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Custom Manufacture

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Abstract. The life science industry, particularly pharmaceutical and agrochemical companies, is increasingly outsourcing the development and manufacture of active ingredients and intermediates for drugs and pesticides to specialised fine chemical companies. The global market for custom manufacture represents *ca.* USD 12 billion today and is growing. As the number of companies involved in custom manufacture is growing, too, there is also increasing competition. Entry hurdles are high and the key success factor is the ability to manage the 'value-speed-quality' triangle. Future challenges for the providers of custom manufacture are the high asset intensity of multipurpose plants, the increasing regulatory constraints and the purchasing power of the mega life science companies.

1. Introduction

Outsourcing, derived from *outside sourcing*, parts of the manufacture of industrial products has been pioneered by the automotive industry which – since *Ford* started producing the famous 'T model' on the first assembly line – has always been sensitive to the costs of goods. Whereas initially only small bits of the overall manufacturing process were entrusted to third-party suppliers, the car companies nowadays leave all but the final assembly to custom manufacturers in their most modern manufacturing plants. Thus, the grass-roots plant for the *Smart*, which comes on stream in Alsace (France) this year, consists of a central unit for the final assembly surrounded by satellite units owned and operated by the custom manufacturers of specific parts like doors, seats, transmissions and axles. *Porsche* went even a step further: In September 1997, in an unprecedented move, it partly farmed out even the final assembly for its successful new roadster, the Boxster, to a Finnish company.

Contrarily to the car industry, in the chemical and particularly in the life science industry, the 'what we sell we make' principle prevailed until the early 70s. This is mainly due to the relative small incidence of the cost of the active substance on the sales price of the speciality (drug, agrochemical *etc.*).

Although outsourcing occasionally was done in the 60s already – *Geigy*, for instance, entrusted *LONZA* with the manufacture of a key intermediate for its 'Diazinon' insecticide as of about 1965 –, custom manufacture really took off in 1973. At that time, *SmithKline & French* launched Tagamet, the world's first blockbuster drug. *SmithKline* was caught 'on the wrong foot' by the drug's spectacular success, which made stomach-ulcer surgery a thing of the past. As the in-house production capacity could not keep pace with the skyrocketing demand, a senior manager travelled around the globe in order to find custom manufacturers for the active pharmaceutical ingredient (API) Cimetidine and its precursors. So a number of fine chemical companies in Europe and Japan got heavily involved in the manufacture of bits and parts of this H2 receptor antagonist. Since then, outsourcing has got a firm place in supply-chain management of the life science industry and a multibillion dollar business for the fine chemical manufacturers.

The 25 years of development of customer/supplier relations that followed have been heavily influenced by the dramatic evolutions in the drug- and custom-manufacturing industries, as well as in the regulatory environment.

Given the predominance of the pharmaceutical industry for custom manufacture of fine chemicals (see next chapter), this industry will be covered in detail in this article. Many findings, however, are valid also for other industries, particularly the agrochemical industry which is the second largest user of custom manufacture.

As illustrated in *Fig. 1*, all major activities of drug companies can be considered in principle for outsourcing. The extent to which manufacturing is actually entrusted to third parties depends both on the *size* and the *strategy* of a given company. In terms of the size of pharmaceutical companies a distinction between three categories is made. In *Fig. 1*, 'big pharma' stands for global companies with sales over USD 1 billion, 'small pharma' for pharmacy-type companies with their own brands which typically are drugs made of combinations of well-known APIs, such as acetaminophen, acetylsalicylic acid, caffeine, *etc.*, and 'virtual pharma' for start-up companies with no tangible assets, except for occasional in-house discovery research based on a specific mode-of-action principle. The total number of pharmaceutical companies is very large. In the USA alone more than 10 000 firms are registered with the FDA. The great majority obviously falls into the categories of 'small and virtual pharma'. In the area of San Diego, California, alone 230 of the latter are listed. Virtual companies rely *per definitionem* on outsourcing, but very few actually have a sufficiently advanced new product

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	Research and Development			Manufacturing		Marketing
	Discovery Research	Clinical Testing	Regis-tration	Manu-facturing	Formu-lation	
Big Pharma	In-House	In-House	In-House	see Fig. 4	In-House	In-House
Small Pharma	Outsourced	Outsourced	Outsourced	Outsourced	In-House	In-House
Virtual Pharma	In-House	Outsourced	Outsourced	Outsourced	Outsourced	Outsourced

Fig. 1. *Position of custom manufacturing within the pharmaceutical industry*

portfolio to require custom manufacture. Also, if they do have new drugs with a potential, they often are licensed to 'big pharma', such as the promising antiviral Amprenavir from *Vertex*, licensed to *GlaxoWellcome*. A – positive – exception is *Agouron Pharmaceuticals,* which outsources the whole manufacture of the API of its successful anti-AIDS drug, Viracept.

This leaves 'big pharma' as main users of custom manufacture. The world's top ten companies are listed in *Fig. 2*. Their combined sales will amount to USD 113.3 billion in 1998 representing 36% of total proceeds of the drug industry. In comparison with, *e.g.*, the agrochemical industry where the top ten generate 75% of the total business of USD 33 billion, this industry is still quite fragmented and attempts for megamergers are continuing. As can also been seen from the table, the leading companies are heavily concentrated in four countries, namely USA, UK, Switzerland and Germany. If the list would be extended to the top twenty, Japan would follow as number five.

Within 'big pharma', the common understanding is that the '3 D's', namely discovery, development and distribution, are core competencies that have to be kept in-house. With regard to outsourcing chemical process development and manufacturing, there are, surprisingly, widely varying attitudes ranging from 'we outsource whatever we can' to 'we produce captively whatever we can'. In *Fig. 3*, an attempt is made to list the leading 'big pharma' companies according to their outsourcing intensity.

On the one extreme, there are a few companies with no manufacturing capabilities at all. Examples are *Wyeth-Ayerst*, a division of *American Home Products*, and *DuPont Merck*, a j.v. of a chemical and a drug giant. Incidentially, many of the world's most successfull drug companies are to be found among the 'heavy outsourcers'. On the other extreme, there are companies that continue to invest heavily in chemical manufacturing such as *Abbott* and *Bayer*. *Glaxo-Wellcome* de-emphasised further expansion of the Singapore facility and also sold two plants, namely Annan, Scotland, (to *ChiRex*) and Greenville, USA (to *Catalytica*). The same accounts for *SB*, which sold its plants in Cidra, Puerto Rico, and *Julian Labs* in Mexico. For *Novartis*, the expansion of in-house manufacturing capacities came to an end with the commissioning of pharmaceutical fine chemicals plants in England and Ireland. *Hoffmann-La Roche* just completed an USD 500 million launch site in Florence, South Carolina, but also farmed out the manufacture of the anti-obesity drug Xenical to *DSM Chemie Linz*. As a consequence of the megamergers that have taken place over the past ten years, even without investing in new plants, there is a lot of manufacturing capacity, albeit 'unorganised', around. The newly formed drug giants typically own dozens of plants which are difficult to run efficiently.

This diversity of attitudes towards outsourcing is quite surprising, particularly as the high capital intensity [1] and unfavourable risk/reward ratio of in-house production is generally acknowledged. As an example for the imponderabilities let's consider the following scenario: A life science company has discovered a new drug or agrochemical. The active substance has successfully passed the initial screening and *in vitro* tests. In order to provide material for the first preclinical and greenhouse studies, respectively, a laboratory process description has been developed. In this procedure, questions regarding the feasibility, economics and SHE (= safety/health/environment) issues

	HQ	Pharma Sales Forecast 1998 ($ Billions)
Merck	USA	16.0
Glaxo-Wellcome	UK	14.0
Novartis	CH	13.4
Bristol-Myers Squibb	USA	12.2
Pfizer	USA	10.7
Roche	CH	10.6
American Home Products	USA	10.6
Johnson & Johnson	USA	8.9
SmithKline Beecham	USA/UK	8.7
Hoechst Marion Roussel	FRG	8.2

Fig. 2. *The world's top ten drug companies*

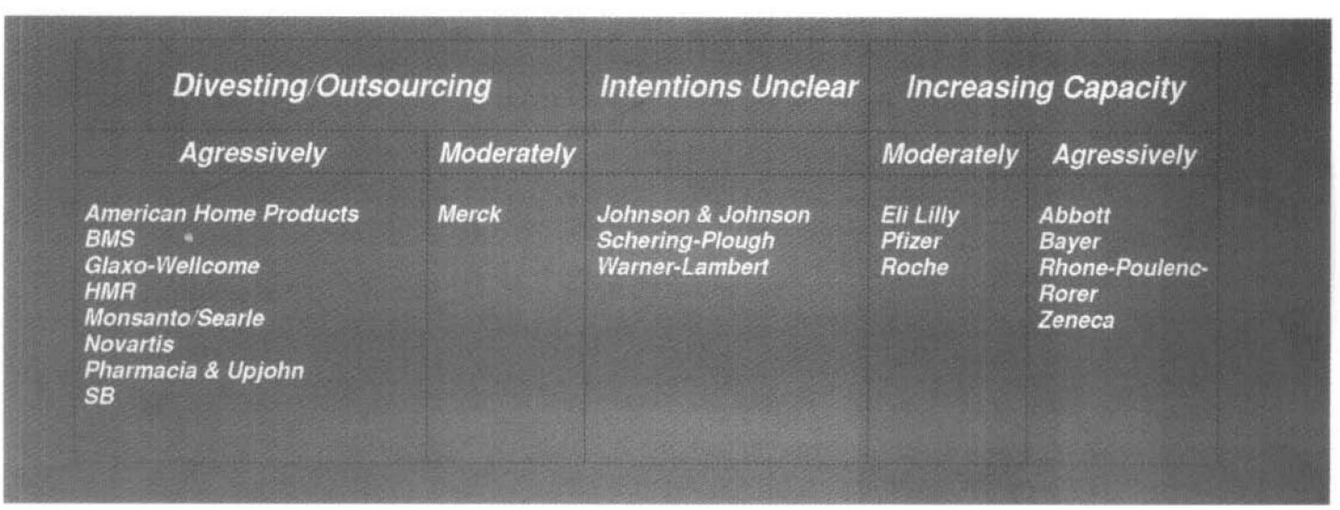

Fig. 3. *Outsourcing in the drug industry*

of an eventual industrial scale manufacture have not been addressed. However, in order to be ready to provide the necessary material once the go-ahead for the launch has been received, an industrial scale plant must be planned and the production capacity has to be defined at least two to three years prior to launch. At this stage, however, it is very difficult to anticipate the future requirement. There are at least three factors which can considerably influence the future sales, namely the number of patients and the size of the crop acreage, respectively, the market share, and the dosage in milligrams per day and grams per hectare, respectively. If each of these factors varies just between 1 and 2, the total requirement will vary between 1:8 (see *Fig. 4*), making the design of the plant a gamble.

On the organisational side, in order to optimise the supply-chain management, manufacturing and procurement are typically combined into one function. *SB* calls it World Supply Organisation and G-W International Actives Supply. This allows the pharmaceutical industry to determine exactly for which stage and stages, respectively, of the value-added chain of any API outsourcing makes most sense. It is still common practice, though, to make the last step in-house.

2. Market Size

The size of the market for custom manufacture is difficult to asses. This is mainly due to the lack of a precise definition for fine chemicals [2], part of which are produced by custom manufacture, and the confidentiality of most contractual arrangements. The size of the global fine chemicals market was estimated at USD 42 billion in 1993 [3][4]. It is further estimated, that *ca.* one half of this is used for pharmaceuticals, 25% for agrochemicals and the rest for an array of other speciality chemicals, such as flavours & fragrances, dyestuff & pigments, feed, food & plastic additives *etc.*

The 'spending pattern' of the pharmaceutical industry is shown in *Fig. 5*. The percentage numbers for M&S, R&D and profit are derived from the annual reports of the top twelve companies. The corresponding share for 'formulation' and 'Active Pharmaceutical Ingredients (= APIs)' had to be estimated.

In the agrochemicals industry which is under more price/performance pressure, bulk actives account for *ca.* 40% of the sales price. Therefore, although the total turnover of the industry is only *ca.* USD 33

	Drugs	Agrochemicals	
1	Number of Patients	Crop Acreage	1 2
2	Market Share	Market Share	1 2
3	Dosage (mg/day)	Application rate (g/hectare)	1 2
	Total		$=1^3 : 2^3$ $=1 : 8$

Fig. 4. *Factors affecting demand for new drugs/agrochemicals*

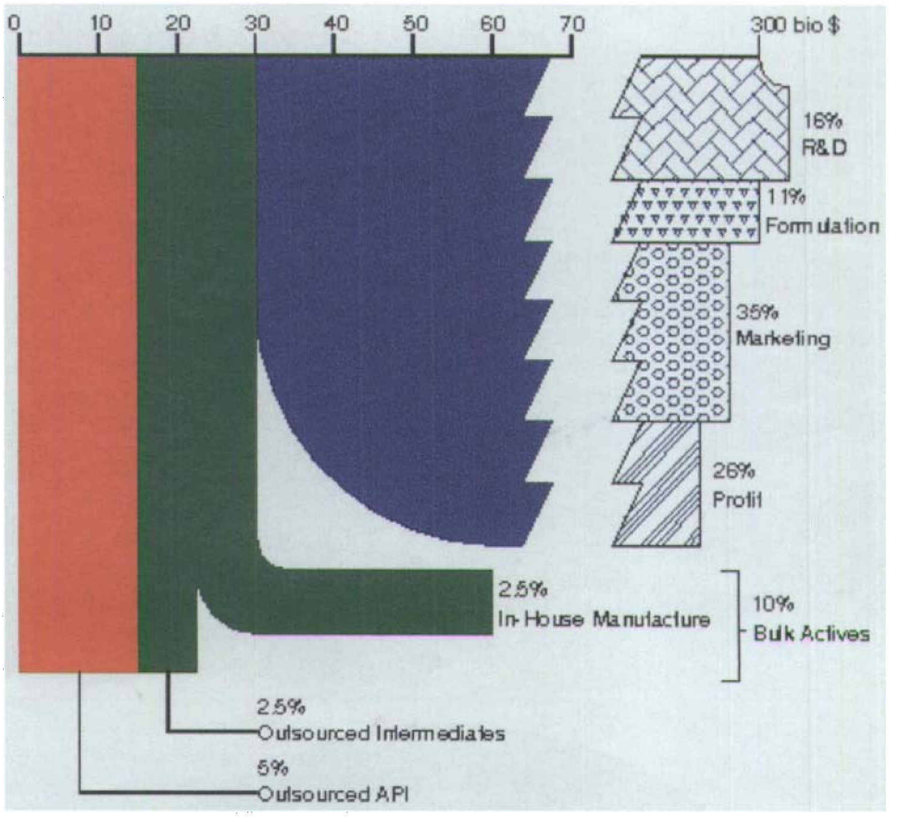

Fig. 5. *Spending pattern of the pharmaceutical industry*

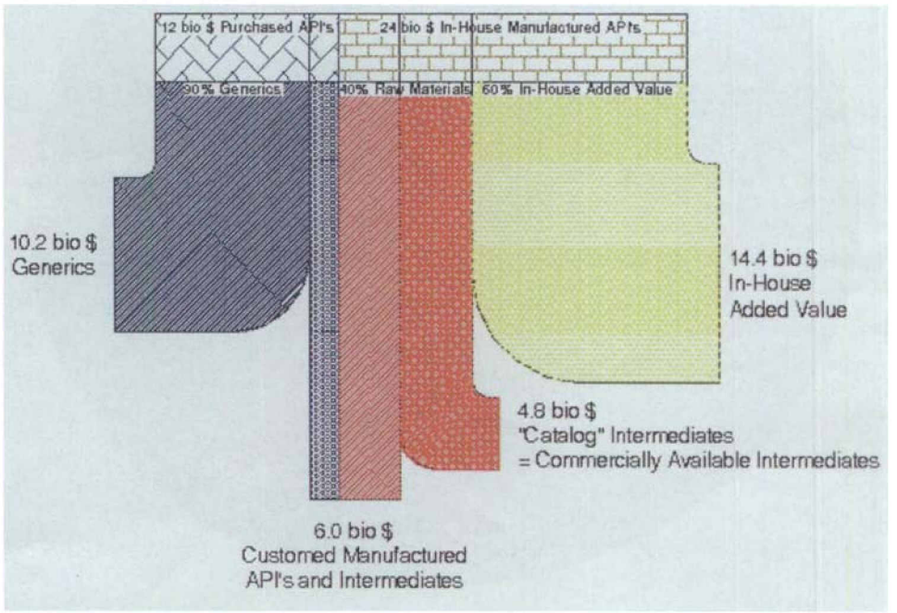

Fig. 6. *Share of custom manufacture*

billion (1996), bulk actives represent a market value of *ca.* USD 13 billion.

In *Fig. 6*, an attempt was made to further break down the pharmaceutical fine chemicals market into 'in-house' and 'custom manufacture'.

The following assumptions were made:

- One third of the APIs used in the drug industry are outsourced. This includes primarily off-patent products.
- As drug companies keep the manufacture of the last step of their proprietary APIs in-house, only a small part of patented drugs, estimated at 10%, is outsourced.
- Two third of the APIs are made in-house from purchased intermediates. The latter fall into two categories, viz:
  - 'Catalogue' or commercially available products, such as acetoacetates, chloroformates and penicillin side chains.
  - Intermediates made under custom-manufacturing arrangements.

Two conclusions can be drawn from *Fig. 6*, namely

1) the added value created in-house by the drug companies being USD 14.4 billion, the free market amounts to (36 – 14.4) = USD 23.6 billion. This number corresponds fairly well with the previous statement, namely that the pharmaceutical industry 'absorbs' 50% of the global fine chemicals production of USD 50 billion, that is USD 25 billion (see above).

2) The total market for custom manufacture in the pharmaceutical industry amounts to *ca.* USD 6 billion.

Assuming that approximately the same ratio of custom manufacturing/total fine chemicals market applies also to the other categories, this would mean that the global custom-manufacturing market amounts to USD 12 billion. This figure represents *ca.* 1.2% of the global chemical market which is estimated at *ca.* USD 1000 billion.

All in all, outsourcing has become a common practice among life science companies. That means that they rely on fine chemical companies like *LONZA* for the chemical development and manufacture of a part or the totality of their active ingredients.

Fig. 7. *Competitors*

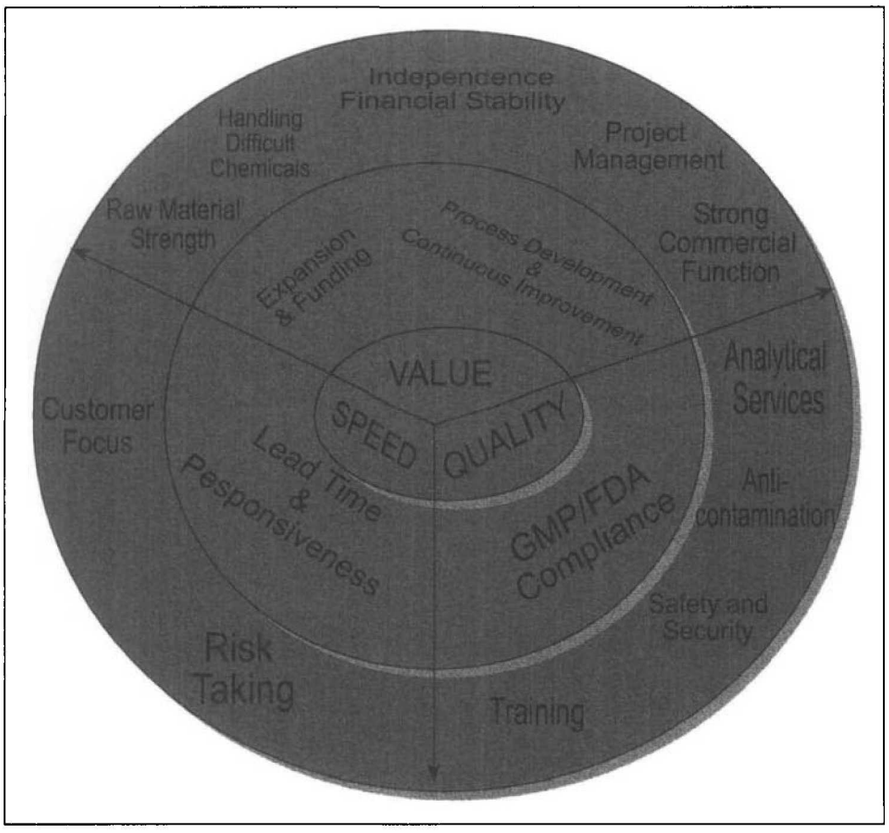

Fig. 8. *Custom manufacture – customer's needs*

3. The Custom-Manufacture Industry

3.1. *Industry*

The leading custom manufacturers are mostly divisions of large, publicly owned chemical companies (see *Fig. 7*). They do not only provide custom-manufacture services but also a line of 'catalogue' fine chemicals. The combination adds stability, economy of scale and provides backwards integration. Other players have emerged from small, privately owned companies. They have primarily been producing drugs in countries in the Mediterranean area and Finland that did not have or did not honour patent laws. Finally, some drug companies themselves venture into custom manufacture, primarily because they want to fill idle capacity. The main driver is overhead absorption, and the commitment is sometimes questioned. Examples are *Abbott*, *ChemDesign* (*Bayer*) and *Dow* in the USA, *Ciba Specialities* and *Zeneca* in Europe and *Mitsubishi Chemicals* in Japan.

The increase in the number companies active in of custom manufacture is quite

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LONZA*'s main production and R&D site at Visp (Switzerland).* In the foreground the fine chemicals complex.

impressive: At the last CPhI (Chemical and Pharmaceutical Intermediates) trade show in London in October 1997, there were 700 exhibitors. Although many of them only have a limited offering and can do toll conversions at best, maintaining best of class status becomes a challenge. Custom manufacturers have to develop core competencies of their own in order to be valuable partners to the life science industry. They have to be based on an in-depth analysis of the requirements of the customers. In *Fig. 8*, these needs, as derived from presentations of a number of key players, are reported. They can all be considered as proliferation around a hub formed by the basic triade of 'Quality-Speed-Value', as defined by *Eli Lilly* [5]:

'A blockbuster drug may produce sales exceeding USD one to two billion per year during its peak sales. At the same time, every day of lost sales could mean thousands or even millions of dollars of lost revenue during that time, money that will pay for the development of that product as well as fund future developments. A decision to enter a therapeutic area must be made quickly and decisively with a full commitment of all resources including those of the suppliers. *Lilly* has embarked upon an initiative called Quality-Speed-Value in an attempt to supply unmet clinical needs in the least amount of time while delivering the maximum value to the shareholders'.

The term 'value' deserves some additional reflection. According to Prof. *J. Kim* of Boston University [6], value to the customer consists of 'operational excellence' (quality conformance, dependability, product reliability, low price), 'technology leadership' (leading edge products

consistently enhancing customer's use) and of 'customer intimacy' (segmenting markets and tailoring products to match requirements).

In practice, a combination of hardware (pilot and industrial scale plants, R&D and analytical laboratories, ...) and software (total quality management, regulatory compliance, operating procedures, supply-chain management, R&D, Marketing, ...) is required for a successful provider of custom manufacture.

3.2. *Production*

The core of a fine chemicals plant involved in custom manufacturing is constituted by one or more multipurpose production trains. Multipurpose means that in the course of a year different processes can be run subsequently in campains. In its simplest setup [7], a train consists of two to four reaction vessels made from stainless or glass-lined steel. Their available volume typically ranges from 0.5–10 m^3. They are located on floor 3 or 4 of the production building. All of the reactors are equipped with heating/cooling coils and at least half of them with reflux/distillation capability. On floor 1 or 2, there are one to two centrifuges plus mother-liquor holding tanks. Dryers are usually located in a separate part of the building. In order to ascertain a constant quality production, rather sophisticated instrumentation is required. The cost of installing such a train ranges from *ca.* 3–10 times the purchase price of the individual pieces of equipment. Auxiliary equipment for other unit operations, such as absorption, extraction, phase separation and catalyst recovery, is installed within battery limits.

Outside the production building, installations for water conditioning, solvent recovery, energy (steam, brine, ...) and inert-gas generation and waste disposal (incineration for liquid and gaseous waste, biological treatment for wastewater, ...), a well equipped analytical lab and a maintenance shop, a warehouse *etc.* have to be available. As a rule of thumb, it can be assumed that the infrastructure adds 40% to the cost of the production plant itself. In the early days of fine chemical manufacturing, 'what happens inside the reactor' was of main concern. The attention now has shifted to 'what happens outside the reactor', and material flow considerations are important both in plant design and operation.

There obviously is a substantial economy of scale in the size of such a plant, both if the number of production trains goes up and the capacity of the auxiliary equipment is increased. If a plant is not capable of generating at least USD 50 million of sales, it cannot be run profitably. Actually, there are *ca.* half a dozen of plants with sales ranging from USD 13 million to USD 48 million for sale. But even if the size is right, a profitable operation is a demanding task, as conflicting targets have to be met, namely:

- consistent high quality production
- good capacity utilisation, including short changeover times
- capability to cope with sudden changes in demand, particularly (some) reserve capacity for increased or new demand
- compliance with SHE and regulatory requirements.

A particularly tricky problem is the capacity-utilisation dilemma (*Fig. 9*): Whereas fine chemical manufacturers add production capacity in discrete steps, the increase in sales typically shows a more smoothed-out line. Thus, situations with overcapacity (*i.e.*, when a new plant comes on-stream) have always alternated with situations where demand exceeded manufacturing capacity. At present, demand and availability for new capacity are drifting apart, and the custom-manufacture industry as a whole is facing a period where capacity is increasingly tight. There are several reasons for this:

- the continuing trend to outsourcing
- the rapid growth of the drug industry [9]
- the profit expectations of the shareholders. The fine chemicals industry, too, is ruled more and more under demanding financial criteria, such as EVA (= Economic Value Added). This makes it more difficult to get approval for capital expenditures, particularly if expansion projects are competing with less capital-intensive projects. The situation is aggravated by the high cost of new multipurpose plants. Specific investments of up to USD 1 million per cubic meter of reactor volume and sales

	Full Utilization	Partial Utilization
Positives	• Full Overhead Absorption • Good Margins	• Better Response to Customer's Needs: -Room for Additional Business -JIT Deliveries
Negatives	• Increased Working Capital • Extended Lead Times (Domino Effect) • Frequent Shifting of Products	• No Incentive for Productivity Improvements • Non Productive Down Time

Fig. 9. *The capacity-utilisation dilemma*

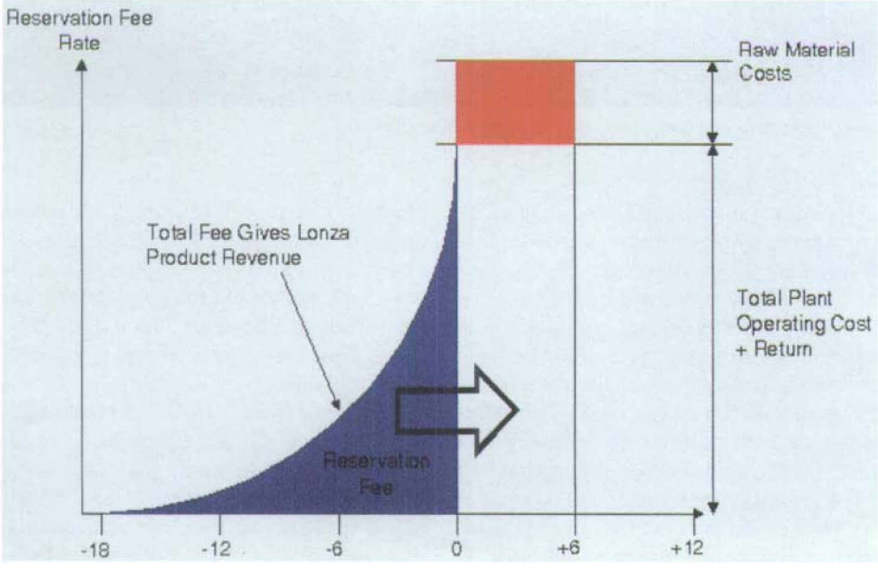

Fig. 10. *Reservation fee*

below 1 USD per asset USD are not uncommon any more. Furthermore, also the risk profile of the fine chemicals business is not particularly attractive. In custom manufacture one runs the twofold risk of the customer being successful with his new drug or crop-protection agent and of being awarded the business. Under these circumstances, investments in grass-root plants are practically not feasible any more.

There is an increasing reluctance by the pharmaceutical companies to back up investment needs of their partners in custom manufacture with iron-clad capital guarantees. A typical attitude would be: 'If we have to cover all the risks, we can quite as well do it in-house'. As fine chemical manufacturers have been heavily promoting the 'partnership' concept, *cf. Lonza*'s '*Leave it to Lonza*' slogan, they are at least partly to blame themselves for this situation. The compromise is risk sharing. It should, however, be pointed out that it should somewhat reflect the different profit expectations of the partners and therefore not be based on a '50/50' model.

Fig. 10 shows a concept for a risk-sharing arrangement. It is an intermediate solution between 'investment guarantee' and 'no commitment at all'. It assumes that the 'outsourcer' wants the custom manufacturer to reserve production capacity now for a production window in the first half of the year 2000. He anticipates to need this capacity, provided that he gets approval for a new drug or crop-protection agent in December 1999. He would then be asked to pay an increasing monthly reservation fee up to December 1999. The cumulative fee corresponds to the total sales price of the six months production campaign, except for the raw materials. If the customers gives the go-ahead for the production, he will be charged in addition for the raw-materials cost, but the total cost for the quantity ordered is exactly the same as without reservation fee. On the other hand, if the order is cancelled between now and end of 1999, the exposure increases reflecting the increasing difficulty to find alternate uses for the plant.

- Cooperation in Regulatory and Validation
- Resources and willingness to get involved in process development
- Pricing issues (e.g. cost, plus a reasonable return)
- Cost reduction and continuous improvement
- Cost savings sharing
- Capacity allocation and expansion funding

courtesy Wyeth-Ayerst[1]

[1] see also Clive Rogers [10].

Fig. 11. *Principles of partnership*

3.3. *R&D*

Research and development in the fine chemicals industry have traditionally been 'supply push'-oriented. Researchers were given the task to find new, higher value-added derivatives for products which already were part of the company's portfolio. Thus, *LONZA* developed a line of γ-chloroacetoacetates and later on 2-amino-4-thiazolyl acetates (= side chains for third-generation cephalosporin antibiotics) starting from diketene, and a series of substituted pyrimidines starting from its captively produced hydrogen-cyanide derivatives malononitrile, malonates and cyanoacetates. With the advent of custom manufacture, a 180-degree change in direction was required and a 'demand-pull' strategy followed. That means, that the new product pipelines of the life science companies were analysed and fits sought between the specific molecules required for active ingredients of the new drugs and agrochemicals on the one hand, and existing technological competences on the other hand.

When it comes to establishing an R&D program for a specific project, the main goal is to develop an economical and environmentally acceptable process for the target molecule within a given time frame. If possible, the process should be also suitable for production in existing multipurpose plants without requiring major adaptations. In order to avoid duplication, the program has to be fine-tuned with the customer. Particularly, the question has to be addressed how much effort did the customer already invest in route selection, sequence selection, process optimisation and analytical methods development. It has proven to be useful to set up a joint team of technical experts both from the customer and the custom manufacturer. This team agrees on the R&D program, the activities, milestones *etc.*

3.4. *Marketing*

Apart from Production and R&D, also Marketing faces new challenges. Whereas traditionally contacts between customers and suppliers in the chemical industry have been limited to purchasing agents and sales persons (if the products were not right away ordered from catalogues ...), a successful partnership (*sic*!) in custom manufacture becomes much more critical and involves establishing both multifunctional and multilevel contacts. Given the complexity of transactions in custom manufacture, customers tend to reduce the number of suppliers ... and select them carefully. Typical criteria for supplier selection are listed in *Fig. 11*. As they can only be reasonably determined on the basis of past performance, the entry barriers for newcomers in custom manufacture are very high, indeed.

The cooperation between the life science company and the custom manufacturer is usually documented by three contracts, namely a 'Cooperation Agreement' that establishes the general rules of the cooperation. It constitutes the 'umbrella' document that applies to all joint projects. For individual projects, an 'R&D Services Agreement' and a 'Contract Manufacturing' agreement are concluded. The former covers the laboratory work, sample preparation and supply of trial quantities from the supplier's pilot plant, the latter the industrial scale manufacture. Critical issues are a.o.

- phasing and reliability of volume forecasts, provisions for large fluctuations
- risk sharing for capital investments
- continuous improvement
- safeguard of confidentiality and intellectual property rights (= IPR). This is a delicate issue, as it touches upon the core know-how of both partners. A simple solution, whereby process rights belong to the supplier and product rights to the customer, does not properly ad-

dress the interests of the partners [11]. In negotiations for strategic alliances (see below), the resolution of IPR issues can constitute a deal breaker.

In the infancy of custom manufacturing, the R&D costs associated with the development of a manufacturing process for the target molecule were typically born by the custom manufacturer, and trial quantities, produced in the pilot plant, were provided at cost. This 'delayed pricing' costing model was based on up-front financing by the custom manufacturer and recovery of the costs during industrial scale manufacture. This integral approach extending over the whole life cycle of an API was justified, because

- outsourcing had to be promoted to an intrinsically 'what we sell we make'-oriented life science industry:
- the life science industry was not familiar with fine chemical companies having custom-manufacture capabilities. *LONZA*, as an example, was practically unknown outside the borders of Switzerland at that time and had to establish itself first as partner to the life science industry.

Nowadays, the life science industry generally recognises that their suppliers provide more than just a molecule. Consequently, a 'value' or 'real time' costing model is now used. The offering includes a.o. the process validation, the edition of a 'Drug Master File', the notification of compounds, the development of analytical methods, the establishment of specifications, the synthesis of specific impurities *etc.* The 'Quality-Speed-Value' challenge has already been mentioned (see *Fig. 8*). It is particularly important prior and during the launch of a new drug or agrochemical.

A case in the airine industry made headlines last fall: *Boeing* had to shut down the production line for its B-747 Jumbos for two or three months, because custom manufacturers did not supply parts on time.

What are the practical implications of a value-pricing approach?

The assumptions of a real case are summarised in *Fig. 12*:

- The name of the target molecule is communicated to the fine chemical manufacturer at the beginning of year one. In order to develop a suitable manufacturing process, 20 man-months have to be spent (*e.g.*, five chemists working four months each on every step of the five-step synthesis), equal to a total expenditure of (USD, CHF, DEM, HFL or whatever) 1 million.
- A 1000-kg pilot plant production of the molecule is carried out in year two. The cost estimate for this production was 2000 per kg, but after the campaign was completed, it turned out that the real cost was 2500 per kg.
- From year three to year seven, 500 metric tons are produced (five years at 100 mt/a).

In the 'delayed pricing' model:

- The custom manufacturer assumes the cost of the research phase (year 1). The rationale is that he has to prove first that he can do it.
- The custom manufacturer sells the pilot plant quantity at the estimated price, assuming a loss of (USD, CHF, DEM or whatever) 0.5 million (year two).
- The custom manufacturer includes a 5% increment on the sales price for the industrial quantities in order to compensate for the R&D and related expenditures in year one and two, and also for unsuccessful projects.

In the 'value or real time pricing model':

- The custom manufacturer invoices the expenses incurred during the research phase at cost.
- The custom manufacturer sells the pilot plant quantity at the real price plus a profit margin.
  The higher than anticipated price was at least partly due to changing requirements from the customer, such as changes in specs and timing.
- The custom manufacturer includes a 2.5% mark-up for R&D in the sales price for the industrial quantities. This allows him to carry on process improvement work, the benefits of which will be shared with the customer.

	YEAR 1: LAB RESEARCH	YEAR 2: PILOT PLANT PRODUCTION	YEARS 3 to 7: INDUSTRIAL SCALE PRODUCTION
Assumptions	Cost: 1 mio (20 man month at 50,000)	Estimated Cost: 2 mio Real Cost 2.5 mio (1000 kgs at 2,000/2,500)	Volume: 500 mt (5x100 mt) Price: 500 per kg: 250 mio w/o R&D contribution
"Delayed Pricing"	Free of Charge 0	Billed at Estimated Cost: 2 mio	Billed at 525 per kg: 262.5 mio (Incl. 5% R&D Contr.)
"Value (Real Time)" Pricing	Billed at Cost 1 mio	Billed at Real Cost + Profit: 3.5 mio	Billed at 512.50: 256.2 mio (Incl. 2.5% R&D Contr.)

Fig. 12. *Value pricing – assumptions*

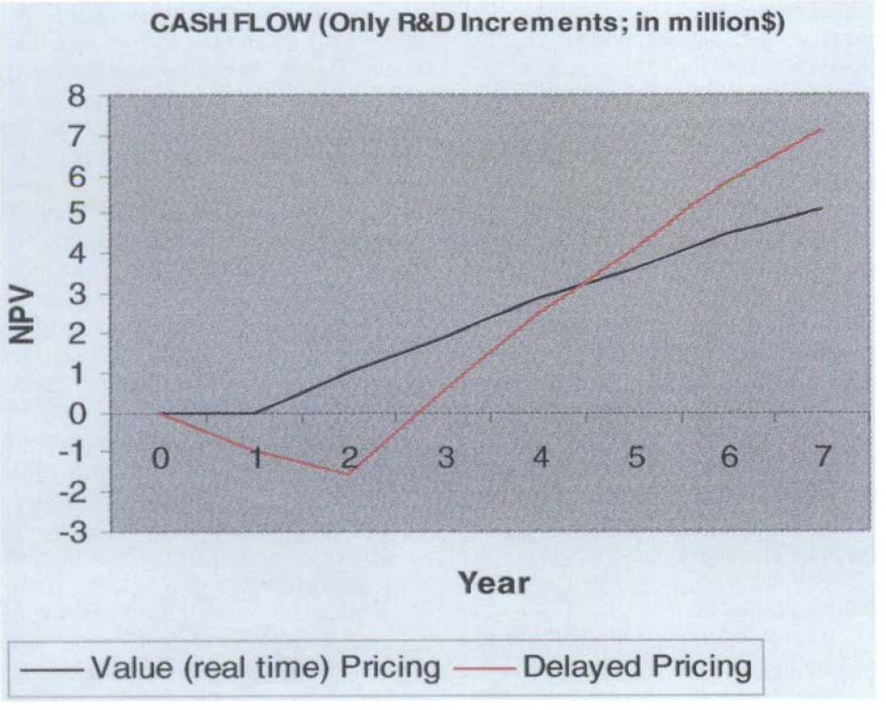

Fig. 13. *Value pricing – cash flow* (only R&D increments)

Which case is more advantageous for the pharmaceutical company?

The NPVs have been calculated for both cases. If the project has a life of seven years (two years of R&D plus five years of actual deliveries), then the NPV is >5 million USD, CHF, DEM or whatever for the 'value-pricing' scenario and >7 million USD, CHF, DEM or whatever for the 'delayed pricing' scenario.

As illustrated in *Fig. 13*, the break even occurs at *ca.* four and a half years. In other words, if the project is stopped before completion of about half of the five year/ 500-mt supply contract, value pricing is advantageous for the custom manufacturer – in the other case, it is advantageous for the drug industry. This is reasonable, as it allows the fine chemical manufacturer to make a certain profit, even if the supply contract is cancelled prematurely. If, however, the contract is fully consummated, the value-pricing model is advantageous for the pharmaceutical company.

The most elaborate form of a cooperation between a life science company and a custom manufacturer is a strategic alliance. It is defined as follows:

A close long-term relationship, where customer and supplier work together to secure for each other and the end customer the best sustainable commercial advantage.

Although there are impressive benefits from such an alliance (see *Fig. 14*), there are also potential dangers and pitfalls, such as proliferation of confidential know-how, large resource requirements for joint teams, overdependency and disenchantment of other customers who consider themselves as 'second rate'. Strategic alliances are not suitable for the great majority of business relationships in the chemical industry, where commodities readily available from many suppliers are traded, but only to relations that involve manufacture of customer-tailored products.

Fig. 14. *Benefits from a strategic alliance*

Year	1990	1991	1992	1993	1994	1995	1996	1997
NCE's	43	43	43	39	47	39	51	47

Fig. 15. *Approval of New Chemical Entities* (NCEs) *1990–1997*

4. Outlook

The threats and opportunities for the custom manufacture industry are governed primarily by the development of demand, the competitive intensity and the regulatory environment.

Development of Demand: The main customer base, 'big pharma', continues to show strong performance which has come in spite of continued efforts to control health-care spending by governments and other health-care buyers, such as US health maintenance organisations (HMOs). First, the use of more effective drugs can itself save money by allowing patients to leave expensive hospital beds sooner [13]. Cutting costs elsewhere in the health system may be a better way of saving money. More and more studies are starting to show that there is nothing as cost-effective as a good drug. Health-care spending on drugs was only 7% of in the USA, and 12% in Europe in 1996. According to IMS, International Medical Statistics, the drug-industry sales can be expected to grow from USD 300 billion to 375 billion between 1997 and 2001, *i.e.*, *ca.* 6–7% per year. The figure includes not just drugs but also diagnostics and diagnostical devices. As these show an above average growth, the demand for APIs, which is of paramount importance for the custom-manufacture industry, will increase somewhat less. On the other hand, there is substantial substitution, too (for instance, in the treatment of rheumatoid arthritis, COX-2 Antagonists might supersede the currently used non-steroidal anti-inflammatory drugs with their associated stomach problems, and the latest class of drugs against high blood pressure, the angiotensin-II antagonists, nicknamed '... sartans' [14], already represent the 4th generation of this therapeutic class). Furthermore, a large number of drugs are coming off patent. In addition to the 139 drugs valued at USD 34 billion whose patents already have expired 280 drugs valued at USD 120–140 billion will loose patent protection within the next ten years. This enormous charge is putting extreme pressure on 'big pharma'. In order to cope with it, it is increasing its R&D budgets (in the USA alone pharma R&D spending is expected to surpass USD 20 billion in 1998, three times as much as ten years ago). At the same time, it is also trying to shorten development times. Whereas they now typically are ten to twelve years *SB*'s new goal reads: '2000 days development time by the year 2000'. Because of sizeable unmet needs, there is a large potential for new drugs: only for thirty percent of all diseases is there a cure. Major evils afflicting humanity are still waiting for an effective treatment, such as obesity, geriatric diseases, *Alzheimer*'s and autoimmune diseases, such as arthritis. On the negative side, the ratio between outsourcing and in-house manufacture will not grow much more. With biotechnologically made drugs there could even be a negative development. Drug companies are more reluctant to outsource manufacture of biopharmaceuticals, because there is enormous proprietary know-how involved and typically the APIs are made directly without isolation of intermediates. Thus, it is difficult to imagine that *Novartis* would outsource the production of its cyclosporin imunosuppressant, Sandimmun.

A good yardstick for measuring the innovative thrust in the drug industry is the number of approvals for New Chemical Entities (NCE's). In *Fig. 15*, these numbers are reported for the period between 1990 and 1997.

The 1993 low coincides with the '*Hillary* effect'. Five years later, 'big pharma' was back to a healthy growth mode. Furthermore, 6290 pharmaceuticals were in active development in 1997, an increase of 4% on 1996. In 1997, the originating countries were USA: 20, Japan: 7, UK: 5, Germany: 5, Switzerland: 4, others: 6,

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confirming again the importance of these five countries for the pharmaceutical industry, this time from the point of view of innovation.

Whereas demand for agrochemicals is expected to grow only slightly on an total dollar basis, substantial substitution is taking place also here. The traditional 'kilograms per hectare' chemical maces are substituted with 'grams per hectare' specialities which need a similar sophistication in manufacturing as APIs. There is, however, a threat from gene technology which allows development of herbicide and pest-resistant crops, making the use of pesticides either right away obsolete or allowing the use of cheap unspecific weed killers.

There are three facets of ***Competitive Intensity*** which all pose a threat to the custom-manufacture industry: First, there is competition **among** industries. Despite the small overall size of the business and the high risk profile, fine chemicals in general and custom manufacture in particular are still viewed by many commodity-based chemical companies as the *panacea* for moving to new frontiers and improving business performance. Negative examples, like *SHELL* which has thrown in the towel and got out of fine chemicals seem not to blur the overall glamorous picture. Because of continuing Mergers & Acquisitions in the life science industry, there are fewer customers for a growing number of custom manufacturers ... and these customers concentrate on fewer suppliers, exerting more purchasing power. Second, there is competition **within** individual companies, particularly if they are also active in speciality chemicals which command a much lower asset intensity (typically > 2 USD of sales per asset dollar *vs.* < 1 USD per asset USD in custom manufacture (see also *Chapt. 3.2*)). Third, there is competition among **geographical regions**: The fine chemicals industry in the Far East already has evolved from manufacturing the traditional 'letter acids' for the dye industry to large-volume generics. Although most APIs used in the 1st world are still produced in the 1st world, it is only a question of time until also sophisticated, confidential processes for APIs and intermediates are transferred to India and China ... and supervised by chemists educated at the industrialised world's best universities.

Environmental: On the one hand, the capability to comply with the regulations governing the manufacture of pharmaceutical and agrochemical actives and intermediates is a competitive advantage. In many instances, it represents right away a *conditio sine qua non* for being accepted as partner by 'big pharma' and agro. On the other hand, it adds substantially both to the cost of building and running a multipurpose plant. Also, FDA rules deprive the custom-manufacture industry to a large extent from implementing process improvements, at least during the launch phase of a new drug. Continuous improvement, an important element of competitive advantage for the custom manufacturer, can only start once the launch phase is over. There is another spectre on the wall, namely the impossibility to produce different APIs in the same production train or plant because of anticontamination requirements. With pesticide fine chemicals, we already are in a situation where our customers no longer accept the production of fungicides and herbicides on the same site, let alone in the same production train.

Conclusion: Custom manufacture will remain a niche business that continues to offer opportunities for midsize chemical companies that succeed in managing the 'speed-quality-value' bias. However, a shakeout will take place among the small and mediocre.

Glossary

Active substances. In the broadest sense, these are substances which, in relatively small quantities, have a significant physiological effect. See also ⇒ Active pharmaceutical ingredients and fibulk active substances.

Active Pharmaceutical Ingredients (API). The specific ingredients of a drug that exhibit the physiological activity. Examples are acetylsalicylic acid in Aspirin and *N*-cyano-*N'*-methyl-*N''*-{2-{[(5-methyl-1*H*-imidazol-4-yl)methyl]thio}-ethyl}guanidine in Cimetidine (= *SB*'s Tagamet).

Agrochemicals. ⇒ Chemical specialities that exhibit a physiological activity in agricultural applications. The main classes are herbicides, insecticides and fungicides.

Backward integration. Manufacture of substances starting from upstream (raw materials, instead from purchased ⇒ intermediates.

Biopharmaceuticals. Biotechnologically produced proteins and peptides for pharmaceutical applications.

Biotechnology. Bioengineering techniques which use certain micro-organisms (*e.g.*, bacteria) for industrial manufacture of organic substances.

Blockbuster drug. A drug that achieves sales > USD 1 billion in a year.

Bulk Active Substances. Designation for unformulated ⇒ active substances, manufactured and handled in bulk quantities.

Chemical Specialities. Formulated active substances. Examples are agrochemicals, drugs, dyestuffs, flavours and fragrances. Contrarily to fine chemicals they are sold on the basis of performance.

Custom Manufacture. Chemical development and manufacture of tailored fine chemicals exclusively for individual customers.

Fine Chemicals. Value-added ⇒ intermediates and active substances produced in relatively small tonnage (< 10^3–10^4 mt/a) and prices above 10 CHF/kg. Contrarily to fichemical specialities they are sold on the basic of specifications and not performance characteristics.

Formulation. The conversion of ⇒ bulk active substances in ⇒ chemical specialities.

Note: In the pharmaceutical industry, this is sometimes referred to as secondary manufacturing.

Intermediates. Chemical substances which are manufactured from ⇒ raw materials in multistage synthesis. Usually produced in larger tonnage and sold at lower prices than fine chemicals.

Life sciences. Comprehensive term covering agrochemicals, pharmaceuticals and food & feed additives.

Raw materials. Chemical substances used for the manufacture of intermediates. Typically derived from petrochemicals. Examples are acetic acid, acetylene, ammonia, hydrogen cyanide.

Note: In the life science industry, active substances are sometimes called raw materials.

Toll Conversion. An custom-manufacture arrangement, whereby the customer supplies a specific ⇒ intermediate plus the process for conversion to the next step.

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[1] Investing in plants for a total in-house manufacture of APIs is estimated to absorb 30% of assets of a drug company, but to generate only 10% of added value.

[2] Are the APIs for heartburn medicines, calcium carbonate and aluminum hydroxide, or painkillers, acetaminophen and acetylsalicylic acid, to be considered fine chemicals?

[3] This would correspond to *ca.* USD 50 billiom in 1997, assuming an annual growth rate of 5%.

[4] R. Willhalm, T. Ruess, SRI International, Chemspec Europe 1995, BACS Symposium.

[5] D.E. Weaver, *Chimica Oggi/Chemistry today* **1997**, November/December, 11–13.

[6] J. Kim, International Manufacturing Round Table Meeting, Cambridge Mass., Oct. 24–27, 1994.

[7] For a more detailed description, see *P. Pollak* [8].

[8] P. Pollak, 'Kirk-Othmer Encyclopedia of Chemical Technology', 4th edn., vol No. 10, 1994, p. 900–918.

[9] For details see chapter 4, Outlook.

[10] C.T.T. Rogers, *Chimia* **1998**, *52*, 269.

[11] For a more extensive coverage, see *M. Gemünd* [12].

[12] M. Gemünd, *Chimia* **1998**, *52*, 255.

[13] One year of AIDS treatment costs USD 10000, one day in a hospital bed costs USD 1000; includes the preparation of samples of the API needed for the testing with some licensing-in from Universities and Virtual Pharma primarily sourcing of APIs, see also *C.C.T. Rogers* [10].

[14] Losartan from *Merck*, Eprosartan from *SB*, Irbesartan from *BMS*, Valsartan from *Novartis*, Candesartan from *Takeda*.