FINE CHEMICALS

1. Introduction

Until the 1970s in-house production of intermediates and active substances for products sold were considered a key competitive advantage by the pharmaceutical, agrochemical, and other specialty chemical industries. As of the 1980s, outsourcing of the chemical manufacturing was gaining ground, and make or buy decisions became part of the supply chain management process. Also, the requirement for more and more sophisticated organic chemicals and biopharmaceuticals has contributed to the emergence of the fine chemicals industry (see section 3.1 Fine Chemical industry) as a distinct entity. This is backward integrated, production oriented, and supplies advanced intermediates and active substances to the specialty chemicals industries. Custom manufacturing, whereby the customer provides the manufacturing process and is served on an exclusive basis, is an important part of the fine chemicals business. The fine chemicals industry has its own characteristics with regard to R&D, production marketing, and finance.

In the chemical business, products may be described as commodities, fine chemicals, or specialties. Various commodities are also known as petrochemicals, basic chemicals, organic and inorganic chemicals (large volume), monomers, commodity fibers, and plastics. Advanced intermediates, building blocks, bulk drugs, bulk vitamins, and bulk pesticides and active pharmaceutical ingredients (APIs) are typical fine chemicals. "Ready-for-use" adhesives, biocides, catalysts, dyestuffs and pigments, electronic chemicals, imaging/photo chemicals, food and

Table 1. **Definitions**

Commodities	fine chemicals	Specialities
single pure chemical substances ...	single pure chem. substances	mixtures
product in dedicated plants	produced in multi-purpose plants	formulated
high volume / low price	low volume (<1000 mt) high price (> $ 10/kg)	undifferentiated
many application	few applications	undifferentiated
sold on specifications	sold on specifications "what they are"	sold on performance "what they can do"

feed additives, flavors and fragrances, ingredients for household and personal care products, pesticides, pharmaceuticals, specialty polymers, veterinary drugs, and water treatment chemicals are all specialties. The added value is highest for specialties.

It is common to both commodities and fine chemicals that they are identified according to specifications, according to what they are (see Table 1). Both are sold within the chemical industry, and customers know better how to use them than suppliers. Specialties are identified according to performance, according to what they can do. Customers are trades outside the chemical industry and the public. Suppliers have to provide product information. An example of the value added chain extending from commodities through fine chemicals to a pharmaceutical specialty is shown in Table 2. The product chosen is Pfizer's anticholesterol drug Lipitor (atorvastatin), the world's top selling drug with sales of $ 10.1 billion (2003). The value added chain extends from a C1 molecule, methanol (left side of the table) all the way to a C33 molecule, atorvastatin. Methanol is a typical commodity, namely, a low price/multiusage product manufactured in large quantities by many companies. Under the heading Fine Chemicals, three examples of fine chemicals used for the manufacture of atorvastatin are listed, namely, the advanced intermediates ethyl 4-chloro-3-hydroxy butanoate and *tert*-butyl (4*R*,6*R*)-2-[6-(2-aminoethyl)-2.2-dimethyl-1.3-dioxan-4-yl] acetate, respectively, and the active pharmaceutical ingredient (API) of atorvastatin itself. As long as the latter, 2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrole-heptanoic acid, is sold according to specifications, it is a fine chemical. But once it is formulated, tableted, and marketed as the anti-cholesterol prescription drug Lipitor (atorvastatin), it becomes a specialty (see CARDIOVASCULAR AGENTS). A precise distinction between commodities and fine chemicals is not feasible. In terms of volume the border line comes at ~1,000 t/year, in terms of unit sales prices the line is set at ~$ 10/kg. Unfortu-

Table 2. **Example for the Value Added Chain in the Chemical Industry Atorvastatin**[a]

Parameter	Commodities		Fine Chemicals[b]			Specialties
			Advanced intermediates		API	
example	methanol	acetic acid	(I)	(II)[b]	(III)[b]	Atorvastatin Lipitor (trademark of Pfizer)
CAS registry number	[67-56-1]	[64-19-7]	[638-07-3]	[. . .]	[. . .]	not available
molecular formula	CH_4O	$C_2H_4O_2$	$C_{14}H_{10}NO_3Cl$	$C_{14}H_{30}NO_4$	$C_{33}H_{34}FN_2O_5$	not available
applications[c]	>100	>50	10	1	1	not available
price indication $/kg[c]	0.2	1.00	20	200	2500	50,000
production t/yr[c]	32×10^6	8×10^6	500	400	500	not available
producers[c]	100	25	10	5	1	1
customers[c]	100	50	10	1	1	>> consumers
plant type[d]	D, C	D, C	M, B	M, B	M, B	F
manufacturing steps	1	2	5	15	20	not available

[a] Ref. 1.
[b] (I) = ethyl 4-chloro-3-hydroxy butanoate.
(II) = *tert*-butyl (4*R*,6*R*)-2-[6-(2-aminoethyl)-2.2-dimethyl-1.3-dioxan-4-yl]acetate.
(III) = 2-(4-fluorophenyl)-β,δ;-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)-carbonyl]-1*H*-pyrrole-heptanoic acid.
[c] Figures are the author's estimate and indicative only.
[d] B is batch; C, continuous; D, dedicated; M, multipurpose; and F, formulation.

nately, the demarcation lines sometimes cut into otherwise consistent product groups. This is, eg the case for amino acids (qv) and vitamins (qv), where the two largest volume products, *L*-lysine and methionine, and ascorbic acid and niacin, respectively, are sold in quantities >10,000 t/year, and at prices below the $ 10-kg level.

2. Research and Development

Product innovation absorbs considerable resources in the fine chemicals industry, mostly because of the shorter life cycles of fine chemicals compared to commodities. Consequently, research and development (R&D) plays an important role. The main tasks of R&D in fine chemicals are to design and develop the synthesis, to transfer the processes from the laboratory via pilot plant successfully to the industrial scale, and finally to optimize existing processes. At all times during this course of action, it must be ensured that the three critical boundary conditions economy, safety, and ecology are met. R&D has to manage the following functions in order to deliver the requested services:

- Literature and patent research: An efficient literature and patent search capacity, which is an absolute must in today's fast paced R&D world, has

to be made available. Provisions have to be made for a periodic examination of all acquired research results to determine whether applications for protective rights (patent) are indicated.

- Process research: This key function has to design new synthesis and has to undertake first experiments to secure the feasibility of the new synthesis.
- Process development: The raw synthesis from process research is developed to an efficient, safe, and stable process. The resulting process description provides the necessary data for the determination of preliminary raw material and product specifications, the manufacture of semicommercial quantities in the pilot plant, the assessment of the ecological impact, and an estimate of the manufacturing costs in an industrial scale plant. Another main task of this function is optimizing and scaling-up laboratory processes, as described in the literature or as provided by the customers, so that the processes can be transferred to the bench scale laboratory or pilot plant and subsequently to industrial scale production. In addition, for all current Good Manufacturing Practices (cGMP) products the critical process parameters and their ranges have to be determined.
- Analytical development: The increasingly complex molecules require a permanent development of new, sophisticated analytical methods and, if required, their validation. In order to fulfill this demanding task, a well equipped state-of-the-art analytical laboratory has to be accessible.
- Thermal safety: Rigorous screening of all processes prior to transfer in the pilot plant or in full scale production is mandatory. Depending on the nature of the process, more or less detailed safety reviews of the chemical and mechanical processes involved like reactions, distillations, rectification, drying, milling and blending operations have to be carried out. This data represents the basis for any risk analysis in all subsequent scale-ups for pilot plant and production.
- Bench scale laboratory and pilot plant: This section serves as an intermediary between laboratory and industrial scale. In development, the viability of the process on a semicommercial scale has to be demonstrated. The process viability is tested in terms of quality. Trial quantities of the new fine chemical have to be manufactured for market development and clinical tests, etc. The necessary data have to be generated to enable the engineering department to plan the modifications of the industrial scale plant and in order to calculate production costs for the expected large-volume requirements. Furthermore, all questions regarding safety and environment have to be answered. A direct transfer from the laboratory to the industrial scale is not recommended because of the inherent safety, environmental, and economic risks. Both, equipment and plant layout of the pilot plant reflect those of an industrial multipurpose plant, except for the size of reaction vessels (bench-scale laboratory $\sim$10–60 L; pilot plant $\sim$100–2500 L), and the degree of process automation. Once a laboratory process has been adapted to the constraints of a pilot plant, has passed the risk analysis, has been validated (only for cGMP products), and demonstration batches have been successfully and repeatedly run, the process is ready for the transfer to the industrial scale plant.

3. Production

3.1. General Comments. Typically, fine chemicals are manufactured in batch multipurpose plants. There are, however, a few examples of fine chemicals produced in dedicated or continuous plants. This can be advantageous if the raw materials or products are gases or liquids rather than solids, if the reaction is strongly exothermic or endothermic or otherwise hazardous, and if the high volume requirement for the product warrants a continued capacity utilization.

In this overview, the focus is on batchwise operated multipurpose plants. Given the wide variety of fine chemicals, the requirements to manufacture, handle, and store these compounds varies greatly. However, what they all have in common is the fact that their efficient manufacturing is driven by technology and high quality considerations. In this article the following two categories of products are considered: *Non-cGMP products*: Advanced intermediates and active ingredients for pesticides, adhesives, biocides, catalysts, dyestuffs and pigments, electronic chemicals, imaging / photo chemicals, fragrances, ingredients for household products, specialty polymers, water treatment chemicals, etc. *cGMP products*: Substances like key starting materials and advanced intermediates for APIs; sterile and nonsterile APIs, which are manufactured via chemical synthesis, biotechnology , extraction, recovery from natural sources, or any combination hereof. Also, products like veterinary drugs, vitamins, food and feed additives, personal care products, flavors, etc, and their advanced intermediates may have to be manufactured according to the cGMP regime.

Depending on the specific properties of the substances, severe restrictions have to be applied in the way these substances are manufactured: Highly toxic, nonpharmaceutical materials, such as pesticides, should not be manufactured in buildings and equipment being used for cGMP production. Highly sensitizing substances (eg, penicillins or cephalosporins), materials of an infectious nature, molecules of high pharmacological activity or high toxicity (eg, certain steroids or cytotoxic anticancer agents) should be manufactured only in dedicated and completely segregated production areas.

3.2. Plant Design. The principles of multipurpose plants are described by the key design parameters in the following sections.

Structure of the Plant. A fine chemicals plant is typically divided into a reaction part, also referred to as "wet section" and a product finishing part, also referred to as "dry section". The logical building block of the wet section is the train. Usually, it consists of three reactors, head tanks, receivers, and a filtration unit (centrifuge or nutsche). The reactors are typically equipped with a heating cooling system, condensers, and after condensers. By definition, a train is a "chemical manufacturing tool" able to handle one chemical step in a fine chemical's multistep synthesis. In the dry section, the drying, milling, sieving, and packaging takes place.

The number of products offered by a fine chemicals manufacturer typically exceeds the number of production trains. Yet, for reasons of economy of scale, the production capacity considerably exceeds the yearly requirement for each product. Furthermore, the product portfolio is regenerated at a fast pace. This set of circumstances leads to the multipurpose plant, as opposed to a dedicated plant. A multipurpose plant has to be capable of handling several types of

chemical reactions and performing a series of unit operations. In the same train up to 20 or even more different synthesis steps can be executed per year.

According to the nature of the products manufactured in a plant, specific containment rules might apply, this is especially valid for cGMP products. In order to minimize any risk of cross-contamination certain activities under cGMP therefore require strict segregation. The degree and the extent of segregation has a direct impact on the investment and operating costs. A helpful overview of different multipurpose plant concepts can be found in Ref. 2.

Size of the Equipment. In the design of a fine chemical plant, the volume of the reaction vessels is extremely critical. This design has to be closely coordinated with the marketing and sales group in order to ensure that the potential customer's needs are met by the capabilities of the plant.

Depending on the different quantities of fine chemicals to be produced in the same multipurpose unit, the concentration of substances in the reaction mixture, and the reaction time, there will be, an upper limit for the size of the reaction vessel and the ancillary equipment. Some factors run countercurrent to the economy of scale and point to small-sized equipment:

- Length of the production campaign: If the time becomes shorter than ~10 working days, the changeover time for preparing the plant for production of the next product becomes too long and burdens the production costs too much.
- Working capital: If the equipment is oversized with regard to the requirement for any particular fine chemical, the interval between two production campaigns becomes too long and excessive inventory is built up.
- Heat transfer: The time required for heating and cooling the reaction mixture and for its transfer among different pieces of equipment becomes too long compared to the reaction time.
- In the case of expensive fine chemicals, the value of one batch in one piece of equipment becomes very high, sometimes in excess of 1 Million $, and therefore the risk of false manipulations becomes excessive.
- The dimensions of existing buildings, tank farms, and the capacity of utilities often determine an upper limit of the equipment size.

In commercial plants, the volume of the reactors varies widely, and typically ranges between 1 and 10 m^3, or in rare cases even larger. As a rule of thumb, the annual capacity for a one-step synthesis process averages ~15–30 metric tons of product per 1-m^3 reactor volume.

Piping Concept. The choice of the proper piping concept is key for any competitive multipurpose plant design. The basic requirements for a piping system are, beside corrosion resistance for a wide array of substances, ease of cleanability (due to quality and costs) and of course a high degree of flexibility in order to ensure the needed multipurpose character of the plant. Typically, the following approaches are available:

- A preinstalled piping system with an adequate number of manifolds and coupling stations, according to the required flexibility: This rather classical

system may be advantageous in cases where the product mix does not tend to be too broad and/or the number of product changes per unit of time is relatively small (Fig. 1).

- A process specific piping concept: This is certainly the system of choice in cases where the products to be manufactured are still unknown during the design phase of the plant. This system is also ideal in cases when the campaign lengths are expected to be short, ie, when frequent product changes

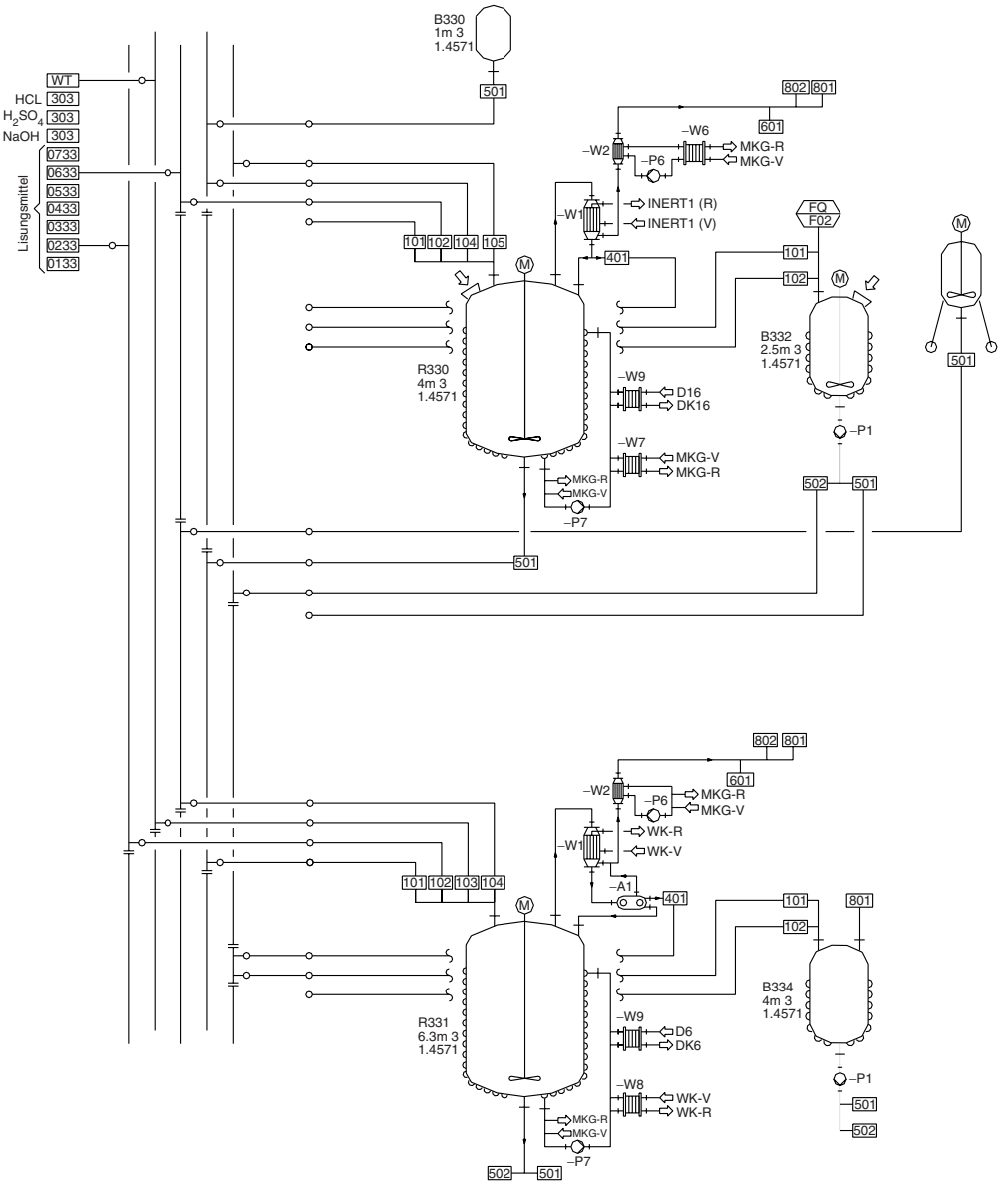

Fig. 1. Piping manifolds for multipurpose plants.

are likely. The process specific piping concept generally minimizes the needed amount of fix installed pipes. Connections between reactors, head tanks, receivers, pumps, filtration units, etc, are installed only as needed, and strictly on a campaign-to-campaign basis. In addition, suitable hoses are installed instead of solid piping whenever possible. This concept also facilitates the cleaning and change-over process, as it minimizes or even avoids "dead legs" (Fig. 2).

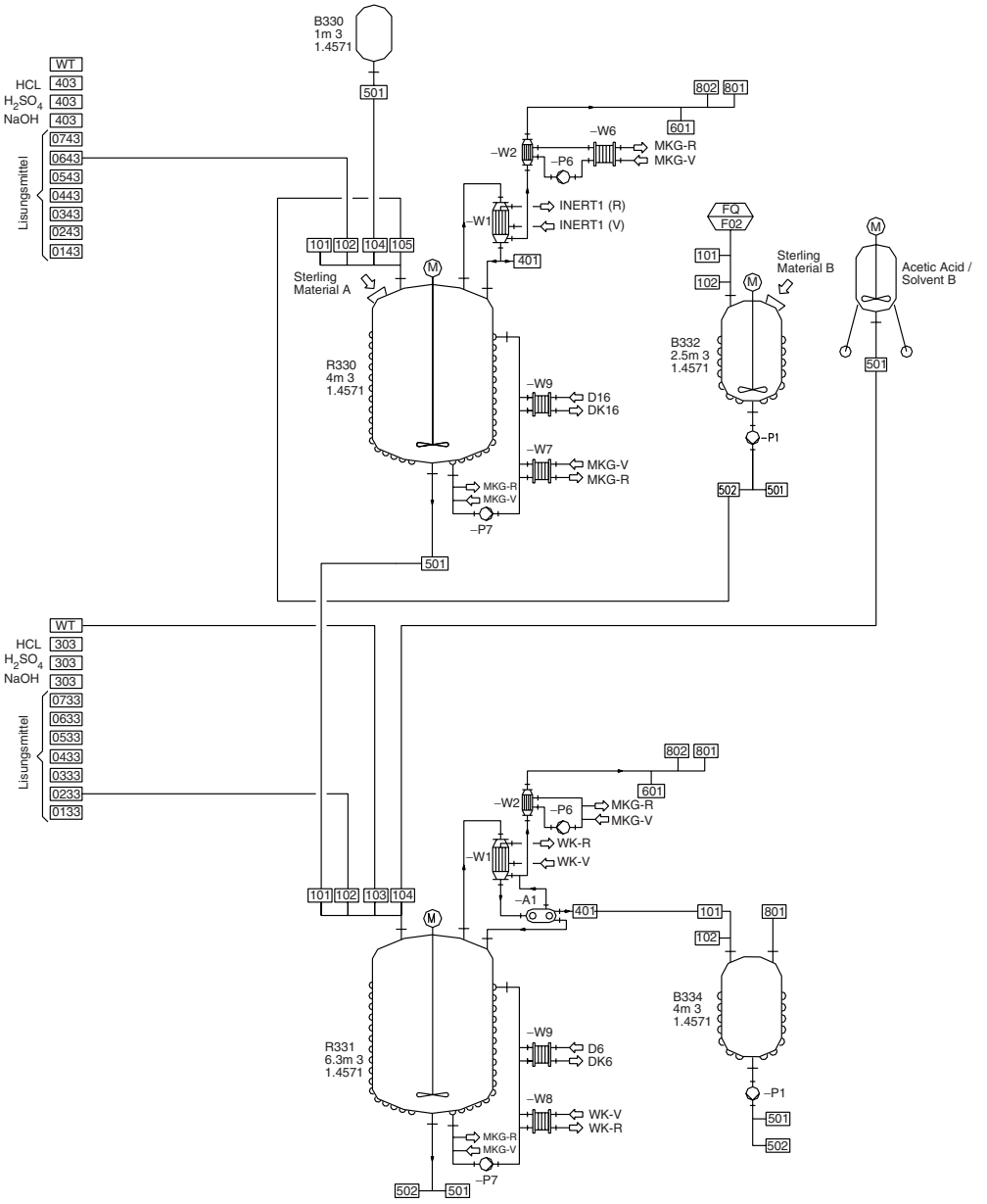

Fig. 2. Process specific piping concept for multipurpose plants.

Automation. The complexity of the plant design, the degree of sophistication, and the quality requirements of the fine chemicals to be produced, the necessity to process hazardous chemicals, the sensitivity of product specifications to changes of reaction parameters, and the availability of a skilled work force all determine the degree of automation that is advisable.

Full process control computerization for a multipurpose plant is much more complex and might therefore also be much more expensive than for a dedicated single-product plant. Whenever possible, all efforts have to be made to choose standard process control systems and to apply standard control software; this is a proven measure to control the investment costs in this segment and will also minimize the risk of having excessive investment and start-up costs due to initiating problems with the computer control system.

The fact that automation systems need to be validated has become a critical aspect of all automation systems that are being applied for cGMP productions. Some guidance on this topic can be found in the U.S. Code of Federal Regulations 3.

Material Handling Principles. The material handling in a multipurpose plant is mainly driven by the following considerations: To optimize direct labor costs versus investment costs by the mechanization of material handling operations. To comply with all pertinent quality requirements regarding safety, hygiene, and cGMP, if applicable.

According to the nature of the involved substances, specific segregation within the production area might be necessary. In order to exclude the risk of any cross-contamination, the following precautions might be taken: dispensing of starting materials and charging of solids into reactors might be located in isolated areas; the transfer of wet solid material from centrifuges or nutsches to dryers should occur either via dedicated transfer pipes or via a solid material tote bin system; and depending on the nature of the products, the unloading of dryers might have to take place in a segregated area (eg, clean rooms for cGMP products).

In the case of cGMP productions, the material flow has to follow strict rules. Specifically, the following activities have to be fully integrated into the material flow process: receipt, identification, sampling, and quarantine of incoming materials, pending release, or rejection; inprocess control laboratory operations; sampling and quarantine before release or rejection of intermediates and APIs; holding rejected materials before further disposition (eg, return, reprocessing or destruction); storage of released materials; and packaging and labeling operations. During the very early design phase, material flow has to be modeled in order to identify these requirements.

Special Equipment. Standard reaction conditions and standard materials of construction available in multipurpose plants are usually:

temperature	$-20^{\circ}C$ to $< 200^{\circ}C$
pressure	10 mbar to 3 bar
material of construction	stainless steel and glass lined

In order to make a multipurpose plant really fit today's broad market requirements, an extension of the standard conditions (ie, adding special

features to enhance the flexibility of a plant) is an absolute must. Flexibility, however, always has its price. Exotic or highly specialized equipment should only be installed in a multipurpose plant if there is a specific need. Excessive flexibility is counterproductive.

Many versatile reactions that have to be carried out at extremely low temperatures have gained significant commercial importance. For example, the very versatile organometallic reactions (eg, conversions with lithium aluminum hydride, boronic acids, etc) may require temperatures as low as $-100^{\circ}C$, which can only be achieved in a special low temperature reaction unit.

Examples of other typical special equipment that should be considered are high temperature reactors, where temperatures can be reached up to $\sim 300^{\circ}C$; high pressure reactors, where pressures up to 100 bar can be reached; fractional rectification columns; thin-film evaporation, liquid–liquid extraction; size reduction of solids; adsorption and absorption units; etc.

Beside the use of traditional stainless steel and glass lining as materials of construction, more exotic materials like zirconium, tantalum, and of course hastelloy and inconel alloys are increasingly used. During the past decade the commercial importance of single-enantiomer molecules has increased steadily. In this context, the ability to synthesize chiral molecules has become an important point. Today there are basically two state-of-the-art ways available to manufacture chiral molecules: ie, a stereospecific synthesis route or the physical separation of the enantiomeres. The physical separation of chiral mixtures can be achieved either by classical crystallization using standard multipurpose equipment, by chromatography, or by the most recently established simulated moving bed chromatography (SMB), which will require the installation of special equipment.

Instead of concentrating these special equipment functions in dedicated units, it is also possible to create semispecific production trains, eg, for hydrogenations, phosgenizations, Friedel-Crafts alkylations, and Grignard reactions.

Quality Aspects During the Design Phase. In order to ensure the required quality of a project, the entire design phase needs to be highly structured. The feasibility study represents the first step in a design phase. A task force, consisting of process engineers, sales and marketing representatives, and other specialists, led by a project leader, develops the definition of the project and a first cost estimate. Typically, the project leader will be responsible for implementing the project. After having checked alternatives and the definition of the project is found to be acceptable, the next design phase, the basic design, is initiated. The result of the basic design phase is a rather precise plan of the project and an accurate cost estimate that will be the basis for the final go/no go decision. The environmental impact of the project and all relevant permitting issues also need to be resolved during this phase. The detail engineering finally will provide the necessary information needed to execute the project.

In the very first design phase, appropriate measures have to be taken, in case the multipurpose plants needs to operate according to cGMP rules. Now the design itself has to undergo a qualification process, ie, the design qualification (DQ). The qualification process is an action proving and documenting that equipment and ancillary systems are properly designed, installed, work

Table 3. **Major Investment Cost Categories of a Multipurpose Plant: Typical Ranges**

Category	Percentage, %
piping and installation (including insulation and painting)	25–30
equipment (reactors, centrifuges, nutsches dryers, tanks, pumps, etc)	≈ 20
building (including heating, ventilation and air conditioning)	15–20
process control, instrumentation, and electrical installation	10–15
engineering	10–15
qualification and start-up	5
contingencies	5

correctly, and actually lead to the expected results. The overall qualification process generally consists of the following steps:

- User requirement specification (URS): Documented definition of the project.
- Design qualification (DQ): Documented verification that the proposed design of the system is suitable for the intended purpose.
- Installation qualification (IQ): Documented verification that the systems, as installed or modified, complies with the approved design.
- Operational qualification (OQ): Documented verification that the system performs as intended throughout the anticipated operating ranges.
- Performance qualification (PQ): Documented verification that the system, as connected together, can perform effectively and be reproduced based on the approved process method and specifications.

3.3. Investment Costs. A typical guidance for the percentage costs associated with a multipurpose plant can be found in Table 3. Note that the equipment costs account for only ~20% of the total investment costs. Beside the building cost, major cost contributors are piping and installation costs, which are 25–30% and increasingly the costs for process control, and electrical and instrumentation, which frequently contribute up to 15% of the total investment costs.

Comparisons between different multipurpose plants show that there are tremendous differences between the investment costs. First investment costs for plants in developing countries, particularly in the Far East, are only a fraction of those in western countries. In the latter, the costs for a state-of-the-art fine chemicals cGMP production train, consisting of approximately three reactors, one filtration unit, and one drying unit may range from 10 to 23 Million $ (see Table 4). Of course, investment costs of plants in full compliance with cGMP standards tend to be higher than the investment costs of non-cGMP plants. The impact of the equipment size on the total investment costs is marginal. Hence, manufacturing costs on a per kilogram basis typically decrease substantially by increasing equipment size (4).

3.4. Plant Operation. *Safety and Ecology Standards.* In today's global economy, it is vital for fine chemicals manufacturers to adhere to international standards for safety and ecology. For that purpose, there are several highly developed systems available like the International Organization for

Table 4. **Benchmarking-Capacity versus Investment Costs of cGMP-Multipurpose Plants**

Criteria	Units	Case 1	Case 2	Case 3	Case 4	Case 5
Description of multipurpose plant						
total number of trains	(–)	2	8	5	6	4
main equipments:						
total number of reactors	(–)	6	26	15	19	11
total number of filtration units	(–)	2	8	5	6	4
total number of drying units	(–)	2	8	3	6	4
total number of main equipments	(–)	10	42	23	31	19
total number of reactors per train	(–)	3.0	3.3	3.0	3.2	2.8
total reactor volume	(m^3)	24	54	22	17	46
average reactor volume	(m^3)	4.0	2.1	1.5	0.9	4.2
Capital investment key figures						
total capital investment	(Mio $)	21	181	87	83	39
capital investment per main equipment	(Mio $)	2.1	4.3	3.8	2.7	2.1
capital investment per train	(Mio $)	11	23	17	14	10
relative capital investment per train[a]	(–)	1.1	2.3	1.8	1.4	1.0
capital investment per m^3 reactor volume [1]	(Mio $)	0.9	3.4	3.9	4.9	0.9
relative capital investment per m^3 reactor volume	(–)	1	4	5	6	1

[a] Ref. 1.

Standardization's *ISO management system, ISO, Geneva*, the *Responsible Care trademark of the American Chemistry Council* program, which is of U.S. origin or the European Union *Eco-Management and Audit Scheme* (EMAS), European Commission, Environment DG. The *ISO 14001* set of *ISOs management system* standards focuses on minimizing harmful effects on the environment and achieving continuous improvement of environmental performance. *Responsible Care* is a voluntary program, initiated be the U.S. chemical industry, to achieve improvements in environmental, health, and safety performance beyond levels required by the U.S. government. *Responsible Care* continues to strengthen its commitments and enhances the public credibility of the industry. Finally, the *Responsible Care 14001* certification process combines *ISO 14001* with the *Responsible Care* program like the revised EMAS includes the *ISO 14001* system.

Quality. Because fine chemicals are sold according to stringent specifications, adherence to constant and strict specifications, at risk because of the batchwise production and the use of the same equipment for different products in multipurpose plants, is a necessity for fine chemicals companies. During the course of the past years, quality and documentation aspects in general have become more and more the success determining factor in the fine chemicals business. This is even more true for cGMP productions.

The *ISO management system standards*, which are implemented and recognized worldwide, play an important role. Specifically, *ISO 9001* deals primarily with management and focuses on the customer's requirements, regulatory requirements, the customer's satisfaction and continuous improvement on all pertinent processes.

Standards for food-grade chemicals in the United States are published in the *Food Chemicals Codex* (FCC) (5), for laboratory reagents in *Reagent Chemicals—ACS Specifications* (6) and for electronic grade chemicals in the *Book of SEMI Standards* (BOSS) by Semiconductor Equipment and Materials International (SEMI). The latter two product categories, with the exception of reagent chemicals used as diagnostics, are not subject to cGMP regulations.

Fine chemicals for the use in pharmaceuticals are to be manufactured according to the guidance for industry *ICH Q7A* (7), ie, good manufacturing practice for active pharmaceutical ingredients. The guidance was developed within the Expert Working Group of the International Conference on Harmonization (ICH) of technical requirements for registration of pharmaceuticals for human use. Since 2001, the document is applied by the regulatory bodies of the European Union, Japan, the United States, and Switzerland. In addition, the U. S. Code of Federal Regulations (8) represents a specific guidance for the United States. A firm producing pharmaceuticals has to be approved by national authorities.

General standards for drugs are typically published in the so-called national pharmacopoeia. The names of the different national pharmacopoeia are formed by pharmacop(o)eia combined with the name of the country, eg, *United States Pharmacopeia and National Formulary* (USP–NF) (9). Attempts to generalize and unify the different national pharmacopoeia are already lasting over a century. The european community signed a convention that resulted in the issuance of the *European Pharmacopoeia* (10). Finally, the WHO publishes a *Pharmacopoeia Internationalis* (11).

A comprehensive training program for all employees is another essential building block to secure adequate quality and safety standards. The program has to incorporate the entire work force involved into any aspect of the manufacturing process and needs to be documented.

All quality aspects within a company are to be controlled by an independent organizational unit. Beside the quality control unit, the quality assurance activities are also part of this operation. Hereby the main aspects to be considered are releasing or rejecting products; reviewing and approving qualification reports; reviewing and approving validation reports (the validation process is a program, what provides a high degree of assurance that a process will consistently produce a result meeting predetermined acceptance criteria); approving all specifications and master production instructions; making sure that critical deviations are investigated and resolved; establishing a system to release or reject raw materials, labeling materials; approving changes that potentially affect intermediate or API quality; making sure that internal quality audits are performed; and making sure that effective systems are used for maintaining and calibrating critical equipment. These criteria are mandatory for cGMP products, however, it is recommended to utilize, whenever possible, the same criteria for non-cGMP products.

Production Planning. Production planning for a fine chemicals company operating one or more multipurpose plants is an extremely demanding task. The goal must be to achieve optimum capacity utilization, which is important for the profitability of the company. However, conflicting interests of marketing, manufacturing, and controlling have to be aligned carefully. Particularly critical is an excellent communication to the marketing and sales group, which determines what quantity of which products can be sold, and manufacturing, which determines how a most advantageous use of the existing equipment can be made and what type of plant is needed in the future. There are both short- and long-term aspects to production planning. A useful tool for the short-term planning is a rolling 18 month sales forecast, which is committing for the first 2–6 months and somewhat more flexible for the rest of the period.

In order to have the necessary minimal critical flexibility for practical planning purposes, a multipurpose plant must contain a minimal critical number of reactors or trains. In addition, we must realize, that a 100% capacity utilization can never be achieved in a multipurpose plant.

Even in the unlikely event that there is sufficient demand to run the plant for the whole year and that for all products manufactured all available equipment can be used, there is still changeover time that is unproductive. Particularly in the case of frequent product changes, great attention has to be paid to the reduction of changeover time, which may take up a significant portion of the production capacity, depending on the campaign length. The optimal campaign length depends on a number of parameters like stability and value of the product, costs of a changeover, storage costs, interest rates, and of course the requirements of the market.

Product changeovers consist of partially overlapping activities, ie, phasing out of the previous product; cleaning the equipment; dismantling, adapting, reassembling, repair and maintenance; final cleaning; and start-up with a new product. Optimum capacity utilization in the two dimensions of time and equipment are crucial to the overall performance. Therefore running a fine chemicals company has been described as “gap management”. Commercially available software is becoming increasingly accessible, which efficiently supports the complex task of production planning in multipurpose plants.

Operating Costs. The main elements determining production costs are identical for fine chemicals and commodities. For a breakdown of typical production costs in its major elements, see Table 5.

In multipurpose plants, where different fine chemicals occupying the equipment to different extents are produced during the year, a fair allocation of costs is a difficult task. The allocation of the product-related costs, such as raw material and utilities, is relatively easy. It is much more difficult to allocate capital costs, labor, quality, safety, maintenance, etc. A possible approach is to define a daily rent by dividing the total yearly fixed costs of the plant by the number of production days. If the daily rent is corrected by an equipment utilization factor, simple products for which only part of the equipment is used can show a good profit margin without providing a good return for the overall investment in the multipurpose plant. For portfolio optimization, not only the profit margin, but also the marginal income per day have to be considered. In other words, marketing has to

Table 5. **Major Cost Elements**

Type of costs	Percentage, %
material costs	35
labor costs	15
energy costs	5
ecology costs	5
quality control, quality assurance	5
repair and maintenance	5
research and development	5
general overheads	10
depreciation	15

be given the task of finding substitutes for products that have low equipment utilization.

In addition, the operating schedule has a significant impact on the production costs. Whereas continuous plants typically run 24 h/day, there is more freedom in establishing operating schedules for multipurpose plants. Depending on the work load and the flexibility of the work force, schedules can be adjusted as needed. Some schedules still include only a one or two shift operation (eg, 8 or 16 h/day for 5 days a week). Frequently, in this case some minimum activity is maintained during the night, such as supervision of reflux reactions, solvent distillations, or dryers. A full 7 days per week operation, consisting of four or five shift crews, each working 8 h/day is becoming the standard. In terms of production costs, this is the most advantageous scheme. Higher salaries for night work is more than offset by lower fixed costs. Also, only part of the work force has to adhere to this scheme.

Pretreatment and disposal of waste effluents, disposal of solid wastes, and the cleaning of process off air are substantially contributing to the manufacturing costs of fine chemicals.

Only a minority of new products studied in R&D enjoy commercial success, thus allocation of R&D costs is another controversial issue. This problem is usually disguised by not including R&D in the cost calculation of individual products, but by placing R&D in the general overhead.

3.5. Examples of State-of-the-Art Multipurpose Plants. Two examples of state-of-the-art multipurpose plants are described below. They represent (1) a large fine chemical plant with an innovative lay-out (Schering AG, Germany), and (2), a typical pharmaceutical fine chemicals plant of a midsize custom manufacturer (Rohner AG; Switzerland).

Multipurpose Plant Example 1 (see Fig. 3). Operating principles of multipurpose plant example 1:

- The futuristic looking hexagonal shaped plant design with satellite buildings is the result of a new developed safety, ecology, and operating concept.
- The building complex that tops 42 m in height, has a diameter of 88 m and a working area of approximately 28,000 m^2, is operated by approximately 100 well-trained chemical operators engineers and chemists.

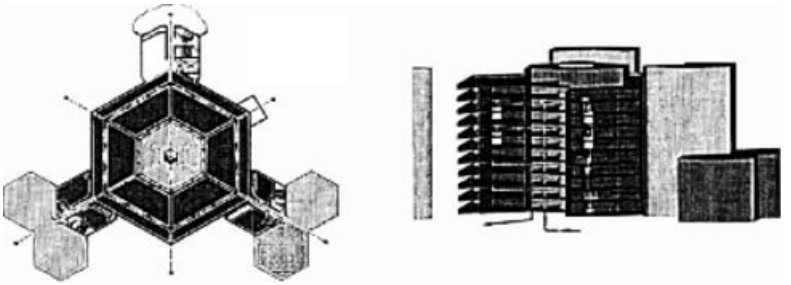

Fig. 3. Multipurpose plant example 1. (Schering. AG, Bergkamen, Germany).

- The satellite buildings contain service areas, laboratories, storage areas, offices, and various utilities (ventilation, electric power, and water for fire protection).
- For the processing flow, a top-down approach was chosen, utilizing gravitational force whenever possible.
- The plant houses six segregated and independent manufacturing areas, in order to separate, eg, corrosive chemistry from final purification steps of APIs.
- Production takes place in strictly closed equipment and is controlled by a state-of-the-art process control system.
- The core of the hexagonal-shaped building is used for the central services, and supply of liquid and gaseous media via a ring pipe system.
- Manufacturing standard: cGMP, intermediates, and API.

Multipurpose Plant Example 2 (See Fig. 4). Operating principles of multipurpose plant example 2:

- Train concept: the logical operating unit of the plant is a train. A typical train consists of approximately three multipurpose reactors (up to a max-

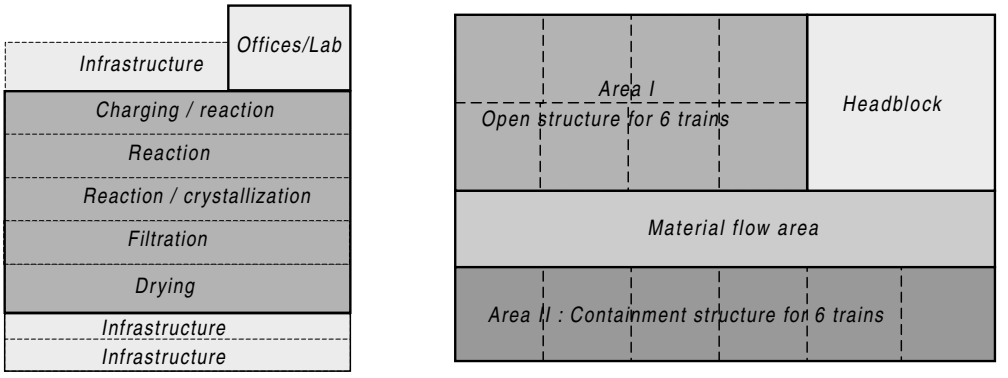

Fig. 4. Multipurpose plant example 2. (Rohner AG, Dynamic Synthesis, Pratteln, Switzerland).

imum volume of 10 m^3 each), one filtration unit (nutsche or centrifuge), and one dryer.

- Production flow of the plant: level 4: charging of starting materials; level 3: reaction; level 2: crystallization; level 1: filtration; level 0: drying, blending.
- Material flow area: reserved zone for material flow.
- Open structure: manufacturing in a maximum flexibility and minimal segregation environment, six trains in same area. The reactors and filtration units of the different trains can be connected as needed. This approach allows a maximum capacity utilization.
- Containment area: manufacturing combined with maximum segregation; six compartments, each housing one train.
- Head block: containing in-process control laboratories, offices, training and meeting rooms.
- Infrastructure: fridge plant, off gas treatment, air conditioning systems, locker rooms, spares, etc); located in the basement or as open air installations on the roof of the plant.
- Manufacturing standard: cGMP, intermediates and API.

3.6. Biofine Chemicals Plants. The production of biofine chemicals, by using biotechnological methods, fundamentally follows the same pattern as the one for synthetic fine chemicals: Preparation and charging of the raw material, reaction, liquid/solid (crude product) separation, product purification, and packaging. Depending on the specific bioprocess used, there are, however, more or less substantial differences in the design and operation of the plant. Simple

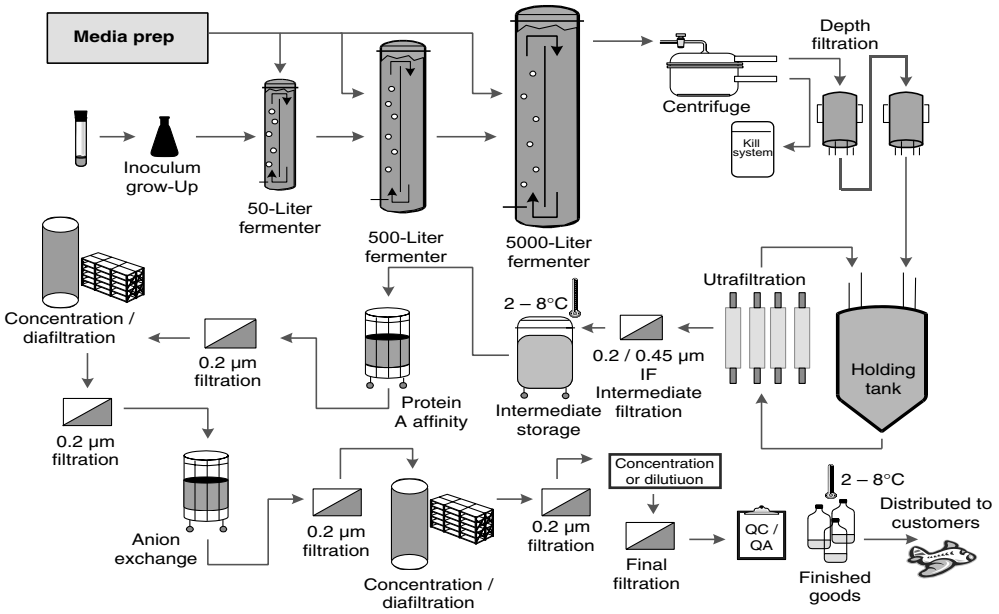

Fig. 5. A 5000-L process for protein production from mammalian cells (Lonza Inc.).

Table 6. **Key Characteristics of Biotechnological and Chemical Manufacturing**[a]

	Biotechnological	Chemical
investment per m^3 reactor volume	~ $ 3–5 million	$ 500,000–1 million
production per m^3 reactor volume and year	several 10 kg	several 1,000 kg
sales per m^3 reactor volume and year	~ $ 5–10 million	~ $ 250,000
value of 1 batch	~ $ 3–5 million (20,000-l fermenter)	~ $ 500,000
product concentration in reaction mixture	~ 2 g /l (before purification, yield ≈ 50 %)	~ 10 %
typical reaction time	~ 20 days	~ 6 h
governing rules	cGMP, BLA)[b]	cGMP, ISO 14000
scale-up factor (1^{st} lab process to industrial scale)	~ 10^9 (μg → 1 ton)	~ 10^6 (10 g → 10 tons)
process development time	~ 2–3 years (one step)	2–3 months per step
plant construction time	4–6 years	2–3 years

[a] Ref. 12. *Note:* All figures are indicative only.
[b] *Source:* Biological license application (product specific). Ref. 12.

fermentations used for specific steps in low molecular weight fine chemicals (eg, conversion of a carbonyl to an amido group, or of a carbonyl to a chiral hydroxy group) can be carried out in conventional multipurpose plants. This is particularly the case if immobilized enzymes are used as catalysts. The production of modern high molecular weight biopharmaceuticals by recombinant processes requires specifically designed plants, where utmost attention is paid to the safeguard of sterility.

For a scheme of a plant for mammalian cell culture production, see Fig. 5. The differences between traditional chemical and modern biotechnological fine chemicals manufacturing are outlined in Table 6.

The combination of high investment and low productivity lead to high production costs. They are not offset by the fact that the production of a biopharmaceutical is a one-step process. Also, the R&D effort required is substantially higher than for conventional chemical routes. For a more complete coverage of the subject see Ref. 13.

4. Economic Aspects

4.1. The Fine Chemicals Industry. Fine chemicals are either produced in-house by pharmaceutical or other specialty companies for their captive needs, or as sales products by fine chemical companies. The latter account for about one-third of the total production value of $ 70–80 billion, and obviously the totality of the trading volume.

There are >1000 companies worldwide involved in fine chemicals production, R&D, and sales. Some have developed from forward integration, eg, BASF (Germany) and Lonza (Switzerland) from fertilizers and simple organic intermediates. DSM (the Netherlands) and UBE (Japan) from coal mining. Others

have emerged from diversification, eg, Dynamic Synthesis (Germany), Ems Dottikon (Switzerland) and SNPE (France) from explosives and Degussa (Germany) from noble metals, or from backward integration from pharmaceuticals, eg, Fermion (Finland), Siegfried (Switzerland) and Zambon (Italy). Several large pharmaceutical companies market fine chemicals as subsidiary activity to their production for captive use, like Abbott (USA), Boehringer-Ingelheim (Germany), Johnson&Johnson (USA), Merck KGaA (Germany) and Pfizer (formerly Upjohn).

Fine chemical companies vary substantially in size. The largest ones have sales of >$ 500 million, the smallest ones of a few million $ /year (see Table 7). The leading companies are typically divisions of large, diversified chemical companies. The majority is located in Europe, particularly in a triangle Basel (Switzerland) / Frankfurt (Germany) / Amsterdam (The Netherlands). Many of

Table 7. **Structure of the Fine Chemicals Industry**

Type	Number	Sales	Characteristics	Examples
big	~10	>$ 250 million	global enterprises with large in-house capabilties (R&D, manufacturing, marketing); typically divisions of large publicly owned chemical companies	Akzo-Diosynth (NL), Avecia (UK), BAYER Fine Chem. (De), Cambrex (USA), Clariant (Switz.), Dowpharma (USA), DSM Pharma Products (NL), Lonza (Switz.), Rhodia Pharma Sol. (UK/USA)
medium	~50	$ 100–250 million	adequate technology toolboxes, 1–2 sites in the home country, limited global marketing organization publicly or privatly owned	Aerojet (USA), Borregaard (N), Dynamic Synthesis (De), Ems-Dottikon (Switz.), FIS (Italy), Hovione (P), Isochem (F), Orgamol (Switz.), PCAS (F), Siegfried (Switz.), Sumika Fine Chem. (Jap.), Zambon (I)
small	>500	<$ 100 million	focused on niche technologies (azide chemistry, halogenations, phosgenation, peptide synthesis, HPAI) typically privately owned	Bachem (Switz), Chemada (ISL), Chemicrea (Jap.), Contract Chem. (UK), Dipharma (I), Divi's (India), Flamma (I), Hikal (India), Kemira Fine Chem. Oy (SF), Nippoh (Jap.), SIMS (I), Synthetech (USA), Zhejiang Huayi Pharmaceutical (China)

the big players, such as Clariant, Degussa, DSM, and Rhodia Pharma Solutions, have grown to their present size through massive acquisitions. They have manufacturing plants at many different locations.

All big and medium fine chemical companies have cGMP compliant plants that are suitable for the production of pharmaceutical fine chemicals. With the exception of biopharmaceuticals, which are only manufactured by a few selected fine chemical companies like Avecia, DSM, and Lonza, the technology toolboxes of all these companies are similar. This means that they can carry out practically all types of chemical reactions. They differentiate on the basis of the breadth of the service offering.

Also, most of the medium sized fine chemical companies are located in Europe, particularly in France, Germany, Italy, The United Kingdom, and Switzerland. Italy, where international drug patent laws where not recognized until 1978, is a stronghold of API-for-Generics (see Section 3.2 The Products).

The small fine chemical companies have only limited capabilities and often specialize in niche technologies, such as reactions with hazardous gases (eg, ammonia/amines, diazomethane, ethylene oxide, halogens, hydrogen cyanide, hydrogen sulfide, mercaptans, ozone, nitrous oxides, phosgene). Their small size, however, is not necessarily a disadvantage. As most fine chemicals are produced in quantities of not more than 10 tons/year in multipurpose plants, there is little or no economy of size (see section 3.3 The Markets). On the contrary, small and mid-sized companies have an advantage in terms of responsiveness and flexibility (14). As the owners typically are the major shareholders, their shares are not traded publicly and fluctuations in their financial performance are more easily coped with. New fine chemical plants have come on stream mostly in Far East countries over the past years, but their turnover rarely exceeds $25 million/year.

A category of mostly European and American small fine chemical companies do not have manufacturing plants and concentrate on Research and Process Development. The global revenues of these Contract Research Organizations (CRO) are ~$ 1.5 billion (2003). Typical representatives are Albany Molecular (USA), CarboGen (Switzerland), Clausen-Kaas (Denmark), Evotec OAI (Germany), Onyx Scientific (UK), PharmEco (USA), Solvias (Switzerland), Syngene (India), Torcan (Canada) and WuxiPharmaTech (China).

4.2. The Products. From a commercial perspective, fine chemicals can be classified either as standard, resp. catalogue, or as exclusive products. Their characteristics are described in Table 8.

In terms of the molecular structure, one first distinguishes between LMW (low molecular weight) and HMW (high molecular weight) products. The small molecules (LMW products) are produced by traditional chemical synthesis and/or enzymatic fermentation; the big molecules are obtained by biotechnology processes.

Within small molecules, *N*-heterocycles represent the most important class of compounds. For instance, *N*-heterocyclic structures are found in the Vitamins biotin (H), niacin (PP), pyridoxine HCl (B_6), riboflavin (B_2), thiamine (B_1), and folic acid. Also other fine chemicals, whose structures are mimicking natural substances have gained great importance in modern pharmaceuticals and agrochemicals. Even modern pigments, such as diphenyl pyrazolopyrazoles,

Table 8. **Differences between Exclusives and Generics**

	Custom manufacture	API-for-generics
business model	project driven	product driven
pricing	"bottom-up"	market price
marketing	direct	agent
customers	"big pharma"	generic houses
competition	captive production	Far East countries
competitive advantage	1–2 suppliers / product project management	price, quality, (DMF)
origin of know how	customer	Drug master files supplier
technical assistance	close cooperation	sporadic
legal assistance	sporadic	intensive
production planning	on order	min / max stock

quinacridones, and engineering plastics, such as polybenzimidazoles and triazine resins, exhibit an *N*-heterocyclic structure.

In the four-membered rings, the β-lactam moiety is part of the classical penicillin and cephalosporin antibiotics. The most prominent example of a drug with a five-membered ring with one N atom is Lipitor (see Table 2). In the five-membered rings with 2 N-atoms, imidazoles are found in both modern agrochemicals, especially the imidazolinones (eg, Imazapyr [81344-34-1]), and pharmaceuticals, such as antimycotics, (eg, Isoconazole, Ketoconazole, and Miconazole), anticancers (eg, Temodar) and antiulcerants (Cimetidine and Omeprazole). Five membered rings with 3 N-atoms, triazoles or triazolones, are found in other antimyotics (eg, Fluconazole and Itraconazole), antivirals (eg, Ribavirin), and antidepressants (eg, Nefazodone hydrochloride [82752-99-61]. Five-membered rings with four nitrogen atoms, tetrazoles and tetrazolines, are found in a variety of modern antihypertensives ("Sartans", like Candesartan, Irbesartan, Losartan, and Valsartan), antibiotics (Cefotetan and Cefazolin), antiallergics (Pemirolast and Pranlukast), and analgesics (eg, Alfentanil). Pyridine derivatives, six-membered rings with 1 N-atom, are found both in the well-known Diquat [85-00-7] and Chlorpyrifos [2921-88-2] herbicides, as in modern chlornicotenyl insecticides, such as Imidacloprid. A vast array of pharmaceuticals and agrochemicals are built around a pyrimidine (2 N-atoms in the 1,3-position) ring structure. An important class are modern antiviral compounds like Zidovudine. The sulfonamide antibiotics (eg, Sulfadimethoxime and Sulfamethazine) set a milestone in modern medicinal chemistry, and half a century later the sulfonyl ureas (such as Amidosulfuron and Bensulfuron-methyl) in modern pest control. Finally, the central ring of the benzodiazepine class of

breakthrough central nervous system (CNS)-drugs like Librium and Valium is a seven-membered ring with two N-atoms in 1.4-position.

An increasingly important role play chiral fine chemicals, where image and mirror image of a drug can have completely different pharmacological effects. Such chiral intermediates and active substances can be manufactured with sophisticated chemical and / or enzymatic methods.

Most recently, the "tides" (ie, nucleotides and peptides) have gained attention as pharmacologically active substances. Smaller peptides, up to a number of 30–40 amino acids, can be manufactured via conventional chemical protecting / coupling / deprotecting methods. Larger ones, such as Calcitonin and Epoetin Alfa, are produced via microbial biotechnology. Biofine chemicals made by the most modern biotechnological process, the mammalian cell culture, are playing an increasingly important role within the pharma market as of the mid-1990s. The first generation products were recombinant human growth hormone (rhGH) and insulin (rhinsulin). It is estimated that these so-called biopharmaceuticals will capture $ 50 billion, resp. 10% of the $ 550 billion global pharmaceutical market by 2005.

4.3. The Markets. The pharmaceutical industry is by far the biggest user of fine chemicals (see Figure 6). It absorbs ~$ 50 billion out of the total fine chemicals production value of $ 70–80 billion (2003). The agrochemical industry ranks second with a use of ~$ 12 billion. The balance of $ 10–15 billion comprises a big variety of uses in specialty chemicals.

Within pharmaceutical fine chemicals, the market dynamics for custom manufacturing and API-for-Generics are different (14). Custom manufacturing of exclusive products has expanded rapidly in the 1980s and 1990s, but has suffered a setback after the year 2000. The market size is ~ $ 10–15 billion. The

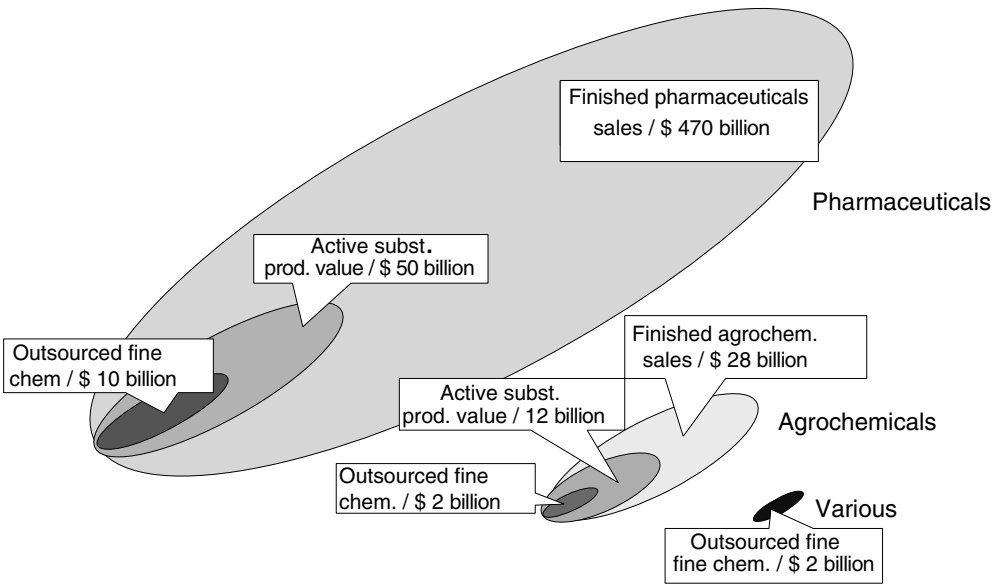

Fig. 6. Structure of the fine chemicals market.

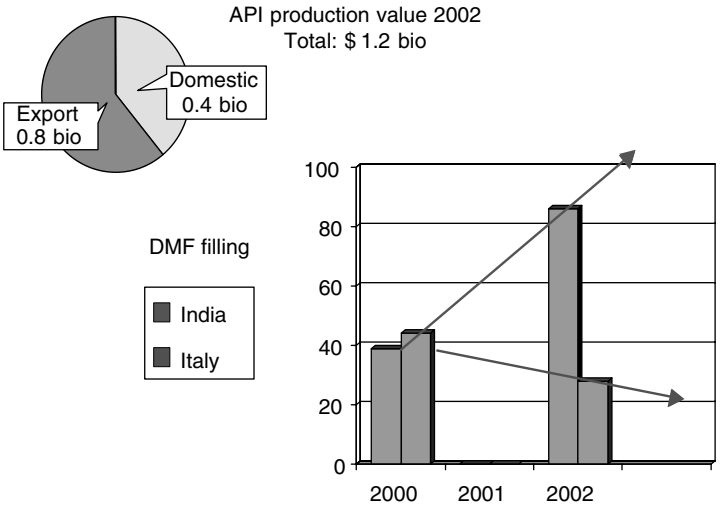

Fig. 7. DMFs filed in Italy and India.

main reasons for the decline are underutilized production capacities within the pharmaceutical industry, which in turn are due to a decline in new drug launches. As ~$ 80 billion worth of proprietary drug sales (reference year: 2002) will come off patent in 2010, the API-for-Generics market will grow substantially over the next years. Most of the new business will go to Far East companies with their "high skill/low cost" advantage, particularly India and China. The number of DMFs (the documents required for a production license) filed in the main producing countries in the western and eastern hemisphere, Italy, and India, respectively, are indicative of the shift (see Figure 7).

In terms of production volumes, an analysis of the 200 top selling prescription drugs has shown that only 23% of drugs are produced in annual quantities of >100,000 kg. More than 40% fall within a range of 10,000–100,000 kg/year, followed by those produced at <10,000 kg/year (33%), (see Figure 8).

Active substances account for ~40%, resp. $12 billion, of the $30 billion global agrochemical market. Whereas the latter has been flat over the past 10 years, the demand for custom manufactured agro fine chemicals has increased due to the shift from large volume high dosage products made in dedicated plants to lower volume, highly active molecules requiring manufacturing processes similar to those for pharma fine chemicals. Thus, in the most important class of agrochemicals, the herbicides, traditional chloracetanilids, which where produced in multi-10 thousand tons/year, have been largely substituted by imidazolinones and sulfonyl ureas. As their production volumes are in the range of several tens to several hundred tons per year, they are suitable for production in multipurpose plants.

The third category of outlets for fine chemicals comprises an array of specialty chemicals ranging from small volume (kilograms to tens of kilograms) sophisticated liquid-crystal substances to high volume plastic/rubber chemicals. However, only small parts of the latter command prices >$ 10/kg, and therefore are fine chemicals. It is very difficult to adequately structure this diverse market.

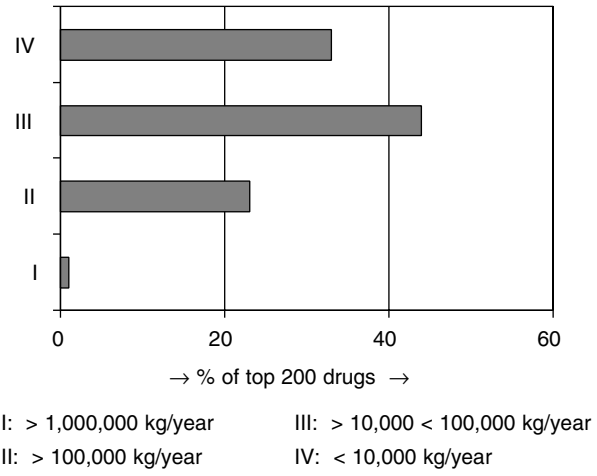

Fig. 8. Production volumes of API for prescription drugs.

The fine chemical business is globalized. The most important trade takes place between Europe (where eight of the top 10 fine chemical companies and major API manufacturing sites of the big pharmaceutical companies are located), and the United States, where five of the top 10 drug companies are resident. The U.S. trade balance deficit is further enhanced by the fact that U.S. drug companies have only limited domestic production capacities and the small size of the U.S. fine chemicals industry.

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