing Practices (cGMP). U.S. regulations also require that all APIs coming into the U.S. must have been manufactured in FDA-inspected facilities. In fact, successful FDA inspections have become badges of honor among API producers worldwide.

IN EUROPE, pharmaceutical companies bear the responsibility of ensuring that API suppliers comply with cGMP standards, Villax explains. In theory, in a self-regulatory fashion, these companies would have inspected the facilities of their API suppliers. What happens in practice is not consistent. Reputable drug companies either audit their API suppliers or source their APIs through reputable brokers. Usually, permission to market a drug is based solely on a certificate of suitability. Issued by the European Pharmacopeia, this document certifies only that the drug product meets the criteria of the pharmacopeia, but the issuer does not inspect for cGMP compliance. "It's as if you had the FDA review without the cGMP inspection," he notes.

The bottom line is that no regulatory body inspects the facilities that make the APIs that go into drugs that end up in European pharmacies. That situation will change in October, when the European Union will implement FDA-style inspections of API facilities in Europe. However, the mandate does not extend to manufacturers outside Europe. That means Asian manufacturers still can export to Europe whether or not their facilities are inspected.

According to Villax, up to 70% of APIs used in generic drugs in Europe now come from India and China, and they enter Europe without oversight of their production by any European

regulatory body. "European manufacturers think this is wrong from a public health standpoint and from a level-playing-field standpoint," he says.

The public health consequences are suggested by a study comparing gentamicin from various sources, carried out by Ulrike Holzgrabe and coworkers at the University of Wrzburg, in Germany [*Pharmeuropa,* **15,** 273 (2003)]. In the U.S. in 2000, 17 deaths were linked to gentamicin supplied by a China-based manufacturer. "Since these cases cannot be explained by the pharmacology and toxicology of gentamicin, it was assumed that they were related to faulty manufacture," Holzgrabe and coworkers write.

Their analysis of 39 samples of gentamicin obtained from pharmacies in Germany and the U.S. revealed seven different composition patterns. Some samples from the same drug company exhibited different composition patterns, and some results suggest that the API in the drug was not from the manufacturer claimed. An API's purity profile is central to drug efficacy and safety. The Wrzburg study shows that the purity profile is highly variable depending on the API source.

Reliance only on pharmaceutical companies themselves to ensure the quality of APIs has not been good enough for the U.S.; European standards should not be lower, Villax says.

From a business standpoint, "we can't compete with Asian products with the standards imposed on us," Villax adds. "We are asking for a level playing field. If we are going to be the subject of European enforcement, so should Asian suppliers whose APIs get into European pharmacies."

Through the European Fine Chemicals Group–a body that aims to be the voice of fine chemicals producers within the European Chemical Industry Council (CEFIC), Hovione and other API producers are appealing to the European Commission to set up an inspection system similar in authority, purpose, and function to FDA's foreign inspection service. Documents related to the issue of cGMP compliance and the consequences of noncompliance have been made available by these companies at **http://www.gmpapi.migg.com <http://www.gmpapi.migg.com>** .

For the long term, European industry insiders are concerned that an emerging skills gap will leave the industry bereft of the human resources it needs to move forward. Tom Shields, vice president of Avecia Fine Chemicals, sounded the alarm last November at the European Fine Chemicals Conference, held in Newcastle, England.

"It is worrying that the number of students studying science and engineering is in sharp decline," Shields said. In 2003, U.K. universities awarded 114,000 undergraduate science

degrees, compared with 160,000 nonscience degrees, he pointed out. From 1994 to 2001, acceptances to undergraduate chemistry programs dropped by 27%, whereas acceptances to business management programs rose by 55%, those to computer science programs rose by 98%, and those to media studies programs rose by 138%.

These data jibe with results of an informal survey by Rosemary Harper, a manufacturing process engineer at Solvay Caprolactones, in Warrington, England, and the U.K. chemical industry's young ambassador for 2004. She described her findings in Newcastle.

Harper surveyed U.K. students in their final two years of secondary education. She found that the most popular subjects among her respondents are psychology and information technology and the least popular is science–that is, physics, biology, or chemistry. She also found that most of her respondents did not know anyone who works for the chemical industry and cannot name a chemical or pharmaceutical company.

Despite evidence that the chemical industry offers well-paid jobs and good career prospects, "we're not attracting young people," Shields said. "Young people are preparing for careers in media, information technology, and general management rather than contributing to cutting-edge science."

What can be done? The most important step is to rebuild the industry's reputation, Shields said. Programs like Children Challenging Industry in the U.K. can help, he added. In this program, visits to chemical companies are worked into school curricula to show children and teachers how the chemical industry contributes to their everyday lives, to explain what chemists and other scientists do, and to give an idea how chemical businesses operate.

OVERTAKEN
India has passed Italy in generic API production

RANK	BEFORE 1998	1998–2003
1	Italy	India
2	India	Italy
3	Spain	China
4	China	Spain
5	Hungary	Israel
6	Israel	Hungary

NOTE: Rankings are based on the number of drug master files logged with the Food & Drug Administration during the indicated periods. API = active pharmaceutical ingredient.
SOURCE: Arthur D. Little Benelux

ANOTHER WAY to rebuild reputation is "to invest, create opportunities through new jobs, in the places we operate," Shields said. At its Grangemouth site, for example, Avecia is creating

opportunities through diversification. Part of the site is dedicated to biotechnology companies. Another is being developed as an industrial park for high-energy users.

"Tell them about it," is Harper's advice to the industry about attracting and retaining young people. Tell them how much pay they can expect, what career paths they can carve and how they can be supported on those paths through training and promotion, and how challenging and fun and important to everyday life are the problems they will be asked to solve. Tell them through nontraditional means, such as through young people in the industry acting as ambassadors, like Harper herself.

"Each and every one of us should be doing something to engage young people," Shields said. "If not, we will lose in what is becoming a very competitive labor market for young people."

MORE ON THIS STORY

CUSTOM CHEMICALS
MIXED OUTLOOK FOR CUSTOM CHEMICALS
EUROPEAN PRODUCERS FACE UNIQUE ISSUES

Chemical & Engineering News
ISSN 0009-2347

1st INTERNATIONAL FORUM
ON BUSINESS DEVELOPMENT
IN API & GMP FINE CHEMICALS

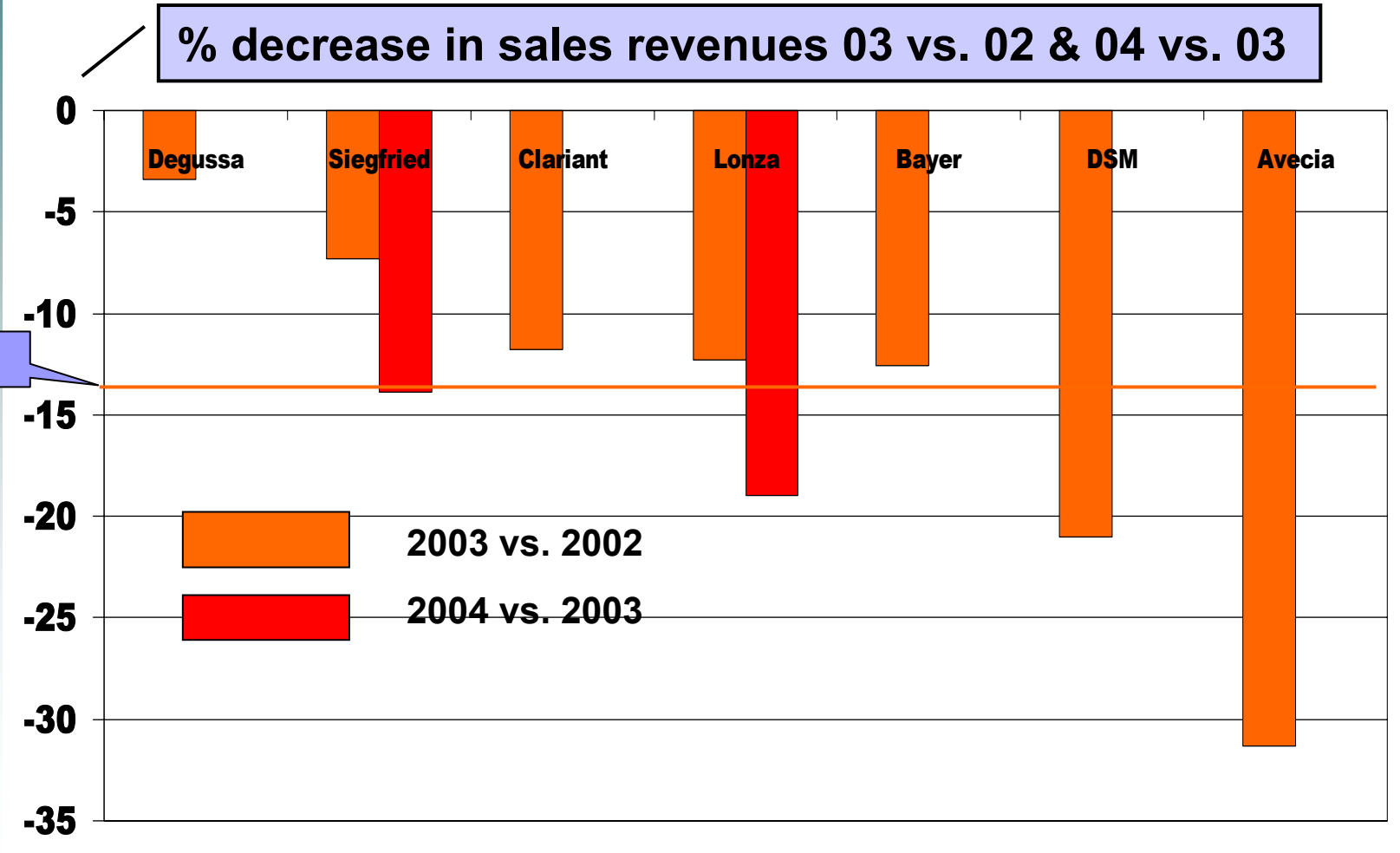
21-22 February 2005

Sheraton Roma, Rome

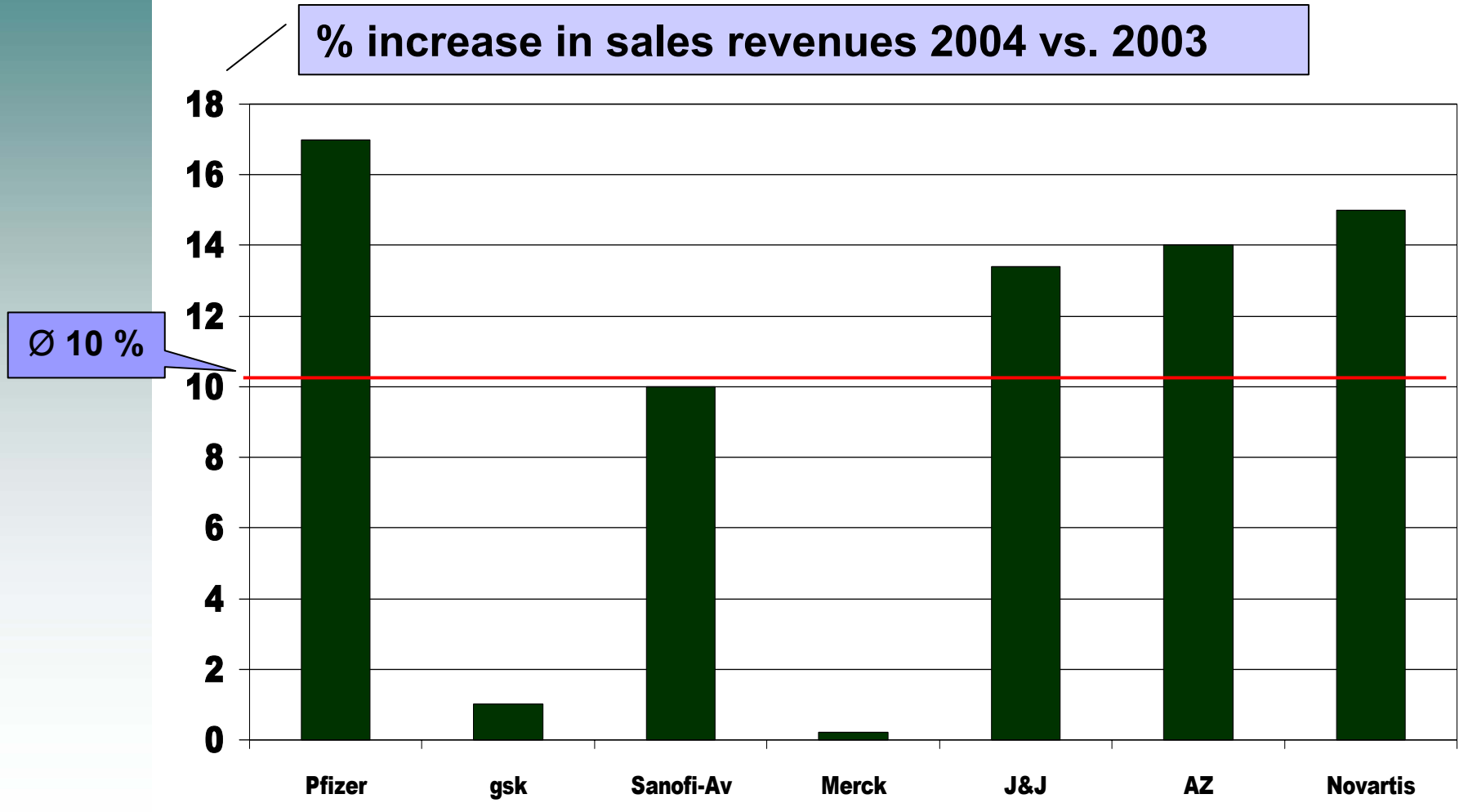
Why Fine Chemical Business Development has Failed

Peter Pollak

Sales Development of Major European Fine Chemical Comp. 03 / 02 & 04 / 03



Sales Development of Major Pharma Companies 2004 / 2003



Big Pharma's Outsourcing Policy

about Strategic vs. Opportunistic Outsourcing ...

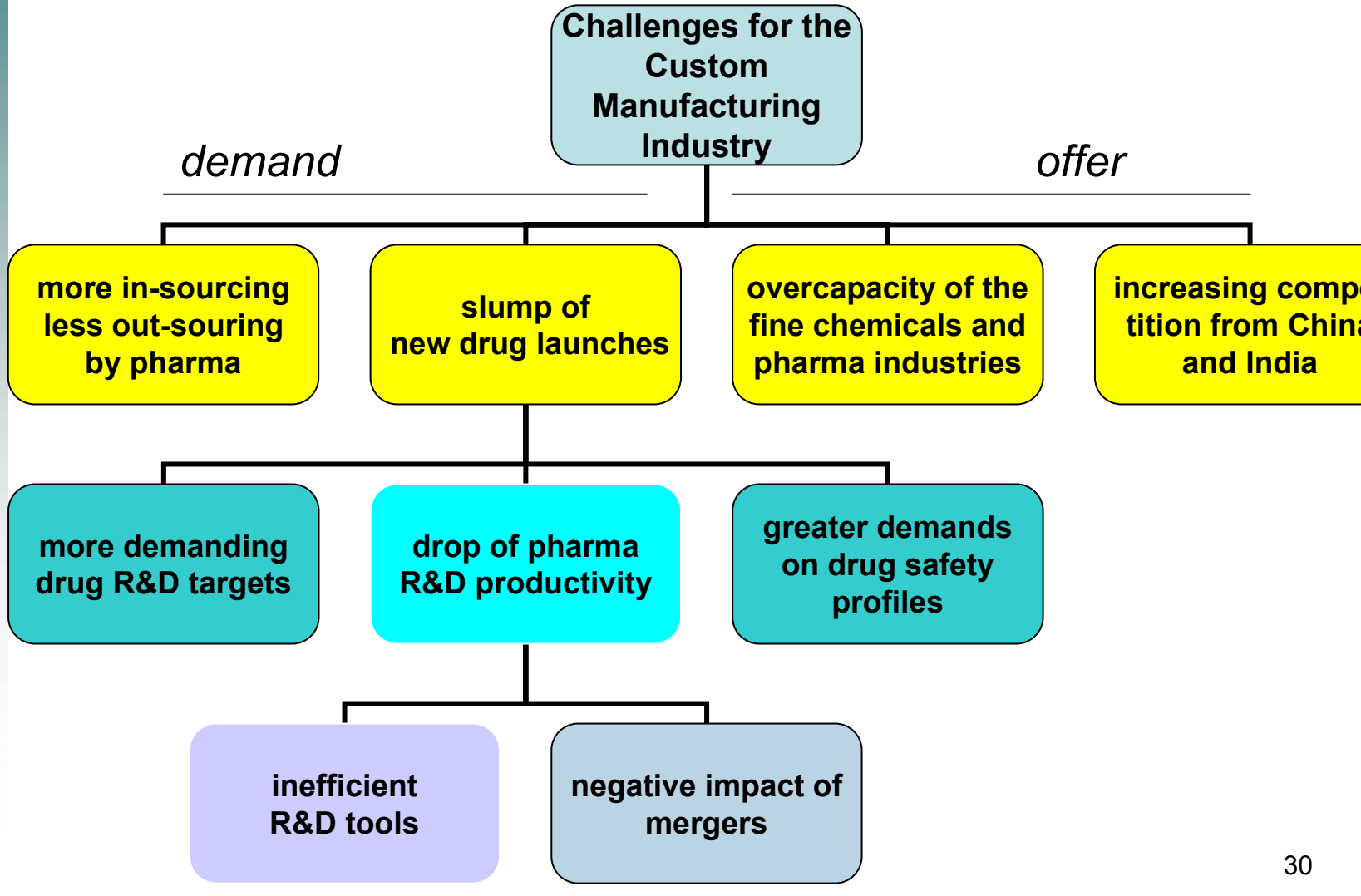
„We are seeing more vividly that truly strategic outsourcing never really took hold in the industry"

Martin H. (Jay) Joyce,
President of the the Pharmaceutical Outsourcing Management Association (POMA)
CMR, 14 April 2003, Focus Report

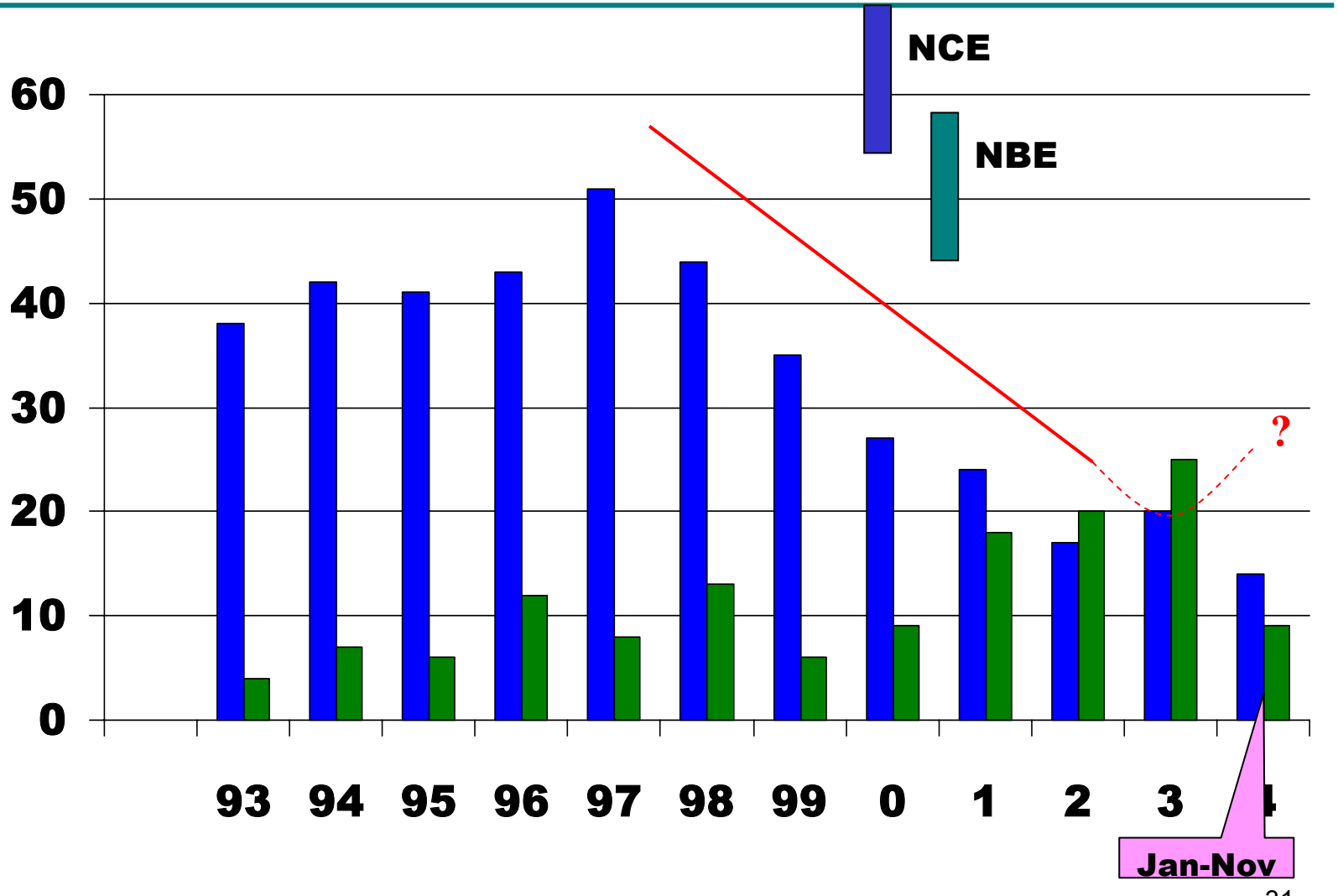
Misconceptions

- Growth of demand is outpacing growth of offering
- „Big Pharma will outsource all chemical manufacturing
- Custom Manuf. is a Seller‘s Market
- Big is beautiful
- We just lack a good organization
- We are the best

Custom Manufacturing: The Offer / Demand Hierarchy



FDA Approvals for New Drugs



Pharma Investment Projects

Company	Product	Location	Investment
Biogen	Pipeline Products	Hillerod, Denmark	$ 340 mio
Boehringer-Ingelheim	Enbrel	Biberach, Germany	$ 250 mio
Genentech + Wyeth	Herceptin	Vacaville, CA USA	$ 600 mio
Hoffmann-La Roche	Avastatin, Herceptin	Basel, Switz. Penzburg, De	$ 350 mio
Novartis	Diovan	Basel, Switz. Grimsby, UK	$ 330 mio

source: CMR, Dec. 2004, PP

Baruch Lev

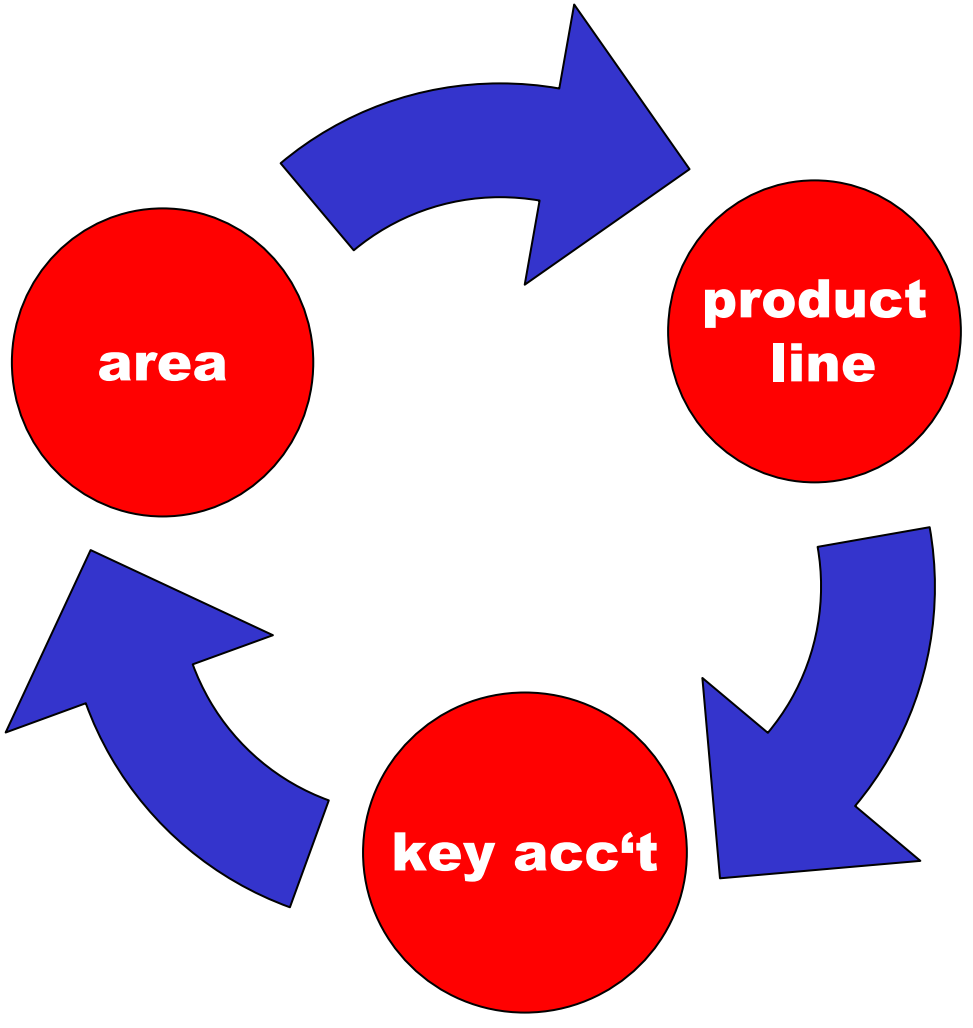
New York University
Stern School of Business
New York
www.baruch-lev.com

R&D and Capital Markets
Journal of Applied Corporate Finance, Winter 1999, *pp* 21-35

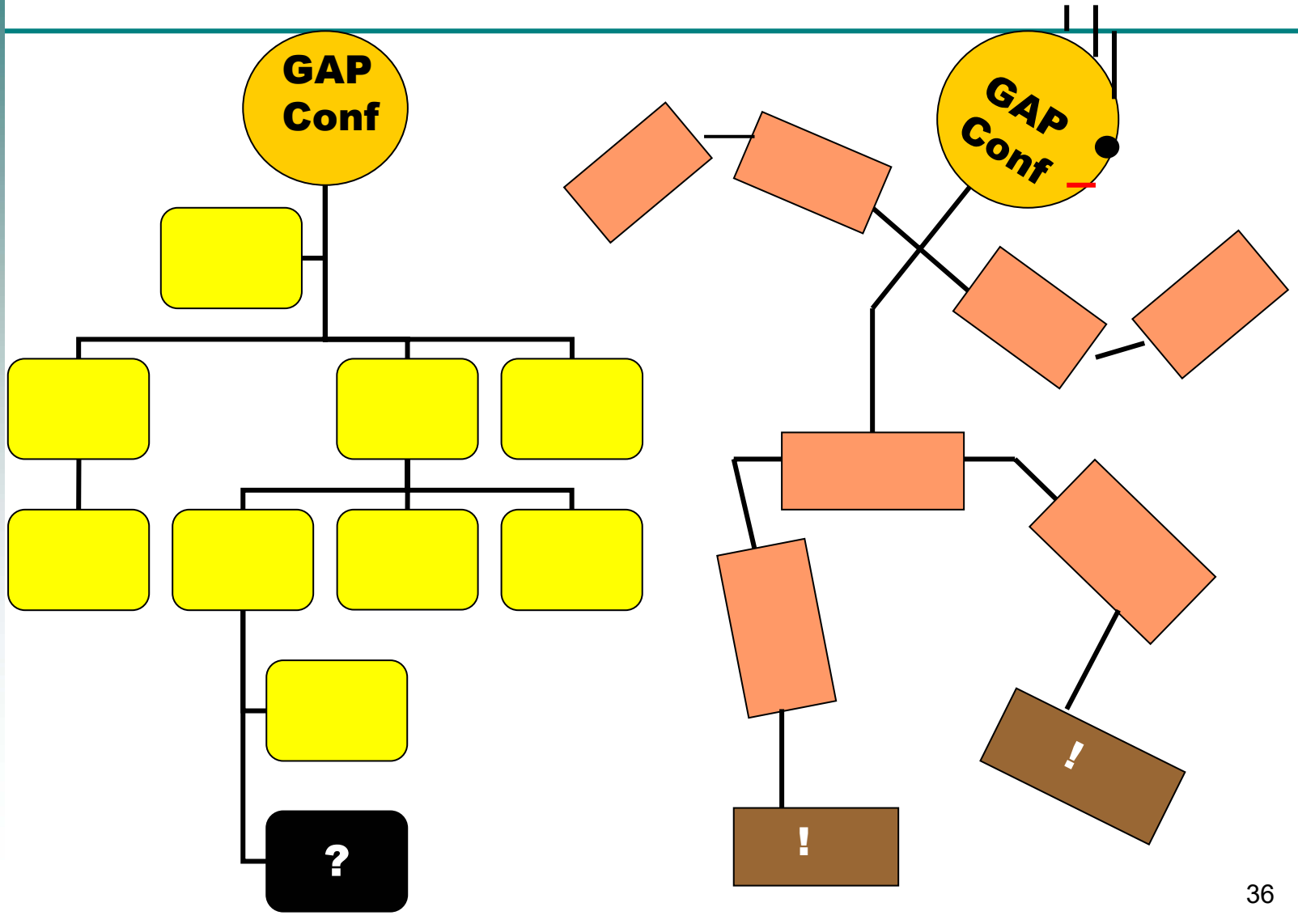
Supply Contracts: From a Seller‘s to a Buyer‘s Market

	prior to 2000	after 2000
contract duration	5 years	1 year
capital guarantee	yes	no
take or pay clause	yes	what is this ?
number of suppliers	sole	lowest offer
volume forecasts	binding	spot orders
price adaptation	↗ price index, etc	↘ x % per year
process improv. benefits	to supplier	to customer
penalties for off-take delays	to supplier	to customer
customer inventions	to supplier	to customer
R&D expenditures	to supplier	to customer

The Organization Carousel



Organization Development



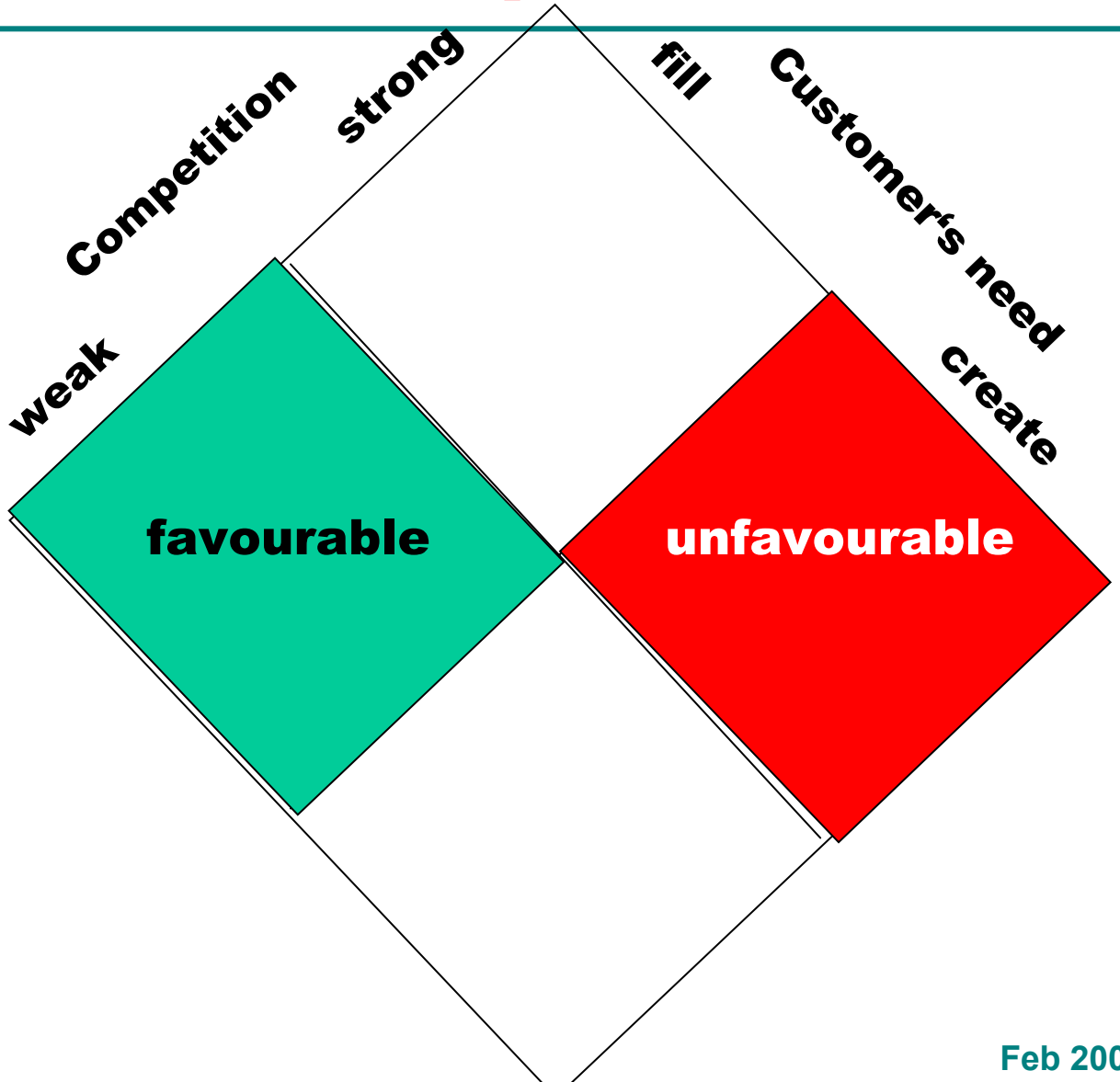
We are the Best – are we?

- **Value:** Cost Leadership, Quality, Reliability
- **Flexibility:** change aversion
- **Speed:** How many days for an offer?
- Risks? Bureaucracy?
- Handling of customer complaints?

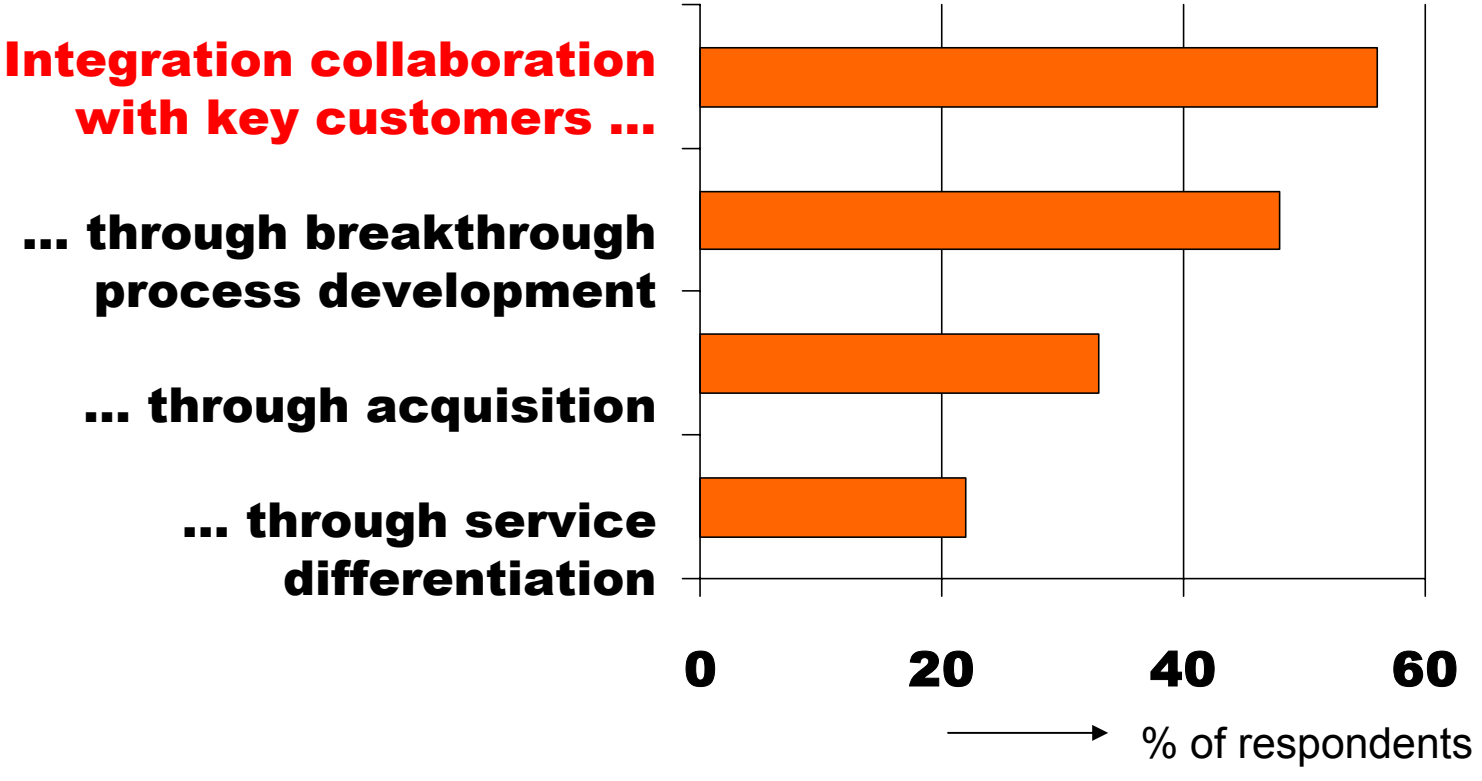
Yardsticks

- **on time**
- **on budget**
- **first time right**
- **change control**

The challenge for Fine Chemicals Business Development



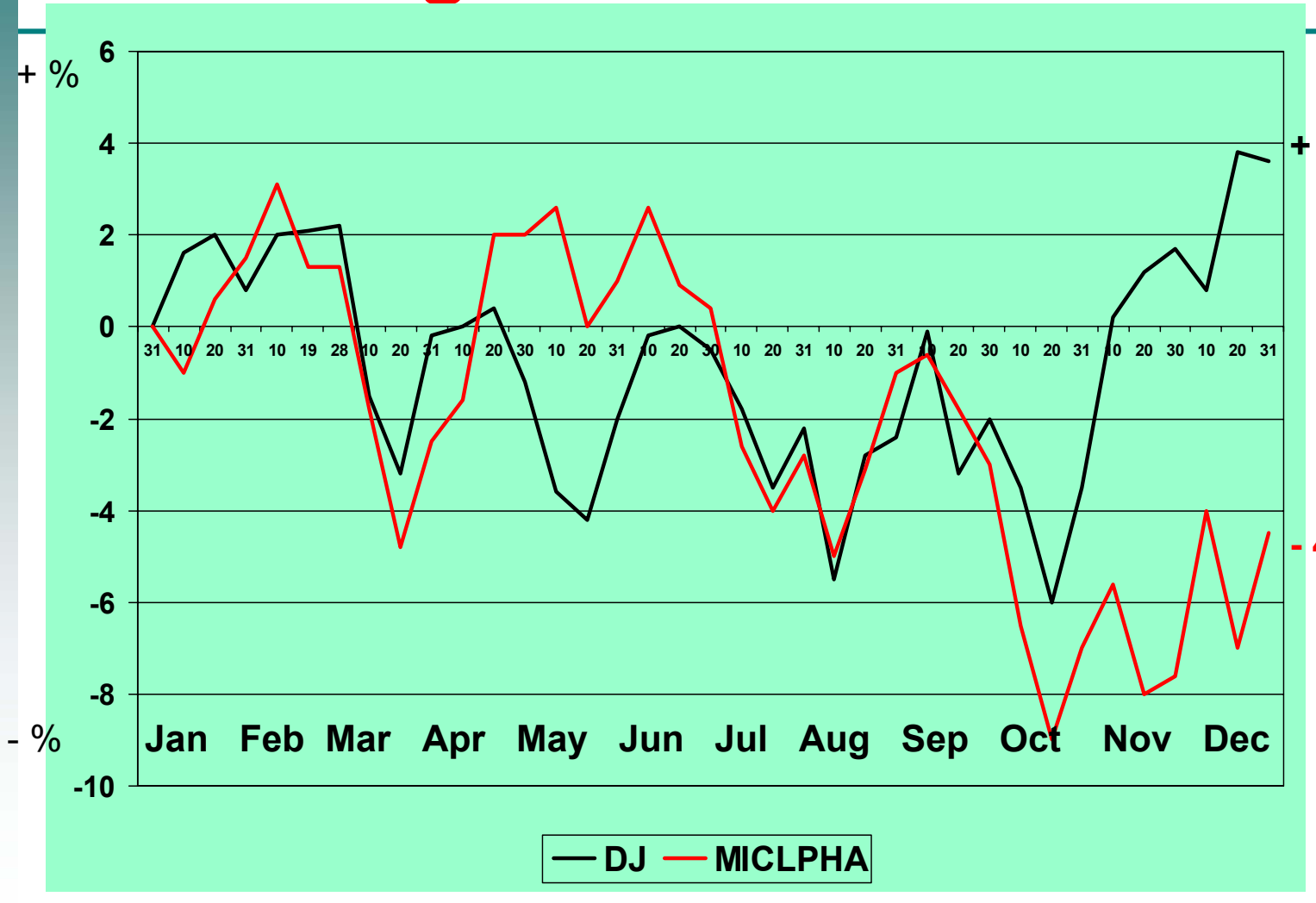
Marketing Excellence



source: accenture, 2003

Dow Jones Industrial vs. Bloomberg Pharma Index

2004



source: Bloomberg (adapted)

Two Bright Spots on the Demand Side

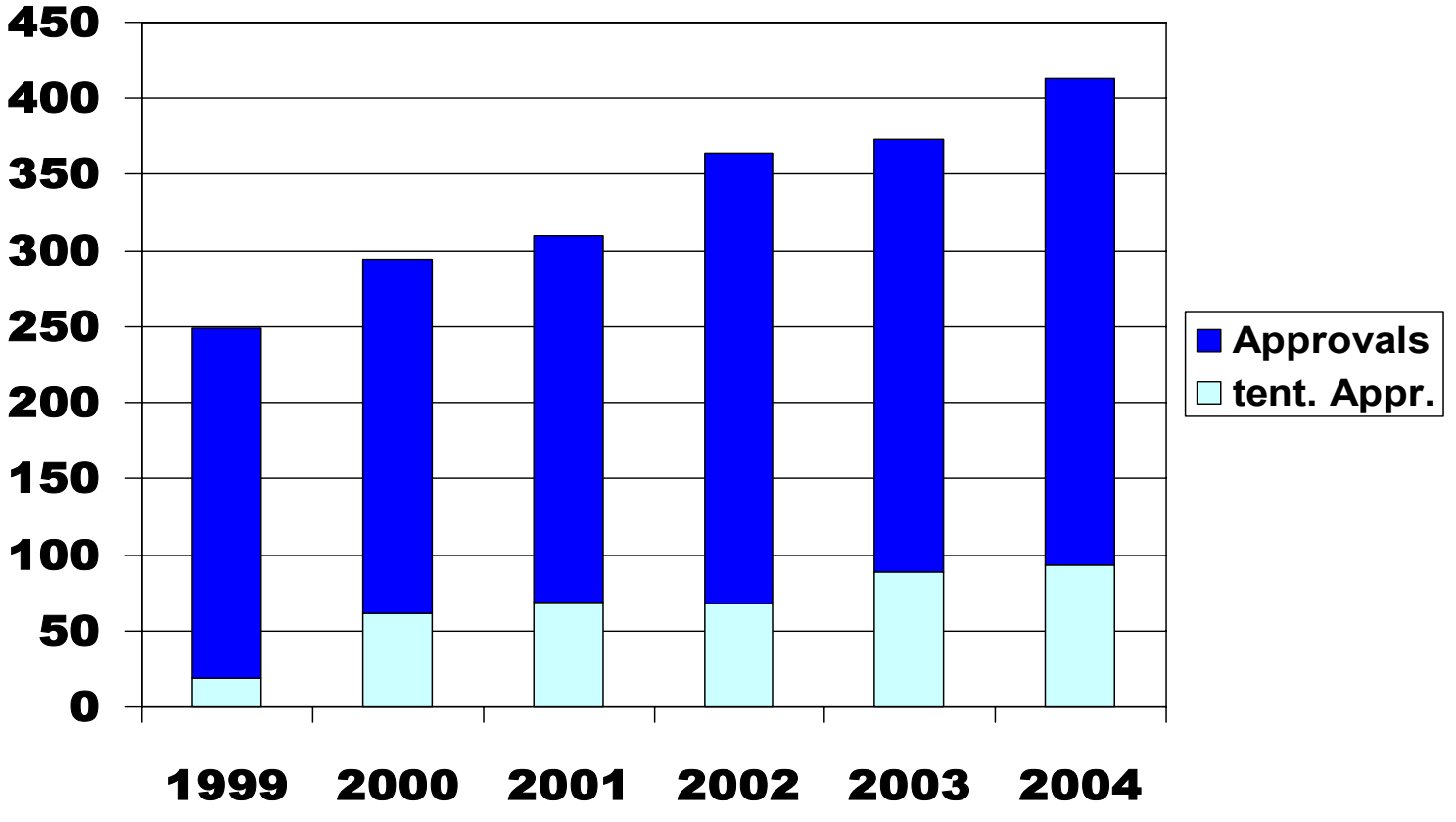
Custom Manufacturing

- Higher R&D productivity & new R&D tools coming to fruition
- Resolving Big Pharma‘s „Two Cultures Splits“
  - ❶ intellect intensive research à la Hollywood
  - ❷ capital intensive development, production and marketing à la Detroit

API-for-Generics

- Continued double digit growth of demand

Generic Drug Approvals



source: FDA / Center for Drug Evaluation & Research

Metro Washington Field Office
Sentencing/Convictions
May 2, 2005, Luigi RATTI, former President and Chief Executive Officer of BIOCHIMICA OPOS sentenced in the USA to one (1) month and two (2) days incarceration; twelve (12) months of home detention; pay a criminal fine of $16,481,000; and forfeit $300,000 to the United States government.
www.eddi-inc.com/news8.cfm

Foreign drug firm pleads guilty to felony charges - Investigator's Reports - Roussel Uclaf S.A. pleads guilty to fraud on behalf of Biochimica Opos Sentenced to Pay U.S. $33 Million
Rousell Uclaf pled guilty and was sentenced under a two count information charging the company with conspiracy and the introduction of adulterated drugs in interstate commerce with the intent to defraud or mislead, in violation of the Federal Food, Drug, and Cosmetic Act.
This case represents the first time that a foreign corporation has been criminally punished based upon defrauding the FDA concerning a drug product which it manufactured wholly outside the United States but marketed to the American public. It is also among the largest monetary penalties ever imposed in a criminal pharmaceutical prosecution.
http://www.infojustice.com

- - - - - -

Metro Washington Field Office
Sentencing/Convictions
www.eddi-inc.com/news8.cfm

The case against BIOCHIMICA OPOS (OPOS) was initiated in 1997 based on a referral from the Office of Compliance, Center for Drug Evaluation and Research (CDER). Eli Lilly had alleged to CDER that OPOS, an Italian manufacturer of bulk active pharmaceutical ingredients, had falsified FDA submissions related to the locations and methods they used to manufacture cefaclor and other drug products. CDER directed that an inspection be conducted on-site at OPOS' facility in Agrate Brianza, Italy, where evidence of falsified production records was discovered.

The ensuing investigation uncovered three specific crimes committed during OPOS's manufacture of cefaclor. First, the company subcontracted out the manufacture of one intermediate ingredient to Archimica, which was proper, but Archimica then re-subcontracted that step to an unapproved firm in Iasi, Romania. Second, OPOS subcontracted out the manufacture of two additional intermediates to Archimica which it was not allowed to do under its own drug master file. Finally, OPOS substituted a required chemical in the processing of cefaclor with a different, unapproved chemical. The investigation revealed Luigi RATTI controlled both OPOS and Archimica and would make 5% of the profits realized by OPOS.

On October 19, 2001, Aventis Pharmaceuticals, Inc., parent company of Roussel-Uclaf and BIOCHIMICA OPOS, was convicted of violating Title 18, U.S.C. § 371 - Conspiracy and Title 21, U.S.C. § 331 (a) - Distribution of Adulterated Drugs. The company was sentenced to pay a criminal fine of $23,193,660 and to voluntarily forfeit $10,000,000 to the United States.

The investigation into the people who were behind the conspiracy continued. The investigation revealed that RATTI orchestrated the creation and maintenance of false records that were used to

mislead the FDA during its inspections of OPOS. The documents stated the drug was manufactured in accordance with the company's FDA submissions but concealed the fact that elements of the manufacture had been subcontracted out to another RATTI-controlled corporation and a Romanian firm that were not authorized to conduct those steps. Those documents also concealed the fact that an unapproved chemical was used in the process of making cefaclor.

On July 16, 2003, RATTI, former President and Chief Executive Officer of BIOCHIMICA OPOS, was named in a sealed indictment. The indictment listed twelve charges, including shipment of adulterated drugs in interstate commerce, making false statements, wire fraud and conspiracy. A warrant was issued for his arrest, but RATTI remained an Italian citizen residing in Switzerland.

On March 30, 2004, RATTI, attempted to enter the United States at the Miami International Airport. He was unaware of the arrest warrant and was arrested and placed in the custody of the United States Marshal's Service. On April 1, 2004, RATTI was detained without bond and extradited to the District of Maryland.

Eventually, on May 2, 2005, RATTI was convicted of violating Title 21, U.S.C. § 331 (d) and 333 (a) (2) - Introduction or Delivery into Interstate Commerce an Unapproved Drug. RATTI was sentenced to one (1) month and two (2) days incarceration; twelve (12) months of home detention; pay a criminal fine of $16,481,000; and forfeit $300,000 to the United States government.

****

Foreign drug firm pleads guilty to felony charges - Investigator's Reports - Roussel Uclaf S.A. pleads guilty to fraud on behalf of Biochimica Opos S.p.A - Brief Article

FDA Consumer, Jan-Feb, 2002 by Carol Lewis
A French pharmaceutical company has been fined $33 million for deliberately failing to disclose to Food and Drug Administration officials all of the locations where the antibiotic cefaclor was being manufactured. The monetary penalty is one of the largest ever imposed in a criminal pharmaceutical prosecution.

Paris-based Roussel Uclaf S.A. was ordered to pay the fine after pleading guilty on behalf of its Italian subsidiary company, Biochimica Opos S.p.A., to felony charges of conspiracy and introducing adulterated drugs into interstate commerce with the intent to defraud or mislead. Cefaclor, approved to treat various infections, was being marketed to American consumers, but was manufactured outside the United States at facilities not disclosed to the FDA. The purpose of the illegal scheme was to increase sales of cefaclor in the United States, according to FDA special agents.

U.S. District Judge Peter J. Messitte in Greenbelt, Md., handed down the fine in October 2001. The case represents the first time that a foreign corporation has been criminally punished for defrauding the FDA concerning an approved drug product manufactured outside the United States and marketed to the American public.

French Drug Firm Pleads Guilty to Felony: Sentenced to Pay U.S. $33 Million
http://www.infojustice.com

Greenbelt- Thomas M. DiBaggio, United States Attorney for the District of Maryland, Assistant Attorney General Robert D. McCallum, Jr., of the Department of Justice's Civil Division, and Bernard A. Schwetz, Acting Commissioner of the Food and Drug Administration announced today that a French corporation, Roussel Uclaf S.A., pleaded guilty to felony charges of conspiracy and defrauding the Food and Drug Administration. U.S. District Judge Peter J. Messitte then sentenced the company to pay criminal and civil penalties of over $33,000,000 pursuant to a plea agreement between Aventis, Pharma A.G.(the successor corporation to Roussel Uclaf) and the United States Attorney's Office for the District of Maryland and Department of Justice.

This case represents the first time that a foreign corporation has been criminally punished based upon defrauding the FDA concerning a drug product which it manufactured wholly outside the United States but marketed to the American public. It is also among the largest monetary penalties ever imposed in a criminal pharmaceutical prosecution.

Rousell Uclaf pled guilty and was sentenced under a two count information charging the company with conspiracy and the introduction of adulterated drugs in interstate commerce with the intent to defraud or mislead, in violation of the Federal Food, Drug, and Cosmetic Act.

According to the statement of facts to which a Rousel Uclaf representative admitted, the case involved Roussel Uclaf's manufacture of the drug cefaclor in 1995 and 1996 through an Italian company, Biochimica Opos S.p.A., which was a wholly-owned subsidiary of Roussel Uclaf. Cefaclor is an antibiotic used to treat various infections, including upper and lower respiratory infections, pharingytis, tonsillitis, urinary tract infections, and skin infections. Although manufactured wholly outside the United States, Roussel Corporation, another wholly-owned subsidiary of Roussel Uclaf, distributed cefaclor and other drug products manufactured by Roussel Uclaf and Biochimica Opos in the United States.

Since that time, through a series of corporate combinations, Roussel Uclaf has become part of Aventis S.A. and its pharmaceutical arm, Aventis Pharma AG. Aventis Pharma, located in Frankfurt, Germany, is now one of the largest pharmaceutical companies in the world.

According to facts set forth in the plea agreement, between April 1995 and September 1996, various individuals, including authorized agents of Roussel Uclaf, willfully sought to mislead the Food and Drug Administration (FDA) about where and how cefaclor was being manufactured. The purpose of the illegal scheme was to increase the amount of cefaclor available for sale by Roussel Corporation in the United States. Agents of Roussel Uclaf misled the FDA by falsely representing that cefaclor was being manufactured at the production facilities listed in an application relied upon by the FDA when approving the drug for use within the United States. In fact, these persons knew that other facilities in Italy, France, and also in Romania were involved in the manufacture of the drug and that these facilities had not been disclosed to the FDA.

FDA regulators need to know the location where approved drugs are manufactured in part so that they can effectively monitor and inspect the manufacturing facilities and methods used in making pharmaceuticals. Thus, pharmaceutical manufacturers who legally import drugs into the United States are required to create and maintain batch production and control records for each batch of a drug product, consisting of such information as the identity of each active and inactive ingredient used, the location of the manufacturing facility, in-process laboratory control test results, a description of each step in the drug's manufacturing process, and the names of all persons performing and supervising each significant step in the drug's manufacture.

In this case, batch production records at Biochimica Opos' facility falsely misrepresented the production method for cefaclor and falsely showed the manufacturing facilities involved in the production of the drug. In or about May of 1996, members of the conspiracy actually provided false cefaclor batch records to inspectors of the Food and Drug Administration who were conducting an inspection in Biochimica Opos' facility in Agrate Brianza, Italy, and thus willfully misled the Food and Drug Administration about where the cefaclor manufacturing processes were located and how the manufacturing process was being conducted. In addition, a set of false records were kept regarding the manufacturing facilities involved, such as raw material log books, a double software application, and work orders.

United States Attorney Thomas M. DiBiagio stated, "Today's massive criminal penalty sends an unmistakable message to all pharmaceutical companies worldwide. If you plan on selling drugs to the American public, you must play by our rules, whether your company is located inside or outside the United States. This kind of fraud will cost you dearly."

"Quality control of pharmaceuticals distributed in our nation is a top priority," said Assistant Attorney General Robert D. McCallum, Jr., head of the Justice Department's Civil Division. "We will not tolerate any company's efforts to skirt the government's stringent requirements for the sake of profit over the health of our citizens. "

Clients, Competitors and Consultants in the GMP Fine Chemicals Market

Guy Villax

ChemSpec Europe 22-23 June 2005

HOVIONE

Agenda

Clients, Competitors and Consultants in the GMP Fine Chemicals Market

- **1999-2005: what happened**
- **Going Forward**
- **Conclusion**

High priced acquisitions

- **Some quotes**
  - On its $545m Rhodia acquisition: ***"With ChiRex, we gain an immediate leadership role in the pharmaceutical contract research and contract manufacturing services arenas."***
  - Deutsche Bank Alex. Brown's 1999 report titled "Pharmaceutical Contract Manufacturing ***"by our estimates, the fine chemical/pharmaceutical contract manufacturing (CMO) industry will grow in excess of 15% per year over the next five years"***
  - Solutia's strategy: ***"we have aggressive goals [to build a] $500 million division within 3 - 5 years"***
  - On its exit from Pharma fine chemicals Honeywell said: ***"..pharmaceutical chemical manufacture is a highly capital intensive business plagued by over-capacity, clinical trial failures, limited new drug approvals, new drug marketing disappointments, and price wars…"***

Acquiror	Acquired to 1994	Acquired 1995-1997	Acquired 1998-2000	Exits 2000
(Miles (USA)) BAYER	ChemDesign (USA)			
Shell (UK)	Synthetic Chemicals (UK)			
Technochemie (Germany)				
Ward Blenkinsop (RU)				
La Mesta (France)				
DSM (Holland)	Andeno (Holland),		koninklijke Gist-Brocades (6149 mUSD)	
			Catalytica (800 mUSD)	
Plaine (Switzerland)				
Gema (Spain)				
Tessenderlo Chemie (Belgium)	Farchemia (Italy)			
Nobel Chemi (Sweden)	Profarmaco (Italy)			
Blasinachim (Italy)				
Cambrex	Akzo Nobel (130 mUSD)	Biowhittaker (129 mUSD)	Irotech (40 mUSD)	
Chirex		Stirling Organics (Dudley facility- 66 mUSD)		
		Glaxo Wellcome (Ardmore facility- 66 mUSD)		
Lonza		Celltech Biologics (52 mUSD)		
BTP plc		PCR Inc (72 mUSD)	Archimica (137 mUSD), Hexachimie (87 mUSD)	
Warner-Lambert		Hickon pharmachen (29 mUSD)		
Catalytica		Glaxo Wellcome (Greenville facility- 247 mUSD)	Wyckoff Chemical (74 mUSD)	
AlliedSignal Inc			Pharmaceutical Fine Chemicals (390 mUSD)	Honeywell
Laporte plc			Inspec Group (1020 mUSD)	
Ascot plc			Chirotech Technology Ltd (97 mUSD)	
PPG			Lipsy Chimie Fine (60 mUSD)	
Great Lakes Chemical			NSC Technologies (125 mUSD)	
Investcorp/Cinven			Astrazeneca (2100 mUSD)	
Cardinal Health			Automatic Liquid Packaging (390	
Clariant AG			BTP plc (1800 mUSD)	
Rhodia			2 UK plants from RPR	
Rhodia			Chirex (545 mUSD)	
				Eastman
				Occidental

$0.7b

$14b

The M & A Frenzy

Company sold		Acquiring Company	acquistion		P/E **)
name	sales *)		year	price	
Archimica	45	BTP (UK)	1998	n/a	≈ 70
BTP	150	Clariant (CH)	2000	1800	≈ 28
Catalytica	425	DSM (NL)	2000	800	≈15
ChiRex	150	Rhodia (F)	2000	545	≈ 30
Laporte	600	Degussa (D)	2000	2000	n/a

*) $ mio, last year prior to the acquisition
**) the numbers connot be exactly compared, as definitions of earniangs differ

DSM re-emerges as front runner to acquire Rhodia

By David Firn in London

DSM, the Dutch chemicals company, has re-emerged as front runner to acquire French chemicals group Rhodia after Clariant, the Swiss speciality chemicals company, abandoned plans to buy it.

A merger of Clariant and Rhodia, the former Rhône-Poulenc chemicals business, would have created one of the world's largest speciality chemical groups, with a market capitalisation of about €5.3bn and sales of $13.6bn (€15.5bn), putting it third behind DuPont of the US and Degussa of Germany.

DSM is understood to be in talks to buy the 25 per cent stake in Rhodia – worth €475m – held by Aventis, the Franco-German life sciences group, created by the merger of the life science activities of Hoechst of Germany and Rhône-Poulenc in 1999. Neither company would comment yesterday.

DSM last month denied reports it was preparing to offer €14 a share in cash and equity for Rhodia, which has seen its share price plunge from €17 in February to about €11 after a string of profit warnings. Since then, DSM has agreed the €1.24bn sale of its stake in Energie Beheer Nederland to the Dutch government, which increases its financial flexibility.

The combination of DSM and Rhodia would create a group with annual sales of about €16.4bn and boost DSM's presence in high-margin fine chemicals, but a deal could be hard to finance. Rhodia has debt of €3bn, and DSM debt of €2.2bn.

Rhodia is understood to oppose a deal with DSM, which is thought likely to insist on taking control of a merged group. Rhodia would have retained some management control in a merger with Clariant, despite being half its size.

Rhodia said a deal with Clariant would offer no advantages for either set of shareholders.

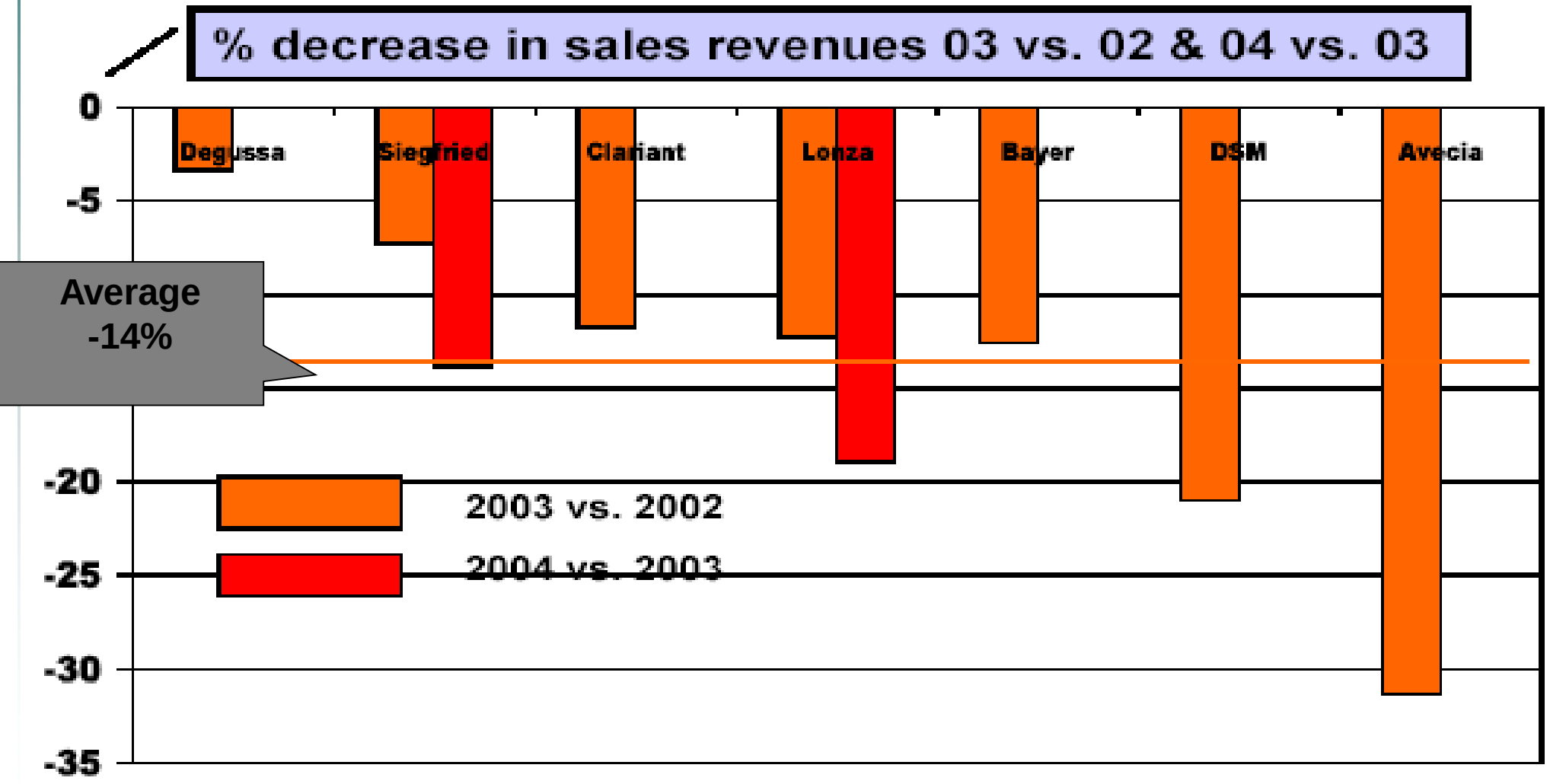
Rhodia and Clariant are suffering financially after overpaying for fine chemicals acquisitions.

Rhodia shares closed down 2.02 per cent at €10.65. Clariant shares were up 1.72 per cent at SFr32.60. DSM closed down €0.10 at €39.95.

...are suffering financially after over paying for fine chemicals acquisitions

FT 23Nov2001

Sales Development of Major European Fine Chemical Comp. 03 / 02 & 04 / 03



Source: P.Pollak
Feb 2005

Misconceptions / Lessons learnt

- **Pharma Fine Chemicals...**
  - **Is not a manufacturing business**
  - **GMP is not a building**
  - **5 years is nothing, 10 years might get you onto a preferred suppliers' list**
  - **Size is not equal to reliability, reach or capacity**
  - **Process development is not a chemistry group**
  - **Regulated intermediates are not APIs**

- **The market changed, innovation migrated...**
  - **Old pharma wants intermediates**
  - **New pharma wants APIs**

- **The New innovators:**
  - **Want: communication, transparency, quality**
  - **Demand: risk-taking, speed and flexibility**
  - **Impose: unthinkable timelines**
  - **Offer: rational and quick decision-making, fair treatment**

In hindsight – 1

Pharmaceutical Chemical outsourcing:

- **For the Chemical Giants – this was a new opportunity:**
  - ⇒ **Non-cyclical**
  - ⇒ **High margin, high growth**
  - ⇒ **Away from commodities, heavy, dirty, chemistry**
  - ⇒ **Profitable customers**

- **For the EU based pharma fine chemical players – this was**
  - **more of the same (technology, plants, compliance...)**
  - **and a new market to add to generics:**
    - ⇒ **A defensive move towards greater technical challenge, away from the Asian threat**
    - ⇒ **Pushed - away from generics by legislation SPC**

In hindsight – 2

- Large Pharma outsourcing hid the real opportunity: The Nasdaq Biotechs represented a big, though discrete, API business.

- The larger traditional CMOs ignored the Biotechs – undeserving clients:
  - ⇒ with no track-record, no products, nothing to show...
  - ⇒ small, understaffed, with no idea about how to do things by the "book"
  - ⇒ who want everything yesterday
  - ⇒ who want an API rather than an intermediate
  - ⇒ who dont expect established relationships

    We have the big clients, we don't need the small fry

- The European Independent API specialist discovered a perfect fit with the Nasdaq Biotech:
  - ⇒ Clients that need speed, agility, flexibility and service
  - ⇒ Cultural affinities: Small size, risk-takers, entrepreneurial spirit, rational decisions, quick
  - ⇒ API compliance
  - ⇒ Issues with crystal form...

    This was an exciting step up from generics

In hindsight – 3

- Size does not matter
  - No economies of scale on the product side
  - Critical mass is quickly reached
  - Big is a marketing liability

- Back-integration is a disadvantage
  - Limits choice and opportunities
  - Imposes a high cost base
  - More ntegration ⇒ Less Flexibility ⇒ More CapEx

- GMP and service is a mind-set
  - Takes time and dedication, rather than cash
  - Demands senior management understanding and leadership

- It starts as a service business, driven by culture

In hindsight – 4

- R&D productivity dropped
- Large Pharma insourced
- Many new approvals got delayed
- Extra pharma fine chemical capacity came on stream

⇒ Red numbers
⇒ Scrambling to fill plants
⇒ Scrambling to meet the numbers

...soon billion dollar goodwill write-offs

Winners and Loosers

The Winners

- The shareholders that sold out: ChiRex, Catalytica, BTP etc...
- The Investment banks, the bankers and the consultants
- Top Management

The Loosers

- The shareholders of the chemical giants because
- they paid too much
- and got,
  - only infrequently good plants
  - and then bundled with many non-pharma sites
  - more usually underinvested / old plants
  - plants never designed to be multi-purpose, flexible or lean

- Those that lost their jobs

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.

GUY VILLAX
Hovione

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:

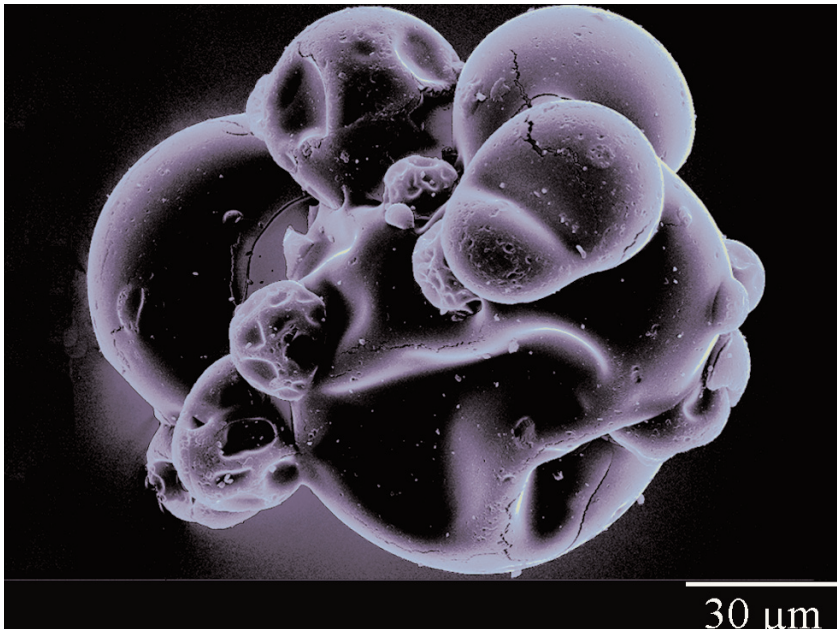
- It focused on manufacturing and ignored the service component;
- It imposed unrealistic sales budgets, cut head count and stopped investing.

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

Guy Villax has been the chief executive officer of Hovione since 1997. Prior to that, he held positions with Hovione in the Far East and Price Waterhouse in London. He has a degree in accounting and financial management from the University College at Buckingham. He is a member of the board of CEFIC's European Fine Chemicals Group.

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.

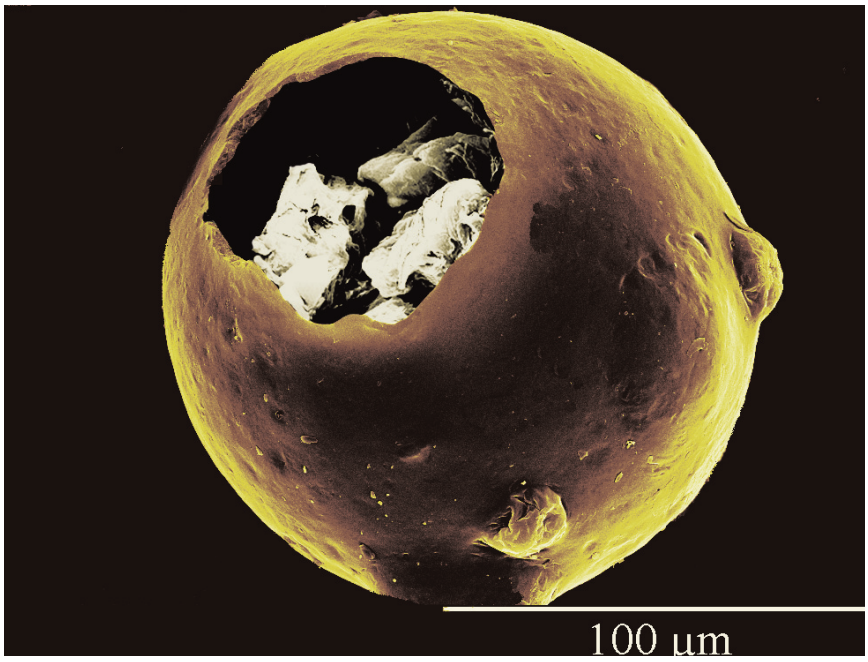
In addition, very often new compounds have unforgiving chemistries. Executing these sensitive processes require a depth of skill and plant sophistication not widely available. This requires expertise in preparing and executing proven acceptable-range studies. And, when the tight safe parameter ranges 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

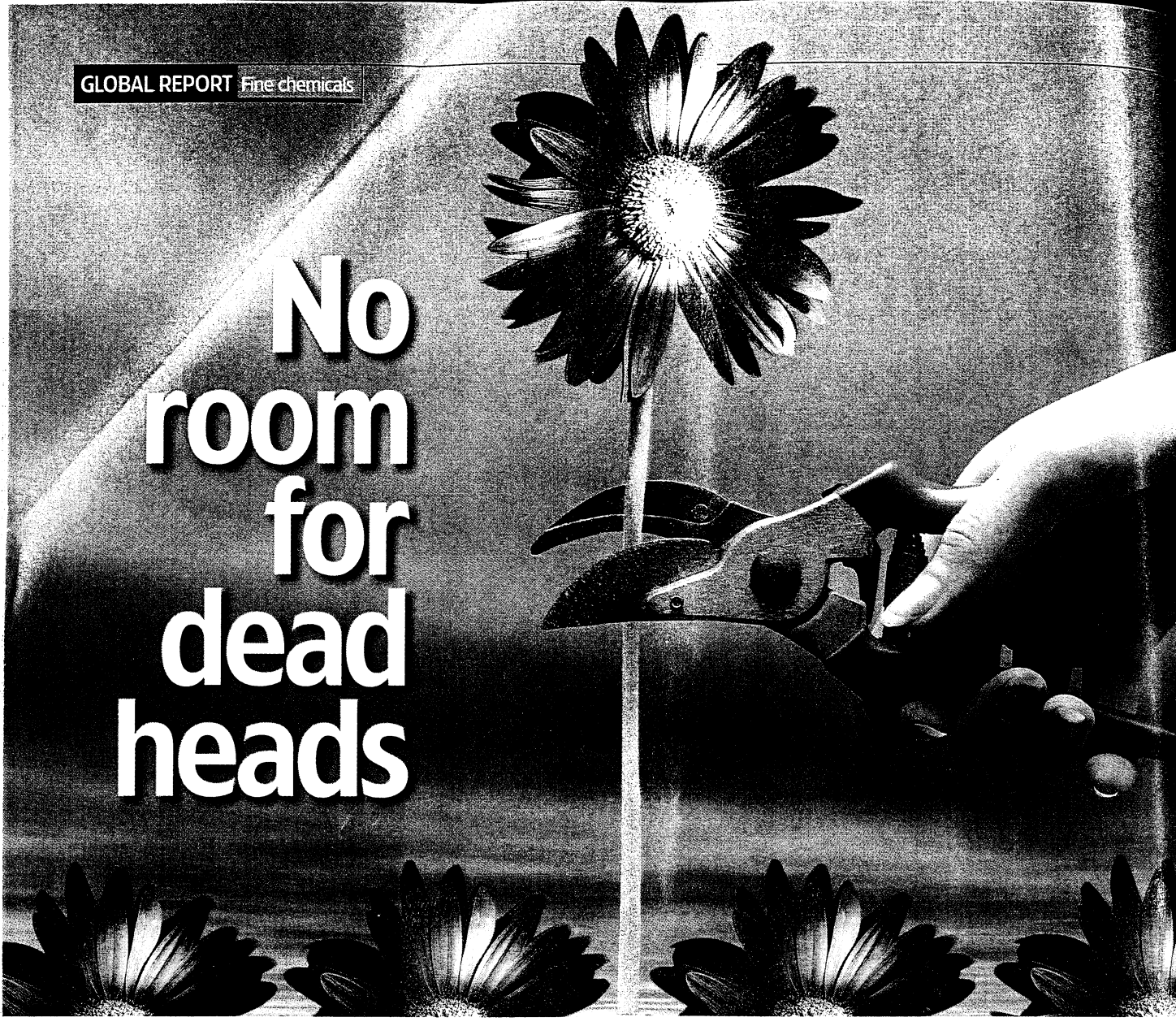
Asia is a serious competitor, and worse than ignoring it is to continue to make sweeping generalizations about the Indians and Chinese. The successful European companies understand that they must be in the continental U.S. to be close to the client, the science and FDA. Furthermore, they have developed 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. ■



No room for dead heads

Five years after its buying spree, the fine chemicals sector continues to put its affairs in order and is looking forward to long-term sustainable growth. **Clay Boswell** reports

DEGUSSA'S OCTOBER write-off of its Laporte acquisition, following Rhodia's of ChiRex and, more distantly, Clariant's of BTP, may signal that the fine chemicals sector has put the past behind it. Overcapacity remains a problem, particularly in the less-differentiated segments most affected by the influx of competitors from India and China, but custom manufacturers believe the argument for outsourcing the manufacture of active pharmaceutical ingredients (API) is more compelling than ever, and for companies offering special technologies, attentive service and stability, the future looks bright.

"The large companies, the new entrants, are cleaning up," says Enrico Polastro, vice president and industry manager with the Brussels office of Arthur D. Little. "Some are likely to exit totally. Established players, the ones with a tradition in the field, appear to enjoy a pick up of demand, as customers return to outsourcing. So after a pruning, if you like, there is a recovery. Whether things will return to the levels we enjoyed in the late '90s, this is something else."

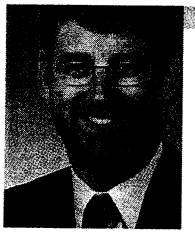
Of the four massive fine chemical acquisitions made around the turn of the millennium, only DSM's $800 million purchase of Catalytica Pharmaceuticals has not been put down as a loss. Clariant was the first acquiror to write off its purchase, in 2003 writing off CHF790 million ($611 million) in goodwill remaining from its £1.1 billion ($1.9 billion) purchase of BTP in 2000. Rhodia, which acquired ChiRex for $580 million in 2000, wrote off €135 million ($161 million) in goodwill in January, followed in August by a €101 million charge for the remaining value of the business. Degussa, which acquired Laporte for about £1.36 billion in 2001, last month announced that it was taking an impairment charge of €710 million relating to goodwill and €120 million relating to other assets.

"These companies bought the fine-chemicals activities at the peak of the cycle," Polastro points out. Growth expectations of 15 percent per year made the sector seem the most attractive in the chemical industry. "Most chemical companies wanted to set a base in this field, and eventually they co-

64

peted to acquire these businesses, paying multiples that at the end of the day were not justified, particularly when growth did not materialize," he says.

"At the end of the day, the value that was vested in organic synthesis was overstated, in the sense that people thought that if they had a brilliant [synthesis] or innovative technologies—it was the time of the chiral dreams, if you want—that this would translate into enormous profit, given that there was chance to get proprietary a position."



"It is one of those classic things: if you can't be differentiated, don't do it"

Nick Hyde, global business director, Dowpharma

Subsequent product failures, delayed launches, pharma mega-mergers and inroads by suppliers in India and China yielded overcapacity and severe pricing pressure, decisively tempering the optimism of the late 1990s. And whereas critical mass was once a hot topic, the notion seems to have fallen out of vogue. "This is still a relatively niche business where economies of scale do not seem to be boundless," Polastro observes. Small to medium-size companies, particularly if they are privately owned and free of the constraints of quarterly earnings reports, do better in a market characterized by long lead times and unpredictability, he says. Ultimately, customers are less interested in the size of their suppliers than in their stability.

RESTRUCTURING

Clariant, Rhodia and Degussa have each restructured to salvage their position. Degussa sold its Radebeul, Germany, facility to generics producer Hexal in March 2004, and the same year began a cost-cutting program. "This program will bring some reductions in headcount at various sites, but we do not expect to shut any down," says Patrik Wohlhauser, head of Degussa Exclusive Synthesis & Catalysts. "The overall environment has indeed forced companies to restructure. But in our view, the market as a whole is improving." Noting that business trends and market prospects "fell short of expectations," in part owing to overcapacity, Wohlhauser says the impairment charge "frees us to focus our energies on our operations. Exclusive Synthesis & Catalysts continues to be a core business. In fact, our Exclusive Synthesis business expects to meet budget for the year. And Degussa overall expects a slight improvement in sales and EBIT for the year."

For its part, Rhodia has mothballed a facility in Holmes Chapel, UK, and closed another in Staveley. Eighty-five jobs, 24 percent of the workforce, were cut last year from the facility at Dudley.

New players are also arriving on the scene, suggesting there is still opportunity in the market. For example, Groupe NovaSep was formed by the merger of NovaSep and Dynamic Synthesis, the fine-chemicals business of Dynamit Nobel, late last year. About the same time, Kemira's fine-chemicals unit in Kokkola, Finland, was acquired by UK-based venture capital firm 3i. The new business, named KemFine, acquired Avecia Fine Chemicals in Scotland, in September.

BASF dramatically improved its standing in the sector with the acquisition of Orgamol, a move that might seem to parallel earlier big-chemical leaps, except for Orgamol's quality and BASF's timing, notes Polastro. "They have built patiently," he says, noting that BASF did not participate in the millenial buying frenzy.

Antonio Germani, director, contract manufacturing at BASF, is "somewhat optimistic" for both 2005 and 2006, though challenges remain. "In the past years, competitive pressure from Asian suppliers has grown," he acknowledges. Additionally, the exchange rate between euro and U.S. dollar is quite adverse for Western companies." BASF's R&D and manufacturing integration (Verbund) is one means for coping with these challenges, he says. The acquisition of Orgamol is another. "It is a strategic step towards expanding our business and achieving sales and profitability targets that will help us sustain continued growth."

MORE THAN KETTLES

The last five years show that success takes more than reactor capacity.

"The CMO market is far from being homogeneous, there is a large difference in financial performance between those that are doing well and those who are not." says Mark Cassidy, business director for small molecules, Dowpharma. "My feeling is that this divide will increase further. Companies that have differentiation will be successful, those that haven't will suffer and the emergence of Asia will impact them much more."

Dowpharma made a strategic decision not to compete in any area where it was not differentiated, adds Nick Hyde, global business director, Dowpharma. The company's decision to close its Smithfield, R.I., facility and exit mammalian cell culture was one consequence. "That is one of those classic things: if you can't be differentiated, don't do it," he says. "What we've been doing subsequently is developing microbial expression technology—Pfenex—in San Diego, and another part of Dowpharma has been developing the plant transgenics and vaccines activities." Hyde says the strategy is paying off in growth of two to three times the small-molecule market average of 5 percent, and even higher in some biotech areas.

Clariant seems to have heeded the lesson in its restructuring, which it carried out in 2003. "When we decided three or four years ago that we wanted to be excellent in the areas we knew well and we are known well for—organic chemistry solutions—we began to differentiate our offerings and investing in our position of having supply capabilities in both the EU and the USA," says Ralf Pfirmann, global business director of Clariant's pharmaceutical fine chemicals business. "Pharmaceutical innovators are acknowledging the robustness of our offering."

The company has also diversified its offering, in late 2004 entering the market for producing controlled substances at its Spring-

CONTINUED ON PAGE 21

SOLD

There have been other shifts in the market. In the last year alone, GenCorp sold Aerojet to American Pacific; Lonza sold its Pasadena facility to Gulf Bayport; Nufarm sold SEAC to Minakem; and Rütgers Chemicals AG sold its fine chemicals business in Mannheim, Germany and Augusta, Georgia, to International Chemical Investors, which renamed it WeylChem. Borregaard sold Borregaard Synthesis in Newburyport, Mass. to Polycarbon Industries and closed its facility in Maddone, Italy. Diosynth put its Buckhaven, UK, facility up for sale; EMS-Chemie spun off Dottikon; and the investors behind Avecia have begun to parcel the business out.

CONTINUED FROM PAGE 19

field, Mo., facility, developing a line of problem-solving reagents—SynSelect Functional Products—and revitalizing its generics portfolio, with plans to expand it by two to four launches per year.

Pfirmann sees "steady, sustainable growth" in the market, but with a caveat. "Pharma companies are becoming more selective in the suppliers with whom they will work."

Beyond a distinct offering, though, success also requires a commitment to service, a commitment Hovione chief executive Guy Villax believes was neglected by the chemical giants. "I think they never considered it relevant and did not organize themselves to address that critical aspect," he says. "The execution of the service element is extremely challenging, as it relies almost entirely on the project team to do good service, that is, it is they that interface with the customer—not the sales person."

Despite the hardships of the last five years, the small and mid-size generic API manufacturers that pursued outsourcing have managed to grow, he says, because they not only had capacity, they also had a track record, proven competencies and management that focused on serving customers well. Further, they had the vision to see that the center of innovation was shifting to the biotech sector. "Till the end of the '90s, who you had buying outsourcing services was Big Pharma. In this decade, the buyers became the biotechs. They need to buy a very different product. They are not driven by tax strategies. They are not in the rent-a-vessel business. They need a complete solution that involves many disciplines, and they prefer people with a track record in APIs, not in intermediates."

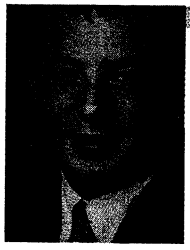
"The model offers flexibility for the separate development of fine chemicals"

Wilhem Stahl, head of R&D/head of marketing pharmaceuticals, Lanxess

OVERCAPACITY

Excess capacity remains a serious problem. "We have seen a number of restructuring activities at various custom manufacturing companies over the last few years," says Wilhelm Stahl, head of R&D and head of marketing pharmaceuticals in the business unit fine chemicals at Lanxess. "This has, however, not yet led to any substantial consolidation of overcapacities." He observes a "slight improvement" in business conditions, and notes that moves by a number of large pharmaceutical companies to consolidate their production sites are generating outsourcing opportunities, but there is a way to go yet. "The market continues to be a buyer's market with considerable competitive pressure."

Lanxess' fine chemicals business has been under serious strain, burdened by underutilization, obsolete assets, and annual losses in the hundreds of millions of euros. The company is responding by carving the fine chemicals business out as an independent company under the umbrella of the Lanxess Group. "I believe this is a necessary step, if we are to successfully implement the new business model," says Stahl. "The new model offers maximum flexibility for the separate development of the fine chemicals business," he explains. "It enables us to drastically reduce costs by closing facilities where capacity utilization is low or the plants are unsuitable. We will deliberately forgo unprofitable business. And finally, all key services will be rendered directly by the new legal entity—in an efficient manner and carefully tailored to support our fine-chemicals business."



"There remains an excess of supply to demand but... we see this being more balanced in the future"

Nick Green, president, Rhodia Pharma Solutions

Nick Green, president of Rhodia Pharma Solutions, believes industry dynamics are favorable. "There remains an excess of supply to demand, but if the present trends continue, we see this being much more balanced in the future," he says. "We have restructured our business in order to improve our costs. At the same time, Rhodia Pharma Solutions is getting closer to customers in order to better understand their needs and offer mutually beneficial solutions. We are also focusing on technologies, like hydrolytic kinetic resolution (HKR) and aromatic bond formation (ABF), that differentiate us in the market. All of these actions are yielding positive results as we seek to improve our operations."

Matt Hanson, market manager at SAFC, expects continued consolidation and fallout as a result of overcapacity. SAFC's business has been "solid," however. "Emerging pharma and biotech companies continue to have moderate success raising capital for developmental projects, and that has created continued buoyancy in the contract manufacturing industry."

Roger Laforce, general manager, marketing/sales, R&D and logistics at FIS, is optimistic. Business is improving, he says, not only at FIS, but apparently more generally, even though the number of NDAs has not increased. "The better situation may be attributed to more outsourcing (also of mature products) but also to more intense marketing and sales activities of the providers," he suggests. "Outsourcing practices have become more challenging—this gives us a chance to show our skills." Pipeline management has become more complex and demanding, he says, with more and smaller projects in earlier clinical phases. "Turnaround times of offers have become incredibly short," he notes. "Full project management is the response."

PIPELINE QUALITY

Clariant's Pfirmann says that virtual or biopharma companies are serving their role as a source of innovation on the way to commercialization very well. "In the last three years, we've had more than 30 active projects with these types of companies."

Pfirmann also makes an observation: While pharmaceutical pipelines are increasing in size and value, FDA approvals are not rising but falling, a dynamic that would tend to limit the growth of the contract manufacturing industry. But he sees a bright side. "This may not be such a bad situation for the custom manufacturer and fine chemical company, however," he surmises. "If pharma companies have smaller pipelines that are healthier, you see a situation in which sustainable, manageable growth can occur. The risk is smaller.

"If you look in the past, major projects with expectations that have not come through have triggered investment that resulted in overcapacity."

The first is a simple declaration that the supplier is indeed that manufacturer, complies with both GMP and what is described in the DMF or the CEP, and that the customer will be informed if there are manufacturing changes. A second point would be yearly updates addressing the annual product quality review, the annual stability study, and change control. And third, copies of any inspection reports by credible health authorities.

Noting that audits are not likely to be done more frequently than once every three years, Villax commented that, for example, "if you get an updated stability study, you will know at least that one extra batch has been done that year. And you will get some data. I think this is important if you are a QP [qualified person]."

- The EFCG benchmarking exercise involves a series of specific questions that the EU and member state health authorities need to consider and address if the API GMP program is going to achieve its intended goals (*see box on p. 12*).

The intention of the survey is to determine authority readiness to enforce the new requirements. It "asks questions such as how many inspectors do you have, what kind of training have they been the object of, what is your plan, how many of you audit, in which geographies, etc.," Villax explained.

Ironically, he pointed out, "those that are supposed to be checked [are] asking whether the police have the resources" to do so. The issue is being raised "because we haven't been given any sense that things are what they ought to be. So we are worried, and we are doing something about it."

The survey is intended to help regulators target "what they should be training their inspectors to do," Villax commented, "because in our contacts with a number of inspectors…it becomes quite apparent that the inspectors don't always know what they should be asking."

EFCG has been raising the types of questions included in the survey "at the European Parliament and most recently the French Parliament," and bringing the issues to the attention of the trade press so that the complexities involved can be better understood and addressed, Villax said. Associations in the member states will help the EFCG executives with the initiative, and EFCG is looking for additional volunteer support in the effort, particularly from Ireland, UK, Belgium and the Scandinavian countries.

- In September 2005, APIC/CEFIC released a comprehensive 70-page guideline for API manufacturers on developing a quality management system.

With references to FDA's systems-oriented 21st century quality initiative, the APIC guideline integrates current GMP requirements as defined in ICH Q7A into the ISO 9001 quality management system framework.

Hovione CEO Analyzes Changing Marketplace

In his presentation at the Berlin conference, Villax provided an in-depth analysis of the changing API marketplace in Europe and how it is being impacted by Asian competition, to help explain the importance of the regulatory issues.

- Villax suggested that the current situation for the European industry was made worse by the exaggerated expectations of the boom mentality that existed in the 1999-2000 period.

At that time, projections were circulating of 15% per annum growth, with companies making aggressive acquisitions and creating inflated goals for expansion over relatively short timeframes. The shorter-term projections did not make sense, the Hovione CEO noted, since "it takes a very long time" to develop a product, get it approved and launch it.

At the same time, Villax noted, there were some contrarians "like Honeywell exiting the business – saying that pharma chemical manufacture is highly capital intensive and is a business plagued by over-capacity, clinical trial failures, limited new drug approvals, new drug marketing disappointments and price wars."

- A review of sales of pharmaceutical fine chemicals by the larger European players shows average growth in the 2002-04 period to have been -14%. "So compared to the expectations and the amount of money spent, the net results were really 180 degrees opposite," Villax pointed out.

He commented that "the stock market bubble really didn't help" the situation. "It made money available for management to do these humungous errors. There was, in my view, huge wealth destruction, only to be followed by job destruction. At a moment when we should have really been building our fine chemicals industry to be strong and lean to put up the fight against Asia, we did the exact opposite – we weakened ourselves dramatically."