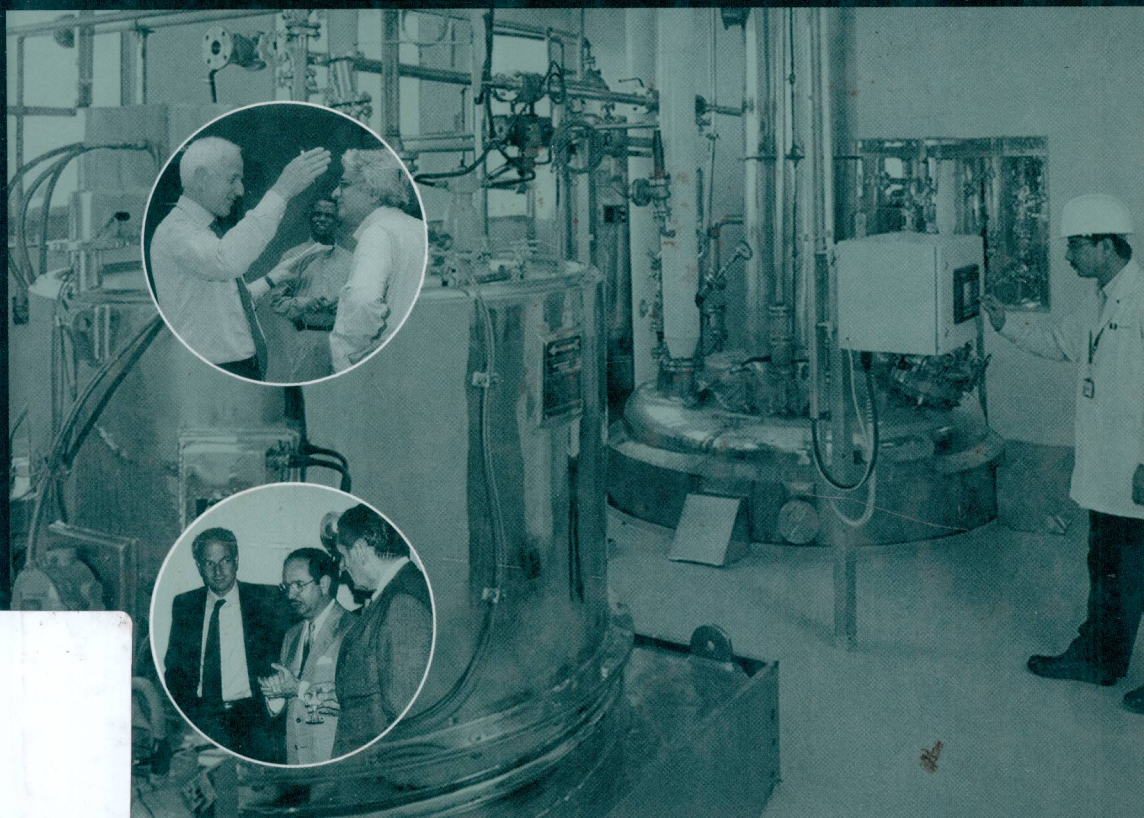


Fine Chemicals

The Industry and the Business

Peter Pollak



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FINE CHEMICALS

THE INDUSTRY AND THE BUSINESS

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Reinach, Switzerland



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FINE CHEMICALS



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To Maria, Barbara, and Paolo

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PREFACE

This book provides an insider's perspective of the status of the fine-chemical industry, as well as its outlook. It covers all aspects of this dynamic industry, with all of its stakeholders in mind, viz. employees, customers, suppliers, investors, students and educators, media representatives, neighboring communities, public officials, and anyone else who has an interest in industrial context. Safety, health, environmental, and regulatory issues are discussed only briefly, as the related subjects are extensively covered in the specialized literature.

The main *raison d'être* of the fine-chemical industry is to satisfy the product and process development needs of the specialty chemicals, especially the life science (primarily pharmaceutical and agrochemical) industry. Sales outside the chemical industry remain the exception. The fine-chemical industry has evolved mainly because of the rapid growth of the Anglo-Saxon pharmaceutical industry, which traditionally has been more inclined to outsourcing chemical manufacturing than the continental European one—and the increasing complexity of the drug molecules. The roots of both the term “fine chemicals” and the emergence of the industry as a distinct entity date back to the late 1970s, when the overwhelming success of the histamine H_2 receptor antagonists Tagamet (cimetidine) and Zantac (ranitidine hydrochloride) created a strong demand for advanced intermediates used in their manufacturing processes. The two drugs cure stomach ulcers, thus eliminating the need for surgical removal of ulcers. As the in-house production capacities of the originators, Smith, Kline & French and Glaxo, could not keep pace with the rapidly increasing requirements, both companies outsourced part of the synthesis to chemical companies in Europe and Japan experienced in producing relatively sophisticated organic molecules. Also, the fledgling generics industry had no captive production of active pharmaceutical ingredients (APIs) and purchased their requirements. Moreover, the growing complexity of pharmaceutical and agrochemical molecules and the advent of biopharmaceuticals had a major impact on the evolution of the fine-chemical industry as a distinct entity. Custom manufacturing, respectively its counterpart, outsourcing, has remained the *Königsdisziplin* (i.e., the most prominent activity) of the fine-chemical industry and “make or buy” decisions have become an integral part of the supply chain management process. The fine-chemical industry has its own characteristics with regard to R&D, production, marketing, and finance. The total turnover of the largest companies, respectively business units does

not exceed a few hundred million dollars per year. The fine-chemical industry supplies advanced intermediates and active substances, frequently on an exclusive basis, to the pharmaceutical, agrochemical, and other specialty-chemical industries. Further distinctions are batch production in campaigns, high asset intensity, and above-industry-average R&D expenditures. The industry is still located primarily in Europe. Custom manufacturing prevails in northern Europe; the manufacture of active substances for generics, in southern Europe.

As of today, the majority of the global \$75 billion production value of fine chemicals continues to be covered by captive production, leaving a business *potential* of \$45–\$50 billion for the fine-chemical industry . . . on top of the inherent growth of the existing business. Despite this huge business opportunity, the fine-chemical industry is challenged by overcapacity and intense competition. As a result of early riches, many chemical companies sought relief from their dependence on cyclical commodities by diversifying into higher-value-added products, like fine chemicals. At present, the industry is going through two interconnected changes. In terms of geography, Far Eastern “high-skill/low-cost” companies are emerging as serious competitors. In terms of structure, the chemical conglomerates are divesting their (often loss-making) fine-chemical businesses. They are becoming mostly privately owned pure players. Although the demand has not grown to the extent initially anticipated, fine chemicals still provide attractive opportunities to well-run companies, which are fostering the critical success factors, namely running fine chemicals as core business, making niche technologies—primarily biotechnology—a part of their business and developing assets in Asia.

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NOTES:

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PART I

THE INDUSTRY

What Fine Chemicals Are

1.1 DEFINITION

The basic principle for definition of the term “fine chemicals” is a three-tier segmentation of the universe of chemicals into commodities, fine chemicals, and specialty chemicals (see Figure 1.1). Fine chemicals account for the smallest part, about 4–5% of the total \$1.8 trillion turnover of the chemical industry (see Section 9.1).

Commodities are large-volume, low-price, homogeneous, and standardized chemicals produced in dedicated plants and used for a large variety of applications. Prices are cyclic and fully transparent. Petrochemicals, basic chemicals, heavy organic and inorganic chemicals (large-volume) monomers, commodity fibers, and plastics are all part of commodities. Typical examples of single products are ethylene, propylene, caprolactame, methanol, BTX (benzene, toluene, xylenes), phthalic anhydride, poly (vinyl chloride) soda, and sulfuric acid,

Fine chemicals are complex, single, pure chemical substances. They are produced in limited quantities (<1000 metric tons per year) in multipurpose plants by multistep batch chemical or biotech(nological) processes. They are sold for more than \$10 per kilogram, based on exacting specifications, for further processing within the chemical industry. The category is further subdivided on the basis of either the added value (building blocks, advanced intermediates, or active ingredients) or the type of business transaction (standard or exclusive products). As the term indicates, *exclusive products* are made exclusively by one manufacturer for one customer, which typically uses them for the manufacture of a patented specialty chemical, primarily a drug or agrochemical. Typical examples of single products are β -lactams, imidazoles, pyrazoles, triazoles, tetrazoles, pyridine, pyrimidines, and other *N*-heterocyclic compounds (see Section 3.1). A third way of differentiation is the regulatory status, which governs the manufacture. Active pharmaceutical ingredients and advanced intermediates thereof have to be produced under

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

2004

Figure 1.1 Definitions.

current Good Manufacturing Practice (cGMP) regulations. They are established by the (US) Food and Drug Administration (FDA) in order to guarantee the highest possible safety of the drugs made thereof. All advanced intermediates and APIs destined for drugs and other specialty chemicals destined for human consumption on the US market have to be produced according to cGMP rules, regardless of the location of the plant. The regulations apply to all manufacturing processes, such as chemical synthesis, biotechnology, extraction, and recovery from natural sources. All in all, the majority of fine chemicals have to be manufactured according to the cGMP regime.

A precise distinction between *commodities* and *fine chemicals* is not feasible. In very broad terms, commodities are made by chemical engineers and fine chemicals by chemists. Both commodities and fine chemicals are identified according to specifications. Both are sold within the chemical industry, and customers know how to use them better than do suppliers. In terms of volume, the dividing line comes at about 1000 tons/year; in terms of unit sales prices, this is set at about \$10/kg. Both numbers are somewhat arbitrary and controversial. Many large chemical companies include larger-volume/lower-unit-price products, so they can claim to have a large fine chemicals business (which is more appealing than commodities!). The threshold numbers also cut sometimes right into otherwise consistent product groups. This is, for instance, the case for active pharmaceutical ingredients, amino acids, and vitamins. In all three cases the two largest-volume products, namely, acetyl salicylic acid and paracetamol;