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Beyond Globalization: Scales and Speed of Production in the Pharmaceutical Industry

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Abstract. Based on a case study on Novartis and its predecessors Ciba-Geigy and Sandoz the article analyzes the evolution of the spatial organization of production in the pharmaceutical industry. The pharmaceutical companies reduced the complexity of the product range, production system and production processes. This was paralleled by a massive reduction of overcapacities and plants. Production processes were reconfigured, integrated and guided on a continental or global scale. An adaptation of the production system to the specific phases of the 'production cycle' allows the pharmaceutical companies to better correspond to the requirements of oligopolistic rivalry for flexibility, speed, reactivity and cost-reduction specific to each phase. The restructuring reflects the ambition to break up spatial fixes which are the result of evolutionary paths of companies and industries.

Longer development times, increased quality demands and tightened competition increasingly pressured the enterprises of the pharmaceutical industry to shorten the innovation time and the introduction time of new medicines. Besides major upheavals in research, development and marketing these efforts also affected the coordination and configuration of the production organization. Certainly, the share of manufacturing on the whole production costs of medicines has decreased and usually amounts to less than 20%. Nevertheless, manufacturing plays a central role in the historic evolution of pharmaceutical companies and their cultural identity. Obviously, the international restructuring of manufacturing cannot be understood in isolation from the dynamics of other corporate functions and activities, which have very specific requirements regarding input of capital and labor, location conditions and organizational capacities and affect the internationalization process of the whole innovation and production apparatus. Numerous other enterprises and actors whose internationalization strategies are linked with that of the large core firms are also involved in the production process of a medicine. Moreover, the debates on outsourcing and production networks challenged the understanding of a vertically integrated firm. Nevertheless, three reasons suggest the need to examine the production organization of individual firms: First, the firms are the legal units of value creation and profit maximization. They are the crystallization of business power. Pursuing their specific restructuring and internationalization strategies, large core firms decisively shape the organization of the value creation process. Second, an exact look at the essential sections of this value creation process within firms allows new insights into the logic of the spatial organization. Many studies and debates on globalization processes argue on aggregate levels of industries or national economics. Third, therefore, there is a substantial research deficit on the spatial implications of corporate manufacturing strategies, namely in the context of their specific path-dependency.

As a case study this article presents the evolution of the spatial organization of chemical and pharmaceutical production at Ciba-Geigy, Sandoz, and, after their merger in 1996, Novartis since the end of the 1960s (with respect to the changes in manufacturing at Hoffmann-La Roche, see Zeller, 2000). It is based on an extensive analysis of the international expansion and integration of these companies (Zeller, 2001). Traditionally, the ‘Basel chemicals and pharmaceuticals’ companies belong to the most internationalized companies in their sector. This article aims to clarify how increasing economic interweavings in the context of globalization tendencies are expressed in a specific reorganization and spatial reconfiguration of manufacturing plants, thus creating new forms of international division of labor. More generally, it seeks to identify the re-and de-territorialization as well as the (dis-)integration processes in production. Therefore, this paper is a contribution to the politically relevant discussions on persistence and shifts of locations in the pharmaceutical industry.

The paper argues that in the course of the increasing international interweaving in the 1980s, the large ‘Basel chemical and pharmaceutical firms’ carried out a path-dependent transformation from extensive expansion into new geographical markets and commercial sectors towards intensive expansion in the pharmaceutical core business in the key markets

of the triad. The scalarity and the degree of vertical integration in manufacturing organization is affected by the complexity of the technologies, the achievement of scale economies, speed requirements, market conditions, the firm's embeddedness in an industrial complex and in important regions, and the (supra-)state regulatory conditions. I argue that neither linear globalization approaches, nor a dichotomous understanding of a transformation from a rigid fordist to flexible post-fordist economic order, nor a generalization of new forms of production networks grasp the dynamics of pharmaceutical manufacturing. Rather these explanations must be reconsidered through an adaptation of the production system to the specific phases of the 'production cycle'. In the context of a specific path-dependent evolution, the pharmaceutical companies try to better correspond to requirements of flexibility, speed and cost-reduction specific to each phase. Finally, these aspects lead to the fundamental question of which economic-spatial logic is hidden behind the current restructuring processes of large firms in the pharmaceutical industry.

After a short introduction to the recent changes in the pharmaceutical industry, the first section tackles discussions on the emergence of global or continental manufacturing concepts, the increased flexibility requirements leading to new forms of industrial organization and the path-dependence of international expansion. The research questions are specified within this frame. In the second section, the most important characteristics of chemical and pharmaceutical manufacturing are explained. The third section analyzes the different phases of the internationalization of manufacturing and presents the essential changes in production concepts in the 1990s. The fourth section discusses the results in light of theoretical considerations, presents a model of a 'pharmaceutical production-cycle' and discusses the restructuring and re-territorialization of the enterprise as a path-dependent process. The article concludes with a summary and raises questions for further research.

1. Paths of international expansion and integration

Developments and challenges in the pharmaceutical industry

The international restructuring of manufacturing must be understood in the context of some specific challenges for the large pharmaceutical companies. In spite of important growth rates - particularly in the USA - the pharmaceutical markets cannot be extended nor the innovation capacities increased to the extent necessary to guarantee a sustained growth for the industry as a whole (Schweitzer, 1997; PhRMA, 2002; IMS , 2000; 2002). Under pressure of an innovation deficit expressed in a dropped number of yearly introduced new active substances (Drews, 1998; Shimmings, 1999; 2000; Southgate, 2001), longer development times, massively increased R&D costs and a shortened life cycle of products and technologies (DiMasi, 1995, p. 382; Mossinghoff, 1995, p. 1085; Drews, 1998, p. 186, 232; PhRMA, 2002, p. 18), the large pharmaceuticals have intensified their research efforts and multiplied their marketing expenses.

The tremendous capital requirements demand advantages of size. Only the largest groups are able to raise the means for the gigantic research and marketing expenditures and to

globally launch the new products as quickly as possible. These tendencies favor mergers, acquisitions and crossed foreign direct investments, which finally lead to an increasingly international interweaving of value chains (Howells and Wood, 1993, p. 41; Taggart, 1993, p. 33; Chesnais, 1997, p. 166; Andreff, 1996b, p. 52; Drews, 1998, p. 232). The reinforced concentration processes were paralleled by the rise of global oligopolies after the end of the 1980s. Hereby, the rivals in the main poles of the triad form a space of rivalry. This increasing oligopolistic rivalry pressured the large pharmaceutical companies to attack their rivals in their home markets with reinforced research and marketing efforts, direct investments and take-overs (Chesnais, 1995; 1997; Zeller, 2001, p. 194ff). The large pharmaceuticals reacted to these challenges by repeatedly restructuring their entire value creation chains and implementing new forms of coordination and configuration. In order to reduce costs, manufacturing, particularly in the launch phase of new drugs, had to be accelerated massively.

From multinational to global strategies

The long upswing from the end of the 1940s till the mid-1970s was characterized by a strongly rising world trade linked with corporate export strategies and an increasing internationalization of the enterprises, which was based on an increase of international direct investments. Multinational strategies were pursued in the 1950s and 1960s mainly by groups from the USA as well as from the Netherlands, Switzerland, and Great Britain. The international orientation of the economies in these countries goes back to the 1920s (Ruigrok and van Tulder, 1995, p. 128ff). The deterministic and hierarchical product life-cycle theory was an expression of the international expansion of US corporations (Vernon, 1966; 1971). The multinational or multidomestic enterprises worked as diversified conglomerates, having sometimes developed over decades, which consisted of a strong group headquarters and comparatively independent foreign subsidiaries (Bartlett and Ghoshal, 1989; Porter, 1986). The activities of the single foreign subsidiaries were normally oriented to the market in which they were located. The structural basis of these '*market seeking*' internationalization strategies was the specific post-war prosperity in the capitalist countries during the glorious thirty years before the mid-1970s.

The large groups reacted to the fall of the profit rates, the structural changes in the world market and their sweeping competitive difficulties in the 1970s and 1980s by changing their internationalization strategies. Foreign direct investments rose in the mid-1980s almost explosively. Bartlett and Ghoshal (1989) prescribed a 'transnational strategy' and elastic 'transnational organization' as best practices (cf. Ohmae, 1990). Moreover, an important concern was to reorganizing and accelerating the innovation processes on an international scale (Bartlett and Ghoshal, 1990). Such an '*efficiency seeking strategy*' (Michalet, 1985, p. 59; Dunning, 1993, p. 59) could establish transnational production networks encompassing all functions of innovation, production and marketing and avoid duplications. However, the multinationals, according to their national origins and the specific industrial conditions, developed a variety of international expansion strategies

which cannot be grasped with simplistic ‘best practice’ recipes (Ruigrok and van Tulder, 1995; Veltz, 1996; Borrus and Zysman, 1997a; Schamp, 2000; Sturgeon, 2002).

Production is organized on the basis of internationally dependent plants concentrated in a small number of important subsidiaries which pursue global, or more often continental, production mandates. Besides wage differences, the multinationals can first of all profit from specialization gains. Core firms build their complex international production networks with own plants and external partners (Chesnais, 1994, p. 107f; Schamp, 1996, p. 213; Borrus and Zysman, 1997a; Sturgeon, 2002). This leads to the closure of numerous factories as well as to the upgrading or downgrading of the continuing plants (Cantwell and Dunning, 1991, p. 52).

However, the global integration of production is limited while competition is largely globalized. But the latter is not anonymous and creates an interdependence between all big rivals of the oligopoly. Every oligopolistic rival designs its strategy in accordance with its perception of the strategies of its most important rivals. Even the survival of large groups can be endangered by the heightened competition in the global oligopoly (Chesnais, 1995, p. 77; 1997, p. 135f). Yet, the competition is settled from largely separated industrial bases in the three poles of the triad. In fact, the degree of interweaving in many industries rises quickly across countries, but mainly within the different poles or between poles of the triad. Therefore, continental rather than global interweaving arises (cf. Ruigrok and van Tulder, 1995; Chesnais and Sailleau, 2000).

The spatial division of labor within multinationals can be extremely complex – on the one hand because of complex organizational structures, on the other because of the numerous possibilities to organize functional and spatial corporate units in a vertical or a horizontal integration. The requirements of the manufacturing plants differ according to the specific organizational and technological tasks they pursue in the whole production system and the geographical distribution of location factors. In the course of the emergence of Japanese groups and of toyotism in the 1980s in the USA and in Europe, many multinationals tightened up their networks, concentrated subsidiaries and replaced peripheral production with external suppliers by means of subcontracting and long-term supplier contracts (Chesnais, 1997, p. 148; Dicken, 1998, p. 214ff).

The fact that the processes of corporate integration take place more on a continental than global scale is not least of all politically-driven. The liberalization and deregulation policies increasingly imposed internationally since the early 1980s, as well as the creation of the European single market and the *North American Free Trade Area* (NAFTA), were essential conditions for the transnational investment boom and the implementation of continental production concepts in numerous sectors (Howells, 1992; Chesnais, 1995, p. 97; 1997, p. 143f). In the pharmaceutical industry, the transnational harmonization of the registration requirements for medicines under the leadership of the FDA (US Food and Drug Administration) and the EMEA (European Agency for the Evaluation of Medicinal Products) has changed the conditions. In addition, the breakthrough of new information and communication technologies facilitated intensified exchange processes.

Global reactivity

Arguing against the flexible specialization thesis and discussing the concept of the *'dynamic flexibility'*, Coriat (1990) emphasized that exactly the combination of flexible and rigid production concepts, which together lead to a structure of flexible mass production, can be successful for large companies (cf. also Veltz, 1996, p. 153). Bathelt (1997: 73) stated that fordist structures are not solely rigid, nor are post-fordist structures always flexible. In his analysis of production and interweaving systems in the German chemical industry, he reached the conclusion that this indicates a continuation rather than a disappearance of fordist principles (Bathelt, 1997, p. 322ff).

The variety of current industrial production forms encourages the conceptualization of mass production and flexibility, regional and global integration, vertical integration and disintegration as a unity, with their numerous intermediate forms and in their interdependence. Mainly, in the 1990s large corporations developed striking capabilities to combine these forms, to use them according to requirements and to implement lean processes (Harrison, 1994, p. 127ff). The further important economies of scale could be achieved with a rationalization of the internal coordination as well as with the creation of external networks (Veltz, 1996, p. 115).

The concepts of 'producer-driven' and 'buyer-driven commodity chains' as well as those of 'wintelism' (Windows and Intel combined) and 'modular production networks' represent attempts to grasp the requirements of industrial mass production for flexibility, as well as new patterns of the international division of labor in the context of globalization of competition. International 'buyer-driven commodity chains'', e.g., in the textile industry and in the retail sector, are a form of international, vertically desintegrated production in the context of 'global commodity chains'. Not vertically integrated firms but the major actors in the final product's commercialization control the value creation process, running over several independent actors (Gereffi, 1996). Implementing new forms of international production networks, mainly US-firms in the computers, software and electronics industry have reacted to the constraints of global competition, the challenge to increase profitability and the intensified race for technological advantages. 'Wintelism' increasingly shifts the competitive power and command over the whole value creation process from the assembler to those who control the technological standards and interfaces. It is the successful response of US-firms to the advancement of Japanese firms and their specific industrial organization models. Complementing 'wintelism,' US-firms created international production networks. They desintegrated the value chain into individual parts which can be shifted to independent producers wherever these may be located (Borrus and Zysman, 1997a; 1997b). Similarly, Sturgeon (2002) emphasizes that lead firms in 'modular production networks' concentrate on market activities for end products while shifting manufacturing to globally operating 'turn-key suppliers'. The modular production networks profit from external economies of scale based on two major advantages: First, geographic flexibility permits to have access to a variety of place-specific factors and markets. Second, shared suppliers can better react to volatile markets and achieve a more intensive capacity utilization.

Commonly, these industrial organization forms lose the ties between market power and property over the means of production. And they are accompanied by a fundamental re-territorialization of the value chains and of power relations. However, despite the increasing importance of third party producers and specialized 'life sciences manufacturers,' little indicates that large pharmaceutical companies would withdraw from production or even research, because only those firms which control key technologies in the discovery of new active substances can assert themselves, organize a fast and safe supply of active substances, and design the marketing of new drugs. This issue will be discussed in sections 3 and 4.

Intensified competition in the course of world-wide oligopolistic rivalry, constraint to amortize R&D-and-marketing expenses, and shorter life cycles make a new product's market-entry speed a crucial factor in competition. Especially in the pharmaceutical industry, reduction of 'time to market' has become a central requirement. Firms have been forced to increase the speed of all relevant processes.[1] The production organization has had to improve its 'reactivity' (Veltz, 1996, p. 157) for the quick launch of new products. The goal is not to increase the flexibility of producing more product variants, but to increase the mix, routing and volume flexibility (cf. Coriat, 1990, p. 67ff.) in order to accelerate the processes. The concerned enterprises face the challenge of an unequal time-space compression. By an efficient global or continental focusing and activity linkage in the sense of a vertical and horizontal (global) switching (Howells and Wood, 1993, p. 142-152), as well as a flexible assignment of the mandates to the internal and external production sites, these speed and flexibility requirements can be taken into account at the total production network level.

Path-dependence of internationalization and embeddedness

The international restructuring of production is path-dependent and only understandable in its historic evolution (Howells, 1996; Nilsson, 1996). Chandler (1990; 1992) has impressively demonstrated the importance the long evolutionary lines have had for the development of organizational capabilities of large enterprises. According to Ruigrok and van Tulder (1995, p. 159-169) none of the largest core firms is really global, 'footloose' or borderless. Large corporations are integrated into industrial complexes. The internationalization runs highly unevenly. In general, the supplier firms are less internationalized than the core firms. The financial institutions, finally, rather follow and facilitate the internationalization process of industrial firms than lead the way. The governments and labor unions act only on a national level. The internationalization strategy of a core firm depends strongly on its industrial relations with suppliers, buyers, finance, governments and labor unions and particularly on bargaining relations in the home base. In this sense, globalization has to be understood not as a fact but as a strategic goal of core firms and as a process (p. 199). Moreover, large firms can also follow a path of

[1] Already Chandler (1977) emphasized the *'economies of speed'* as a decisive factor promoting vertical integration to ensure maximum utilization of equipment and the rise of the modern American corporation.

reconcentration, recentralization and retreat. Equally, the internationalization degree of separate corporate functions has also progressed very differently. Most core firms still hold the majority of R&D in their home country or keep it under home control (Pavitt and Patel, 1999). Also a globalization of the finances is considered to be too insecure. The strongest internationalized enterprises come mainly from small countries. 'Institutional thickness', a high density of different institutions, and various interactions between actors and institutions in a region serve to strengthen the *'local embeddedness'* of corporate functions (Amin and Thrift, 1994; Dicken, et al., 1994; Henderson, et al., 2001, p. 24ff).

Every globalization strategy must be placed in the context of the historically founded internationalization paths of the core firms of industrial complexes. Therefore, the internationalization process can only be understood within the framework of a reconstruction of historical processes. With regard to the pharmaceutical industry, the process by which large firms counterbalance the partly contradicting requirements of speed, flexibility, cost-minimalization and market-penetration must be examined as well as the effects specific corporate strategies have on the dynamics of manufacturing coordination and configuration. The linkages of local, regional, national, continental and global influences and constraints suggests grasping the evolution of industrial production in a multiscale understanding (Swyngedouw, 1997; Henderson, et al., 2001, p. 19).

2. Production of pharmaceuticals

The production process in the pharmaceutical industry can be distinguished into two sections. The first section consists of the production of the physiological active substances. In the second phase, these are processed into pharmaceutical delivery forms and packaged (Taggart, 1993, p. 7ff; Bathelt, 1997, p. 267; Roche, 1998).

Production of the physiological active substances

The production of the physiological active substances takes place mostly over several stages of chemical synthesis. The different process sections incorporate several unit operations: mixing the raw materials, processing the reaction mixture, separation of the reaction products, cleaning of the product as well as processing and return of the by-products.

Increasingly, the active substances are gained by biological fermentation and / or extraction from vegetable and animal materials. Mostly, bacteria, yeasts, moulds and cell cultures serve as a basis for the biotechnological manufacturing processes of antibiotics, vitamins and pharmaceutical active substances in the form of metabolism products on an enzymatic way. The processes take place in bio reactors (fermenters) in which, in an optimal environment, the organisms breed rapidly and the intended biology syntheses take place. Afterwards, the active substances are extracted by complex separation and cleaning procedures.

The chemical and biotechnological productions usually take place centrally. The different steps of production can however, be held in plants far away from each other. The production plants are extremely capital-intensive. Because the amounts of the final products are usually not very large, transportation cost is not a relevant factor. Small pharmaceutical firms and specialized generic producers acquire the active substances mostly from specialized manufacturers.

The factors time (acceleration of product launch), GMP (quality) and safety are crucial for the conception and operation of manufacturing plants. A high flexibility in hard- and software is required to enable a plant to cover a maximum of process steps with a minimal installation density. Design change flexibility, mix flexibility, part flexibility and routing flexibility are components of a structural flexibility (cf. Coriat, 1990, p. 67ff) or functional flexibility (Harrison, 1994, p. 129). This allows the product-specific adaptation of the facilities and material flows and the production of new products within the shortest time. Volume flexibility refers to the quantity of output. Crucial is a quick adaptation of installations when the product must be changed in order to shorten dead times and hold a high utilization rate. However, flexibility can increase cleaning expenditures in order to fulfill official GMP-requirements and to prevent cross-contaminations.

Based on the installation density and flexibility of the pipe systems, three different plant types can be distinguished (Jermann and Müller, 1996). A mono-site is a highly-automated plant for the continual cost-effective production of the same step. A multi-product site is a highly-automated site for the cost-effective production of a defined reaction type in different steps for a specific product mix. A multi-purpose site serves the production of a large variety of steps of future active substances whose structure and syntheses are not known at the time of building the plant. While at the mono-site the process units are based on a low installation density, the multi-purpose site disposes of a high installation density. The higher the site flexibility, the shorter the dead times and the more reduced the re-installation works for a product change (table 1).

Tab. 1. Connection between flexibility and investments at product changes

Type of site	Flexibility			Investments at product changes		
	high	medium	low	high	medium	low
Mono site			■	■		
Multiproduct site		■			■	
Multipurpose site	■					■

Source: Jermann and Müller (1996, p. 553)

Production of galenical forms

After the active substances have been ground they are processed into medicines in specific galenical presentations, like tablets, capsules, drops, uvulas, ampoules and ointments in the pharmaceutical, respectively galenical, production. After weighing and mixing the active substances and auxiliary materials, different pressing, stirring or mixing processes follow,

according to the delivery form. Particularly complex is the production of sterile medicines in ampoules infusion bottles, which takes place in sterile rooms.

These physical processes strongly differ from the demands and qualifications of the production of chemical active substances. With the exception of antibiotics and hormone preparations, it is to a certain extent possible to produce different products with the same equipment. The galenical production phase is essentially less capital-intensive, but more labor-intensive than chemical production. Many sections of the production process do not require a special employee-qualification level. The amounts of the active substances being supplied to the galenical production sites are usually small and the carriage low. This is why decentralized production has better permitted penetration of local markets. Because size and capital equipment are not so relevant in this area, here we also find smaller firms specialized in selected product assortments. The packaging processes are adjusted quite specifically to the respective delivery forms. They take place in a compact assembly line in which different engines are switched in a row.

3. Expansion, integration and re-territorialization of manufacturing

From international expansion to extensive multinationalization and diversification

The internationalization process of the Basel chemical and pharmaceutical companies can be divided into four phases, each marked by a specific form of international expansion, corporate organization and division of labor. The first phase of internationalization began immediately after the establishment of CIBA, Geigy, Sandoz and Hoffmann-La Roche in the 1860s and 1880s and was still based on ‘extensive exportation’. Indeed, the former three firms made use of manufacturing plants for chemicals and colors in Germany and somewhat later also in France due to Basel’s border situation already in the 1880s and 1890s. Hoffmann-La Roche focused from the beginning on pharmaceuticals and has run a manufacturing plant in the neighboring German municipality Grenzach since the establishment of the firm in 1886.

The second phase of ‘early multinationalization’ was paralleled by a diversification of the firms. It had already started before the turn of the century, but mainly developed between both world wars. Protectionism forced the firms to start their own production activities in all important markets of Europe and in the USA. CIBA, Sandoz and Hoffmann-La Roche already employed an extensive network of pharmaceutical plants in Europe at this time. The supply of active substances took place largely from Basel although CIBA and Hoffmann-La Roche had created chemical plants in New Jersey already before World War II.

In the 1950s an ‘extensive multinationalization’ and diversification started. Based on the sweeping economic upturn, the companies established new pharmaceutical plants first in

Europe and North America. Geigy, which entered into the pharma business only during World War II, expanded this area from the beginning on a multinational level, often by means of production and marketing collaborations. In the course of expansion in India, Pakistan and almost all countries of South America in the 1960s and 1970s, the firms built pharmaceutical plants or at least a packaging facility in almost every country of a certain importance. Particularly CIBA, and after the merger with Geigy in 1970, Ciba-Geigy, and Hoffmann-La Roche built widely distributed production infrastructures. In Asia Sandoz relied more on third party producers. Building a multiplicity of factories, the companies pursued the aim of better conquering local markets. Based on their multinationality, they made use of considerable ownership and internalization advantages compared to purely nationally operating firms (cf. Dunning, 1993, p. 76-86). Basically, the galenical manufacturing was under the primate of the market-oriented production until the mid-1980s.

Because of capital intensity and higher risk, the expansion of active-substance chemical manufacturing happened in a more concentrated and selective way. Besides the plants in Basel, which had always been of the highest strategic importance, CIBA, Geigy and Hoffmann-La Roche expanded their production bases in the region of New York / New Jersey in the 1950s, 60s and 70s. The companies reacted to the import substitution policy of governments in Asia, Latin America and Africa rather involuntarily by establishing smaller chemical synthesis facilities in some important countries such as Brazil, Argentina, India, Pakistan, South Africa and Egypt in the 1960s. Still in the 1970s, the global procurement and production of pharmaceutical active substances coexisted with smaller specific procurement and production concepts on national levels according to market conditions.

The crisis and the first important slump of profitability after World War II that occurred in the mid-1970s did not directly cause a strategic turnaround. Only after an intermediate phase of reorientation and testing different expansion strategies and following retreats, the companies launched a sweeping manufacturing restructuring. This far-reaching reconfiguration of the intra-firm division of labor in the late 1980s and 1990s can be characterized as a phase of ‘multi-continentalization’, ‘selective global integration’ and ‘intensive expansion’.

Multi-continentalization, selective global integration, intensive expansion

After repeated declines in profits in 1986/87 and in 1990 (Zeller, 2001, p. 218, 246), it became obvious that only a fundamental reorganization of the whole value creation process could create the conditions for a reconstitution of profitability. At the same time, the pharmaceutical companies had to react to the challenges of the sharpened oligopolistic rivalry and the innovation deficit. Therefore, in the years 1992-94, Ciba-Geigy, Sandoz and Hoffmann-La Roche started completely reorganizing the development departments first, followed by the research departments (Zeller, 2002a; 2002b). At the same time, production also experienced far-reaching changes. After an extension and modernization of the infrastructure in chemical production at the end of the 1980s and beginning of the 1990s,

both firms launched extensive reorganization and reconfiguration programs in galenical production in the early 1990s.

The merger of Ciba-Geigy and Sandoz to Novartis in 1996 strongly influenced the production organization. However, the efforts undertaken in the years 1996–99 were conceptually less a fundamental change than a radicalization of the restructuring and re-territorialization already started in the early 1990s. Based on very different measures to increase productivity, and finally also on the destruction of capital, the 'Basel pharmaceutical companies' (like most competitors) have succeeded in massively increasing profit rates since the early 1990s.

Global focusing chemical production

Both Ciba-Geigy and Sandoz concentrated a large part of their chemical manufacturing in Basel, though Ciba-Geigy used a geographically broader-based production system than Sandoz's already in the 1970s. Since the end of the 1980s Ciba-Geigy organized the active substance supply on an increasingly centralized global level. The required amounts are so low that the carriage is hardly significant. The nationally and regionally specific marketing considerations lost their importance compared to the cost-effective and efficient production of the active substances. With centralized manufacturing in flexible multi-purpose sites, economies of scale as well as economies of scope could be achieved. Ciba-Geigy had concentrated its chemical production increasingly on both Basel sites, Klybeck and Schweizerhalle, as well as Grimsby in North England. It put into operation modern multi-purpose facilities in Klybeck and Schweizerhalle in 1988. These modernizations caused a strong increase of the share of investments effected in Switzerland in 1986 and the following two years. In the 1990s the chemical plants in North and South America and in India were either closed or only maintained for very limited tasks. Moreover, Ciba-Geigy Pharmaceuticals produced specific intermediates in other corporate divisions' plants like Pamplona in Spain and Santa Monica in India.

Sandoz built a new chemical plant at the Basel site St. Johann and established a completely new factory for active substance manufacture in Ringaskiddy, Ireland, between 1990-94. While reorienting and rationalizing other corporate activities, Sandoz Pharmaceuticals changed from a one-pillar to a two-pillar strategy at the end of the 1980s. It closed or sold some facilities oriented to local markets in the course of the concentration to Basel and Ringaskiddy in the early 1990s. For certain products the pharmaceuticals division of Sandoz relied on the production system of its subsidiary Biochemie Ges.m.b.H., and especially on its fermentation facilities at its main location in Kundl, Austria. In addition, Ciba-Geigy and Sandoz maintained their relations with third party manufacturers.

After the merger Novartis did not execute a radical adjustment in chemical production and still relies on the three Basel production plants, Klybeck, Schweizerhalle and St. Johann, as well as on Grimsby and Ringaskiddy. The shutting down of the manufacturing facilities for specific products in Summit and East Hanover (each in New Jersey) already introduced by

the predecessor firms was concluded. Additionally, Novartis operates plants in the large markets of the south like Resende in Brazil as well as Kolshet and Mahad in India which however, execute only locally limited production mandates (figure 1).

Fundamentally, active substance production can be distinguished in a pilot or supply production as well as in three phases of market production. The pilot production produces the active substances for development purposes, particularly for clinical studies. These are essentially smaller amounts than after the registration of the drug. The facilities are used flexibly because the procedures have yet not matured. The launch production supplies active substances needed for introducing a new drug during the first two to four years. Crucial to this phase is the punctual and fast supply of the required amounts of active substances. But still in this phase, the manufacturing procedures are optimized before the second generation of low-cost-manufacturing starts. Now, it is aimed to cost-effectively produce the required amounts of active substances. When the existing capacity has to be made available for new products and after follower products or even generics have already entered the market, it is suggested to relocate parts of manufacturing in a third phase. The chemical synthesis steps and cleaning processes for a product are often effected on different manufacturing sites. Ciba-Geigy had several products whose preliminary stages were produced in Grimsby, with the final stage in Klybeck or Schweizerhalle, although this was not always desired. Mostly, pragmatic considerations determine the choice of the site.

Ciba-Geigy and Sandoz operated specific pilot facilities for development purposes in Basel and Summit, respectively East Hanover, in direct proximity to the most important R&D-centers. To facilitate the know-how-transfer, it was useful to have the pilot plants in spatial proximity to R&D activities. Despite the shut down of chemical production in New Jersey, Novartis decided to continue a small pilot production at the R&D location in East Hanover.

To accelerate manufacturing during the introduction phase, Glaxo and Hoffmann-La Roche developed so-called launch concepts in the mid-1990s. Hoffmann-La Roche globally concentrated chemical-launch manufacturing in two highly flexible multi-purpose facilities. It established one of these launch sites at the main location in Basel and opened a second site in Florence, South Carolina, in 1998. Both locations include pilot facilities (*Herriott*, 1996; *roche magazin*, 1997). In a less strict and more pragmatic way, Ciba-Geigy also began to implement a launch concept in the early 1990s. After new manufacturing capacities were created in Grimsby, the facilities in Schweizerhalle were modified to execute the task of a launch site. The following phases of *low cost manufacturing* were effected by all chemical production plants according to available capacities. Sandoz, however, because of its centralized production structure and the rather small volume of its preparations, did not develop a real launch concept. After the merger, Novartis Pharmaceuticals used the whole chemical production apparatus on its Basel sites Schweizerhalle, Klybeck and St. Johann to manufacture active substances during the launch phase. Low-cost-manufacturing was by the majority located in Ringaskiddy and Grimsby. This launch concept has never been implemented rigidly. Soon Novartis Pharmaceuticals started a more pragmatic and flexible approach using the all five sites for launch and 2nd generation production. The assignment of mandates depends on the available capacities, the

speed of adjustment of facilities and the desired intra-firm financial flows *(Zimmermann, 2000/02)*. However, the application of these concepts often raises more challenges than expected. Because of unsatisfactory quality production, mandates allocated to Ringaskiddy were shifted back to Basel.

Strategically, the launch production is particularly crucial. The locational persistence on Basel is a result of the enormous amounts of bound capital, sunk costs (Clark and Wrigley, 1997) and very long pay-back terms. A chemical production plant needs a large infrastructure for its energy supply as well as for waste water and waste air treatment. These enormous expenditures suggest a spatial concentration of chemical production. This bound capital could be shifted only accepting enormous further expenses. Moreover, Basel is corporate-wide the only location where research, development, supply production, launch production and mature mass production are spatially close together. Especially under the requirements of 'faster time to market', communication and knowledge transfer between these corporate functions is important. Nevertheless, the importance of spatial proximity of development and launch production has decreased. In the near future, an optimization more than an extension of the existing manufacturing infrastructure is scheduled *(Wetter, 1998)*. Therefore, Basel will remain important for chemical manufacturing.

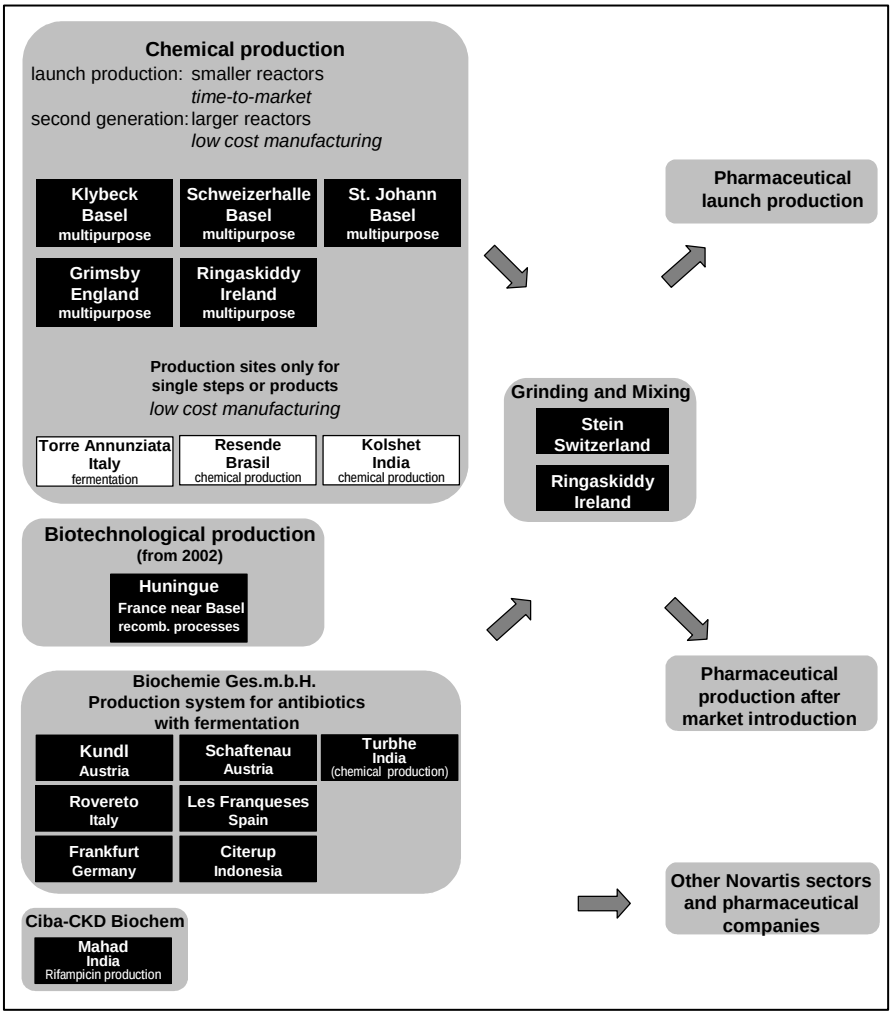


Fig. 1 Production of pharmaceutical actives substances at Novartis in 2001

Global focusing and multicontinentalization of pharmaceutical production

While continuously increasing capacities mainly in Asia and starting to close galenical production plants in Europe in the mid-1980s the pharmaceutical divisions of the 'Basel companies' hesitantly initiated a first turn, which in the early 1990s led to an extensive restructuring and reconfiguration of the whole production apparatus in Europe, North America and South America. This resulted in an essentially closer interweaving of specialized galenical plants on a continental level.

Ciba-Geigy launched the concept called 'EFI' (España, France, Italia) at the beginning of the 1990s. This concept assigned specific galenical delivery forms for the supply of the markets in Spain, France, Italy and Belgium to three sites; Barbera del Vallés near Barcelona, Huningue near Basel and Torre Annunziata near Naples. At the same time, four plants in these countries were shut down. The launch of new products was mainly guaranteed from the site in Stein, near Basel. In the same period, Sandoz realized its 'Euroguide' concept. It specialized five factories in Europe to a certain range of galenical forms and assigned to certain plants the task of launching specific galenical forms. Thus Sandoz placed a stronger emphasis on the life cycle aspect. Furthermore both firms were undertaking extensive reorganization programs in the USA at the time they merged. Ciba-Geigy had built a new plant at the site in Suffern, New York, to which the remaining production from Summit, New Jersey, would be shifted *(Haas, 1997)*. Immediately before the merger, Sandoz was relocating the majority of its pharmaceutical production in East Hanover to the strongly extended site in Lincoln, Nebraska. The historical main locations of the firms in New Jersey – Summit and East Hanover – were designated primarily to accommodate large research and development centers as well as the headquarter functions of the US-subsidiaries in future.

The merger to Novartis was an occasion and at the same time a condition for another restructuring round. What had been suggested and begun with the concepts of the early 1990s now, after the merger, has been energetically continued with the 'Europool' concept (figure 2) and an extensive restructuring in North America (figure 3 and table 2). A radical adjustment of the production infrastructure was carried out in Latin America (figure 4). Only in the important markets in South-East Asia did an extensive expansion continue, with the establishment of new production plants and joint-ventures until the mid-1990s. After a presence had also been erected in Vietnam and China, Novartis Pharmaceuticals began straightening the infrastructure by shutting down or selling manufacturing plants in Taiwan, Thailand, the Philippines and South Korea. In Europe Novartis Pharmaceuticals implemented the 'Europool' concept. This major restructuring and reconfiguration combined the factories in seven countries into a network *(Krebser, 1998)*:

- With the exception of France and a longer transition period in Turkey, only one plant continues to operate per country. The 'Europool' consists of sites in Huningue (F), Orléans (F), Horsham (UK), Barbera del Vallés (E), Torre Annunziata (I), Levent (T) and Bakirköy (T). The sites in St. Johann (Basel), Nuremberg (D), Sarria (E) and

Horsforth (UK) were shut down by the end of 1999 or, as in the case of the former Sandoz-site in Milano, sold in a management buy-out.

- Each of the seven remaining plants has the mandate to produce a range of galenical delivery forms normally as a European and in certain cases as a global 'supply center'. The frequent solid delivery forms can be produced at different sites. These manufacturing mandates are assigned on a continental level according to market conditions and the desired flow of financial returns.

- Some sites are transformed into 'launch sites' and receive the mandate for introducing specific delivery forms.

Implementing 'Europool,' Novartis Pharmaceuticals combined the approaches of both predecessor firms which had, in fact, a similar objective but were not so sweeping. Novartis' conception was oriented more towards the steps Sandoz had already begun earlier. But mostly it relied on Ciba-Geigy's plants. Only Orléans[2] and Levent of Sandoz continued their operations in a first period. This was favored by the fact that Ciba-Geigy had massively modernized the factories at Barbera del Vallés, Torre Annunziata and Huningue in the years before the merger. Therefore, Novartis Pharmaceuticals initially referred more to the conceptual structures of Sandoz while relying more on the fixed structures of Ciba-Geigy.

The extent of restructuring and reconfiguration in pharmaceutical production on a global level was massive: of 52 galenical factories which Ciba-Geigy and Sandoz contributed globally to the merger, Novartis Pharmaceuticals has so far shut down 27 (figure 5). In accordance with a concept formulated in 1998, Novartis Pharmaceuticals wants to operate only 20 galenical plants in 2002 *(Acklin and Achenbach, 1999; Galle, 2000).* Massively reducing the number of galenical plants, the firms did not only pursue the goal of rationalizing and simplifying the processes by implementing specialized facilities. They also dismantled considerable overcapacities. Daniel Vasella, Chief Executive Officer at Novartis, estimated the capacity utilization in the whole pharmaceutical industry in the mid-1990s at only about 50% (Vasella, 1996, p. 6). In the factories specialized in galenical forms, Novartis strove for an increase in utilization rate from 40% to 75% with two shifts *(Erbacher, 1998).*

In early 1998 Novartis estimated the savings to be achieved by the reorganization at about 200 million CHF annually. In Europe, the restructuring in manufacturing cost about 270 million CHF, from which 159 million fell on social expenditure, 80 million on technical investments and 40 million on new registrations, transportation and other issues. The closure of the factories amounted to another 70 million CHF. The personnel costs were, with the exception of Japan, not a criterion for closing because they are a minor factor in

[2] This plant was sold to the Greek firm FAMAR in 2000 which has continued working for Novartis from January 2002. FAMAR is an expanding pharmaceutical contract manufacturer.

pharmaceutical production. In Europe the program led to a dismantling of about 400 jobs, and world-wide approximately 1100. On a longer term the reorganization was expected to lead to a further reduction of about 1000 jobs in North America, Latin America and Asia *(Erbacher, 1998)*. The reduction of employees did not predominantly affect Basel and Switzerland; during the merger period in the years 1996 and 97, for example, the employees in New Jersey suffered greater job cuts.

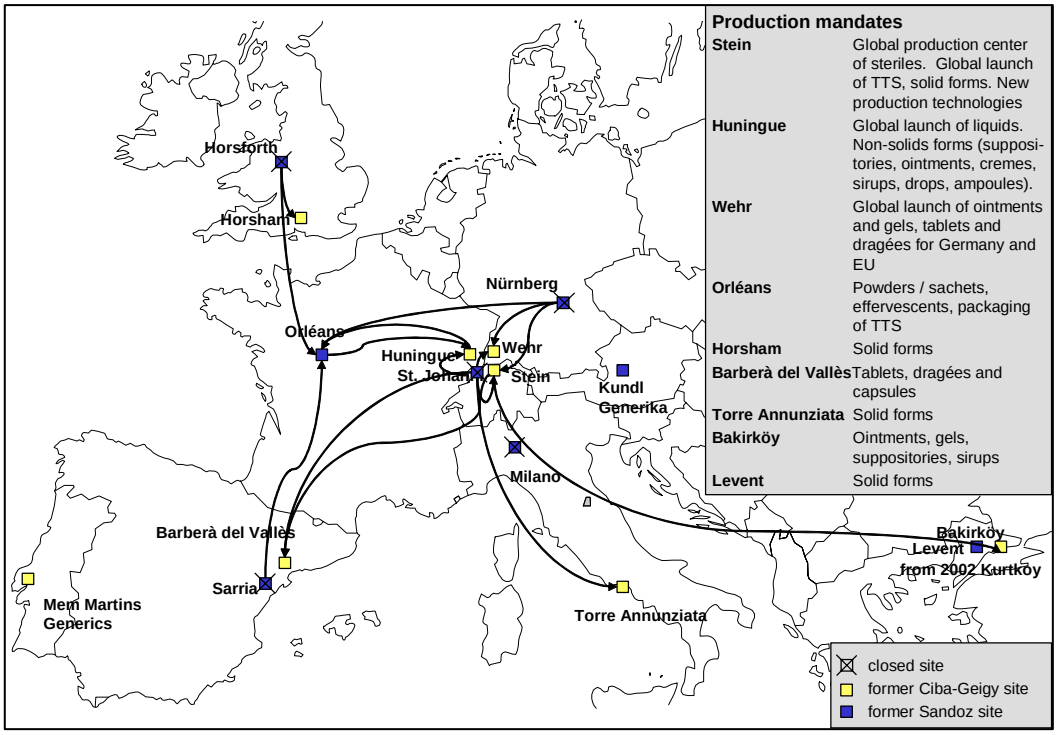


Fig. 2 'Europool' concept of Novartis

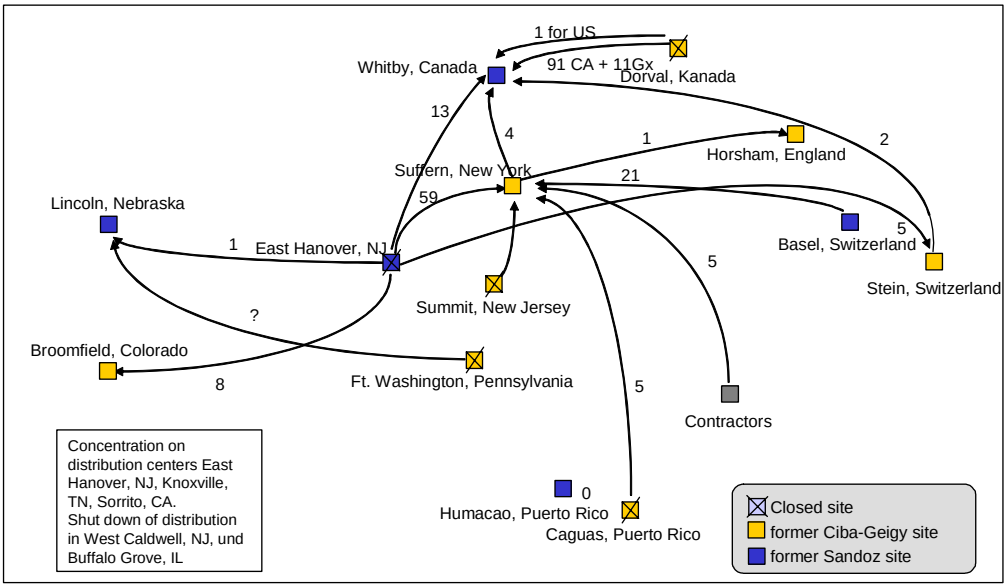


Fig. 3 Production system of Novartis Pharmaceuticals in North America. Transfers of production mandates in pharmaceutical production after the merger of Ciba-Geigy and Sandoz

Tab. 2 Competence concentration on specific sites in North America after the Novartis merger

Competence concentration

	Compressed tablets	Coated Tablets film coated	Coated Tablets sugar coated	Oros coated	Capsules	Powders	Creams	Liquids	Suspension	TTS
Suffern										
Whitby								SM, RX	RX	
Lincoln								SM, RX,Gx	SM, RX	
Outsourcing										

Business concentration

	Business types			
	Rx	SM	Gx	AH
Suffern				
Whitby				
Lincoln				
Broomfield				

Main sites

Secondary sites

Rx Patent protected, prescription medicaments
SM Selfmedication (OTC)
GX Generic
AH Animal Health
Sector of former Agribusiness division (now Syngenta)

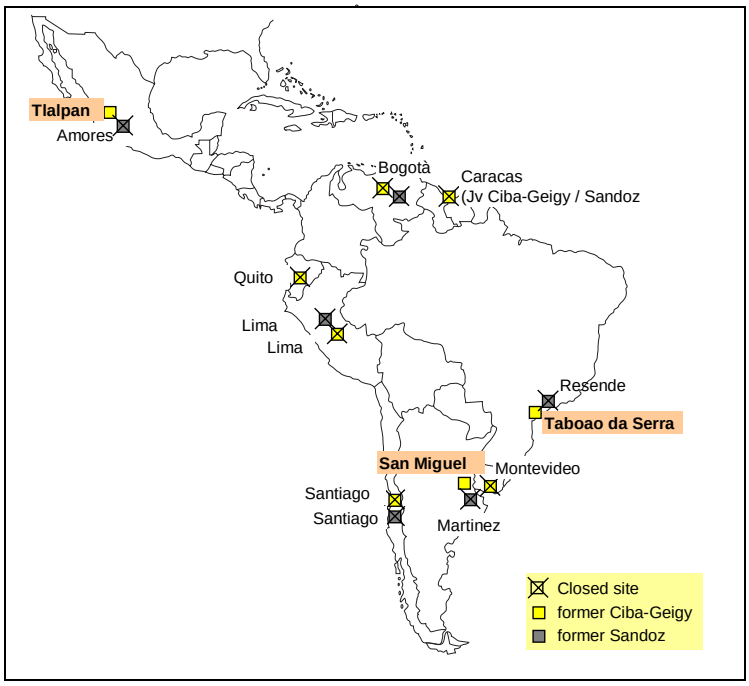
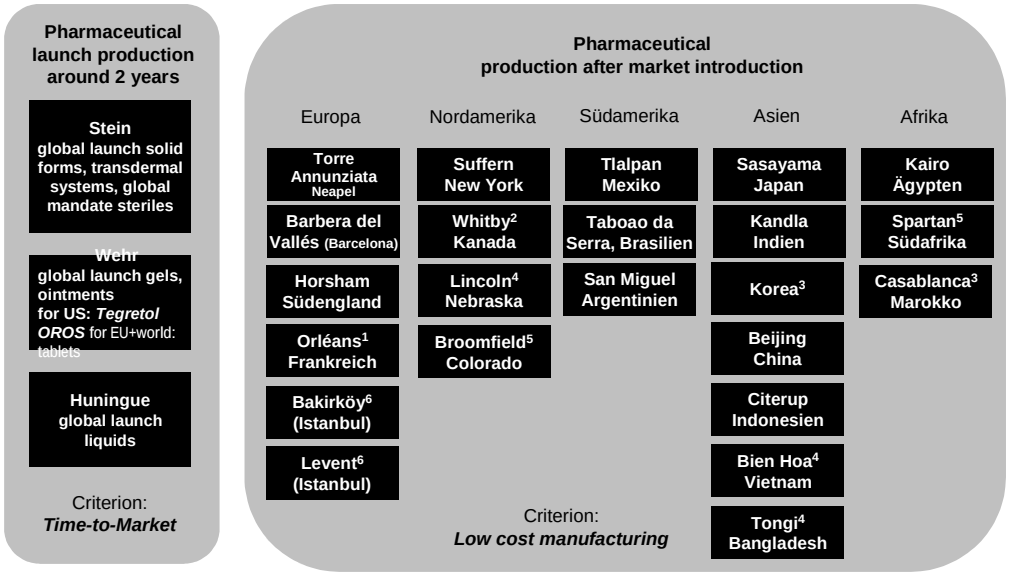


Fig. 4 Novartis' concentration of pharmaceutical production in South America

Pharmaceutical packaging is very complex because of the variety of required packaging presentations. According to the specific concept, packaging facilities can be switched directly after manufacturing or operated separately. On-line packaging is suggested when the preparations are packaged identically for several countries. However, with country-specific packages and small volumes, it is more rational to package the drugs in a firm's

own facilities or at a partner firm's facilities in the local market. Novartis pursues the latter option particularly in the Scandinavian and Eastern European countries (*Krebser*, 1998).

In contrast to the predecessor firms Novartis implemented a continental, in some cases a transatlantic and, more restrictedly, even a global perspective of restructuring. The pharmaceutical manufacturing was arranged into the large regions Europe, the USA, America (Canada and Latin America), Japan, the Asia-Pacific and Africa. In each case the reorganization of manufacturing took place within these territorial units, and it exceeded these units for special tasks as the assignment of global launch mandates to certain plants. After this description of the restructuring, some aspects will be analyzed more exactly in the following paragraphs.



1) Sold to Greek firm FAMAR (effective from 2001)
2) Sold to Canadian firm Pantheon (effective from 2001)
3) To be sold
4) Transferred to Novartis Consumer Health, produces OTC-drugs
5) Transferred to Novartis Generics, produces generics
6) It is aimed to replace Bakirköy and Levent by a new

Fig. 5 Novartis' concept of pharmaceutical production in 2001

Stressing the launch phase to accelerate the product introduction

Novartis extended the site in Stein near Basel to create by far the biggest and most important pharmaceutical factory of the company. It is the launch site for solid forms, transdermal systems and sterile medicines. The pharmaceutical launch site for ointments and creams is nearby, the plant in Wehr in southern Germany. The site in Huningue, which is located in the French neighborhood of corporate headquarters, is responsible for launching liquids. This means that all launch sites are located within a maximum vicinity of 30 kilometers to the most important research and development facilities, chemical manufacturing plants and corporate headquarters in the region of Basel. To facilitate knowledge transfer from development departments concerned with up-scaling-processes, it

can be useful to locate not only the chemical but the pharmaceutical launch in spatial proximity to important research and development facilities. Therefore, the pharmaceutical manufacturing plants in the region of Basel were revalued by the new production concepts.

As in chemical production, a specific launch concept serves to accelerate 'time to market'. The facilities' specialization in certain presentations also in the launch phase helps create organizational and technical experience. After a phase of about four years, the production mandate is shifted to plants in the local markets in order to prepare the capacity for new products. The site in Suffern (New York) assumes launch tasks for solids only when very large amounts are needed, or when the preparation is exclusively marketed in the USA. The facilities in South America or Asia are not appointed for this strategically central task *(Krebser, 1998; Sodano, 1997).*

The scales of delivery-form focusing on specific plants normally depends on the degree of complexity of the production technology in use. The bigger the technological complexity of the production plants for a delivery form, the more spatially concentrated its production. This is why the complex production processes for sterile preparations and their primary packaging are highly concentrated to achieve economies of scale and economies of scope by technological focusing. The production processes of solid forms are less complex and therefore, can be more decentralized. At launch production it is the time factor which requires a concentration of production.

Separating market segments

Following Ciba-Geigy and comparable to Hoffmann-La Roche, Novartis began partly structuring the manufacturing of over-the-counter medicaments (OTC) and generics in separate production systems. In contrast, at Sandoz the same tablet machine, for example, had produced prescription tablets, generics and OTC-products. Nevertheless, Novartis' pharmaceuticals sector also continued producing orders for the OTC and generics sectors. In parallel, Novartis Generics and Consumer Health (OTC) erected their own European production networks. The generics and OTC sectors acquire the needed active substances either from Novartis Pharmaceuticals or from external partners (*Aronson, 1996*; Bruch, 1997; *Hausmann, 1997; Krebser, 1998*).

The characteristics of the markets in each case raise specific problems for production. The market for prescription drugs is often quite stable after the introduction phase. The products' volume growth can be relatively well forecasted and the production adapted. However, the generics-market is less stable. Here, the supplier must jump into niches on a short-term, produce rapidly with short lead-times and often in many different package presentations. The demand for OTC drugs also fluctuates stronger *(Krebser, 1998).*

The separation of the production system into the commercial sectors of patent-protected medicines, generics and OTC-drugs was also an expression of the partly different business interests of management in these sectors. It was paralleled by a more general tendency in the pharmaceuticals industry. The separation of the commercial sectors increases the

accountability and transparency of the cost structures. In this sense, the assignment of production mandates between the firm sectors happen the same way as with external partners *(Sodano, 1997)*. But the production system must also be seen in the context of the changes in overall corporate structures. First, the firm organized generics and OTC together with pharmaceuticals and the eyecare business of Ciba Vision as semi-autonomous sectors of the Healthcare division. At the end of 1998 Novartis launched a strategic re-orientation in the Nutrition and Consumer Health sectors. This was accompanied by the integration of the OTC-business into the newly formed Consumer Health division, which consisted, moreover, of the business units Medical Nutrition and Health & Functional Nutrition.

Outsourcing and increasing importance of specialized producers

Although in chemical production the importance of third producers strongly increased since the 1990s, until the merger with Sandoz Ciba-Geigy had outsourced less than 10% of active substance manufacturing to third producers, in particular the products whose patents had expired *(Caveng, 1997)*. The spatial concentration of the chemical industry favors entering collaborations with neighboring firms. For example, the chemical firm Rohner in Pratteln near Basel offers intermediate stages for pharmaceutical active substances. Producing pharmaceutical active substances is a core business of the fine chemicals division of Basel-based Clariant, one of the largest specialty chemical firms. Also Lonza which has its headquarters but no production facility in Basel, for some years has been focusing on chemicals and biologics for the pharmaceutical industry.

Chemical factories in India have particularly achieved a position as third suppliers of specific intermediate products and synthesis steps on an international scale. The degree of vertical integration in active substance manufacturing depends not least of all on an enterprise's *life cycle management* and technological facilities. Certain companies with a strong competence in fermentation processes offer producer services including multinationals like Pharmacia UpJohn, Bristol-Myers Squibb, Abbott Laboratories (Law, 1999b) and Biochemie Ges.m.b.H. of Novartis (antibiotics business). On the other hand, Eli Lilly, Pfizer and the former Hoechst (now Aventis) sold certain fermentation facilities (Barber, 1998).

The rise of internet trade in chemicals and intermediate products offers further possibilities for the pharmaceuticals industry to accelerate supply-chain management and to buy certain materials more specifically (Law, 1999a). Commissioning third producers to manufacture single synthesis steps is increasing. This concerns, first of all, a product's early synthesis steps and outsourcing of older products (figure 6) [3]. However, relocation or outsourcing as cost-effective global sourcing is only relevant for certain chemical intermediate products. In pharmaceutical production, firms can outsource the packaging, for example, when the range

[3] In the early 1990s various multinationals built chemical active substance factories in Singapore, Ireland, Puerto Rico and Bahamas. In this context a discussion on *‚offshore manufacturing'* happened in the pharmaceutical industry. India and China were mentioned as future manufacturing locations. However, there was a warning not to complicate the manufacturing logistics following short-term cost considerations (Polastro, 1994; Hase, 1994).

of their own presentations is too wide, the market of a country has to be supplied very quickly, they do not dispose of their own facilities in the concerned market or in-house packaging would be too costly.

Sometimes, third party production is a more flexible and more risk-saving pre-stage to self investment. In contrast to Ciba-Geigy, Sandoz frequently instructed local third producers to manufacture or package galenical forms in the expansion markets in Asia during the 1980s and 1990s *(Krebser, 1998)*. Particularly in the areas of OTC and generics, many pharmaceutical companies have erected a system of third producers. In this way they can flexibly and quickly introduce new products. When a product is well accepted by the market, the company can decide to begin the production *in house*.

However, in the context of an extensive restructuring program, outsourcing serves to reduce a firm's own productive apparatus as well as to minimize investments and risk without essentially reducing the output. Novartis Pharmaceuticals optimized outsourcing and increased production by third parties in the course of the restructuring programs in Europe and in other regions. Nevertheless, it is remarkable that the galenical outsourcing to third producers did not increase in North America in the first period during the extensive reorganization of production after the merger. On the contrary, some production mandates for their own products were integrated again in house *(Sodano, 1997)*.

The senior management of *Technical Operations* understands manufacturing as a service which produces the required quality ordered by the marketing department at a reasonable price.[4] It has to constantly ask 'to make or to buy'? But the assignment of production orders to third parties must be considered in a consolidated way, because outsourcing high volume products would automatically raise the costs of the remaining in-house manufacturing *(Krebser, 1998)*. Figure 6 illustrates that the propensity for collaborating with external producers in active substance manufacture is higher in early chemical synthesis stages and increases in the course of the product life cycle. In order to omit risky investments, clinical supply production can also partly rely on third-party producers. The final synthesis stages, especially during the launch phase, normally remain produced by the pharmaceutical core firm. Because, however, the average profit rates of third chemical manufacturers are clearly below those of the specialized pharmaceutical companies, it is hardly to be supposed that this area will exceed a certain degree on a longer term (Polastro and Tulcinsky, 1998). Indeed, contract manufacturers have come under pressure because of overcapacities in the whole industry and tough price competition. The pharmaceutical core firm rather than the contract manufacturer dictates pricing terms and demand. Some leading contract manufacturers started developing their own product lines (e.g. in generics) or proprietary platforms (Polastro and Tulcinsky, 2001). Additionally, the pharmaceutical industry is highly regulated. The safety regulations of the FDA and the EMEA requiring substantial investments can increase entry barriers. Therefore, despite some similar phenomena in

[4] It became a dominant opinion in the pharmaceutical industry that the tasks of *technical operations* consist in manufacturing services for the marketing (Goldberger, 1991).

pharmaceutical production, there is no broad move toward ‘wintelist’ strategies (Borrus and Zysman, 1997a) or ‘modular production networks’ (Sturgeon, 2002).

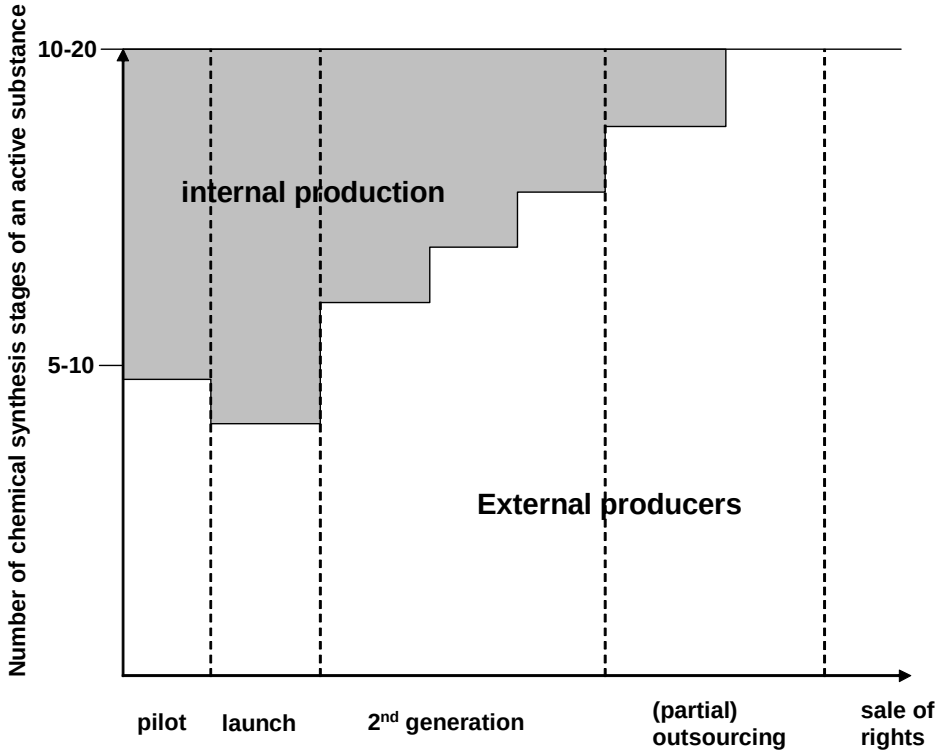


Fig. 6 Propensity for collaborating with external producers in chemical production

4. Restructuring production, speeding up processes and reconfiguring scales

After having described Novartis Pharmaceuticals’ restructuring and reconfiguration of production, the essential changes (figure 7) will be judged in light of the debates presented in the first section.

Restructuring production to rigid flexibility and rise of profitability

The fundamental goals of restructuring and reconfiguring the chemical and pharmaceutical production in the second half of the 1990s were improvement of profitability, a massive reduction of fixed and variable costs, maintaining quality, a fast reaction to market changes, fast and global product launches as well as the acquisition and defense of a leading position in the global oligopoly. The measures to reach these goals included three strategic thrusts: reduction of the complexity of the product range (what is produced?); reduction of the complexity of the production network (where is produced?); and reduction of the complexity of the working processes (how is it produced?) (cf. Bruch, 1997; McGillivray, 1997).

Reduction of the complexity of the product range. Creating global brands and global standard formulations was a step in this direction. Almost all important preparations Novartis launched in recent times, like *Diovan, Exelon or Gleevec,* roll-out globally standardized under the same name and in largely similar formulation. Drugs directed to national markets are an exception. This simplifies the development and production processes. Market-specific and customized adaptations of the products remain possible. But they are moved to the last possible point in the supply chain. Still many different packaging presentations are needed. This led to a system of *'rigid flexibility,'* which reduces the complexity of the production process. Because particularly older products cause a high complexity with hidden expenses, an active life cycle management recommends giving up these products either by outsourcing to third producers or by selling the rights to other firms. A *harmonization* of aromas, colors, sizes and packing sizes of the remaining product range also serves to simplify the production organization.

Reduction of the complexity of the production network. Reducing the plants and improving coordination of the remaining facilities leads to a reduction of fixed costs and achieves synergies in overhead expenditures. Based on the possibilities opened by the European single market and NAFTA as well as the harmonization of the registration processes of medicines, production plants acquired or established earlier to serve local markets now can be assigned within the framework of superior production networks. Bundling key facilities and phasing out redundant installations help *to reduce investments and overcapacities*. The installation of *centers of competence*, with specific continental or global production mandates, targets more than ever an optimal capacity utilization, the creation of critical masses, a reduction of the range of technological equipment and the achievement of *economies of scale*. Specializing factories in specific markets like patent-protected, over-the-counter or generics allows the facilities and planning to be better adapted to specific requirements relating to amounts, fluctuations and technological complexity.

Reduction of the complexity of production processes. The historic evolution often resulted in complex production networks. Simplifying the concatenation of activities in the supply chain ('vertical switching') helps to improve transparency and accountability of the cost-structure. By shortening the waiting, transit and inventory times, which often claim considerable phases of the production cycle, congestions in activity flow can be eliminated. An optimization of batch sizes makes better use of the facilities and human resources, improves routing and volume flexibility and, at the same time, corresponds more flexibly to the requirements of the sales departments. The remaining relative variety of the product range requires flexible facilities that can be adjusted and cleaned as quickly as possible (Ehrhard, 1991; cf. Coriat, 1990, p. 69). The improved, faster processes shorten the turnover time of the circulating capital, reduce administration, diminish work steps and remove duplications. At the same time, the variable costs are lowered by a more optimal use of human resources. If, however, the time and capital requirements for a transfer, technical or organizational change are estimated to be too tight, it can be more meaningful

to accept the existing status for a transition period. The sunk costs favor the persistence of a production system.

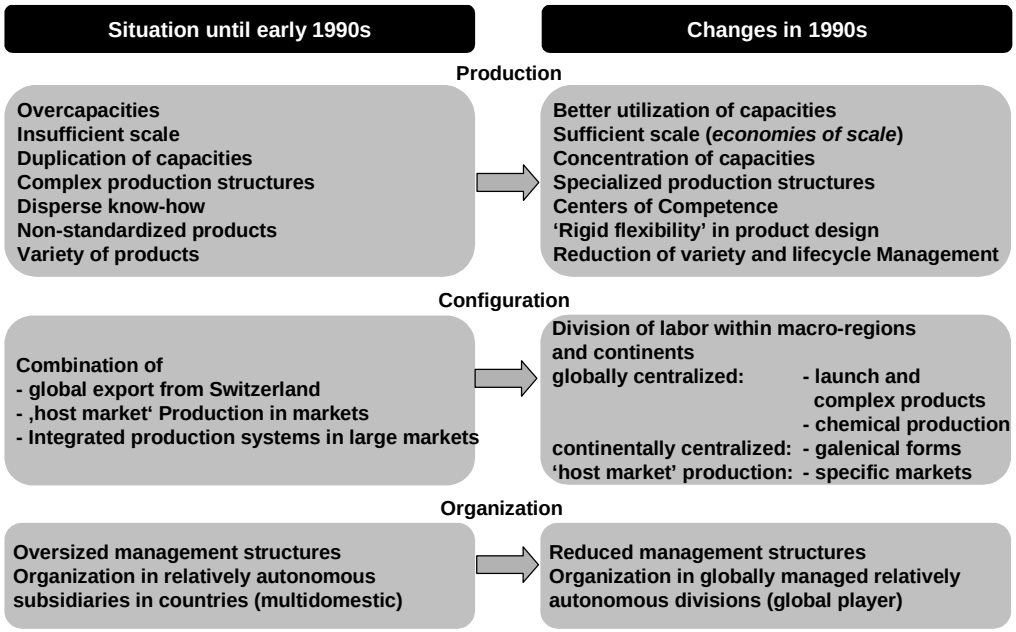


Fig. 7 Changes of production principles in the 1990s

Scales of the production cycle

Despite the increasing standardization of drugs, the pharmaceutical industry faces the challenge of dealing with different market conditions. This refers less to the geographic and more to the temporal and sectoral differentiations. The oligopolistic rivalry forces the firms to accelerate the introduction of new medicines in most possible markets. The production system must meet the requirements of economies of scale, flexibility and, almost importantly, the speed of the product launch. This is why the production procedures and management priorities have been designed more strictly to specific requirements of different phases in the life cycle of a drug. Systemizing the launch phase in chemical and galenical production, the firms pursue at least three aims: first, the quick introduction helps to gain market power in a lot of markets; second, the turnover speed of the circulating capital is accelerated, and third, already in the launch phase, economies of scale and specialization can be produced. The acceleration of the launch requires concentration of production on a few sites, each equipped with the newest and most flexible technologies operated by well trained and motivated personnel.

In the clinical supply phase, production flexibility is necessary. The launch phase works under the primacy of *'time-to-market'*. In the following phase, an optimal *'low cost manufacturing'* has to be installed. In galenical production, the necessary flexibility of the overall system is not reached by a more complex and more expensive facility structure, but rather by a spatial configuration of several specialized production plants mostly on a

continental scale, which has to be optimized constantly. The increased assignment of production mandates to third parties also increases structural flexibility of the whole system. However, to guarantee an appropriate routing, part-and-mix flexibility, an optimally coordinated system of internal sites is needed. The requirements, different in each phase, lead to specific principles of coordination and configuration. An appropriate global or continental integration of the sites represents a specific method to achieve organizational economies.

The model of a *'pharmaceutical production cycle'* presented here (table 3) prioritizes the – according to the stage in the cycle – contradicting requirements of speed, flexibility and cost-minimization. In part it takes up Coriat's concept of *'dynamic flexibility,'* which assigns to flexible multi-purpose sites the role of opening up growing market segments and recreating oligopolistic conditions. The accumulation of experience by task specialization contributes to lowering the average costs by learning- and experience-curve effects, even with frequent changes of products in launch sites (Coriat, 1990, p. 137ff and chapter IV). However, focused *low-cost-manufacturing* must be automated. The firms combine new, flexibly usable technologies and conventional mass production at different scales (see also Bathelt, 1995a; 1995b). The 'pharmaceutical production cycle model' emphasizes that organizational, spatial and temporal structures vary over stages of the product-cycle (cf. Robertson and Langlois, 1995, p. 555), but not in the sense of deterministic product-cycle models (cf. Vernon, 1966). It contradicts dualistic approaches of a transformation from rigid fordist to flexible post-fordist production patterns, including Coriat's overestimation of economies of variety (Coriat, 1997). Not variety but reactivity is a major characteristic of the present chemical and galenical mass production of drugs. Remarkably, Sturgeon (2002) did not differentiate his modular production networks model to the specificities of life cycle stages. I argue that exactly the importance of this specificity in some industries influences the extent of vertical integration and opportunities offered by modular production networks. Under oligopolistic conditions, improving the reactivity is crucial to temporally achieve monopoly rents.

Tab. 3. Pharmaceutical production cycle

	Pre-market	Market			
	Pre-launch Supply production	Launch Production	2nd generation production	(partial) outsourcing	Sale of rights
Chemical production					
Aim	Testing of optimal and most rational manufacturing process	Fastest production to deliver first markets, high reactivity	Cost-effective production in big amounts	Cost-effective production in big amounts, recreation of own production capacities	Recreation of own production capacities and simplifying of marketing strategies
Productions principles	Highly flexible supply production	Faster-time-to market	Low-cost-manufacturing	Low-cost-manufacturing	Low-cost-manufacturing
Type of sites	Pilot plants, small, flexible	Flexible multipurpose sites	Flexible multipurpose sites, multiproduct and mono sites	Flexible multipurpose sites, multiproduct and mono sites	Flexible multipurpose sites, multiproduct and mono sites
Configuration	Concentrated near R&D sites, head-quarters and/or major subsidiary	Globally concentrated in most modern sites	Relatively concentrated + external producers	Relatively concentrated depen-ding on location of external producers	Depending on configuration of third firm
Spatial interweaving	Near (chemical) development	Development dep. Other production sites, galenical production	Other chemical production sites, galenical production	Other chemical production sites, galenical production	Other chemical production sites, galenical sites of firm
In house / extern	Mostly in house, specific (biotech-) products possibly external	Last steps always in house, early steps possibly external	Last steps always in house, early steps increasingly external	Increasingly external	External
Galenical / pharmaceutical production					
Aim	Improvement of delivery form and testing of optimal and most rational manu-facturing process	Fastest production to deliver first markets, high reactivity	Cost-effective production in big amounts	Cost-effective production Outsourcing is more seldom than at chemical production	Recreation of own production capacities and simplifying of marketing strategies
Productions-principle	Small, flexible sites	flexible depending on technology and amounts	Limited flexible depending on technology and amounts	Limited flexible depending on technology and amounts	Limited flexible depending on technology and amounts
Configuration	Concentrated near R&D sites, head-quarters and/or major subsidiary	Concentrated in most modern sites, global production mandates	Continentally concentrated; national, continental and global production mandates depending on specialization of production technology	Decentral depending on location of external producer, external production eventually in peripheral markets, in part specific packaging	Depending on configuration of external firm
Spatial Interweaving	Development department.	Development department, chemical production	Chemical production, internal or external packaging	Possibly internal galenical production	Depending on configuration of external firm
In house / extern	In house	In house	In house Packaging possibly external	Depending on external firm	External

Internationalization as expression of specific expansion paths

Scales of integration

Research and development is spatially distributed extremely selectively over a few nodes in the triad. The activities of chemical development and up-scaling are connected to the *supply production* for the clinical studies. These activities took place mostly in spatial proximity to the launch sites and / or R&D-centers. But these spatial connections have loosened in recent times. The configuration and coordination of chemical and pharmaceutical launch production, very complex galenical delivery forms (sterile production) as well as chemical low-cost-manufacturing correspond to a *global focusing*. These activities are company-wide and centrally organized. The pharmaceutical company is intended to link the synthesis steps which must be done up to the finished active substance in the most optimal way by a *vertical global switching*, even if these are located in geographically different locations. However, particularly at chemical launch production, it is useful to produce a maximum of steps at the same site. Whereas the pharmaceutical launch production proceeds globally focused, after successful market introduction the plants in Europe and North America normally assume continental mandates (*continental focusing*) for specific delivery forms (Howells and Wood, 1993, p. 142-152).

Not the so-called low-cost countries but the rich regions of Europe and the USA, where the most important manufacturing and research sites have been located historically, have profited most from this development. Exceptions are Ireland, some southern states of the USA, Puerto Rico and Singapore mostly because they offered tax cuts and favorable regulatory conditions[5]. The 'Basel pharmaceuticals' have always effected the largest and strategically most important investments in the regions of Basel, New Jersey / New York, and in research, for some years in California and Boston.

Finally, the spatial scales of production mandates can neither be generalized nor rigid. This highlights the fact that a globalization of production happens only under certain conditions. It is not crucial that the firms organize their activities on a global scale, but rather that they try repeatedly to structure the scales of their activities within the margin of technical, economic and political possibilities. Therefore, the global strategies not only provoked a 'dé-territorialization' (Andreff, 1996b, p. 47; 1996a, p. 387). The periodical transformation of the production systems during the last thirty years has rather been marked by processes of re-territorialization of the whole production apparatus and, of upgrading specific locations. These processes have led to essentially closer and at the same time geographically highly selective interweavings. In general, the requirements of coordinating the value chain have risen massively. Creating firm-wide standards and a corporate culture,

[5] To be mentioned are the chemical plant in Ringaskiddy in Ireland erected by Sandoz in the early 1990s and the chemical *launch site* in Florence, South Carolina, put in operation by F. Hoffmann-La Roche in 1997 as well as the *offshore manufacturing* in Singapore, e.g. of GlaxoWellcome (Howells and Wood, 1993, p. 146; Polastro, 1994).

companies try to compensate the increasing geographic distances with organizational and cultural proximities (cf. Gertler, 1997, p. 51; Sierra, 1997; Zeller, 2002a).

Novartis' restructuring and streamlining of the manufacturing system happened in the context of all US and European rival's struggles to reduce costs and risks and accelerating their processes (Polastro, 1996; Zeller, 2000). Most large pharmaceutical companies have undertaken similar steps toward a concentrated and centralized active substance manufacturing, a strong focus in pharmaceutical manufacturing and a reduction of the number of suppliers to fewer, but strategically more important, partners (Polastro, 1996). This is not surprising, because the constraints of oligopolistic rivalry pressure the largest rivals to improve and adapt their strategies in part to those of their rivals.

Path-dependence and power relations

Based on very early internationalization and multinationalization in the 'Basel pharmaceuticals,' a geographically unequal expansion and decentralization happened in manufacturing to better penetrate the markets between the 1950s and 1980s. In contrast, the 1990s were marked by a massive re-concentration and centralization of the manufacturing organization, in chemical manufacturing more than in pharmaceutical manufacturing. In the context of a global harmonization of regulatory conditions, the design and dosage of prescription drugs have been increasingly standardized worldwide, although for very specific reasons also 'national' products can be continued. Mainly OTC and generics markets are still nationally segmented. Companies focused on patent-protected prescription drugs are increasingly pressured by oligopolistic rivalry in recent times not only to develop so-called 'blockbusters,' which achieve at least one billion US dollar sales soon after their introduction, but to design 'megabrands' which devour gigantic marketing means already before the launch.

The path of international restructuring as well as of organizational coordination and spatial manufacturing configuration at every multinational is the result of historical processes. These are marked by expansion steps often effected opportunistically, takeovers, geographical distribution of facilities, traditionally applied production principles, evolution of markets, integration into the whole industrial complex and infra-firm contradictions (e.g. between corporate management and management of strong subsidiaries or divisions). Therefore, the restructuring processes, the transnational integration of the production system and the speed of their implementation are always an expression of specific power relations to rival firms, suppliers, the buyers, the financial sector, governments, labor unions and within the firm (Ruigrok and van Tulder, 1995; Tulder, 1999; Henderson, et al., 2001). The conditions in Basel and Switzerland characterized by a disciplined and well-trained workforce, weak labor unions, an unproblematic access to capital as well as highly supportive local authorities and political actors have provided a favorable platform for international expansion. At the same time considerable exit barriers exist because the production plants represent enormous capital investments and sunk costs which cannot be depreciated in a short-term. These processes in their sum and over a longer time lead to an

economically sub-optimal infrastructure. On the one hand, early internationalization provided the Swiss chemical and pharmaceutical multinationals better opportunities to profit from a strong presence in foreign markets such as the USA. On the other hand, this presence sometimes became a too-tight corset of fixed capital. Therefore, restructuring in the early 1990s and in the course of the Novartis-merger also represents efforts to break up these spatially fixed structures abruptly and to transfer them into new *'spatial fixes'*[6] according to current needs or those expected in the future. The development of this up-breaking and rebuilding of spatial fixes depends on earlier spatial fixes and can be interpreted as a spatial form of creative destruction in order to periodically increase profitability. At the same time, restructuring also serves to change the power relations within and between management as well as with labor unions on different spatial scales. Endowed with the ability to repeatedly produce and reproduce new scale configurations of their facilities, corporate management shifts power relations with labor unions in their own favor (Zeller, 2000).

5. Conclusion

In contrast to the previous multinationalization, which was marked, first of all, by an extensive expansion in numerous markets, international restructuring led to a process of intensive global expansion and integration. This consisted less in a geographical expansion than in a striving for a dominant position in the most important markets and specific therapeutic areas.

Profitable production became impossible not only on a national but also on a decentralized multinational scale. The core activities of the value chain were reconfigured, integrated and guided increasingly according to specific requirements on a continental, transatlantic, triadic or global scale. Large pharmaceutical companies rationalized the processes and massively diminished considerable overcapacities, reducing the number of plants. This process of creative destruction was accompanied by extensive investments for the renewal of the production and research infrastructure, the incorporation of new technologies as well as the transformation of the work organization.

Mass production was not replaced but was rather enhanced on a new level. Adaptation of the production system to the specific phases of the 'production cycle' allows the pharmaceutical companies to better correspond to the requirements of flexibility, speed and cost-reduction specific to each phase. These phases have their specific organizational and spatial expressions. The pharmaceutical companies have succeeded in increasing profits substantially. Important location regions, for example the region of Basel, have by no means lost their outstanding importance in spite of a massive reduction of employees.

6 David Harvey uses the notion of *'spatial fix'* in a broad sense characterizing strategies of encountering phenomena of over-accumulation in capitalism and creating a socio-spatial coherence (Harvey, 1982, p. 427; 1989, p. 33). This notion can be well applied to mark the periodical spatial reconfigurations of production systems leading to new – from an entrepreneurial point of view more coherent – spatial fixes'.

The reorganization of research and development as well as production is never expressed only as a de-territorialization but also as a re-territorialization. Even worldwide acting firms are always integrated in specific bargaining conditions, power relations and *spatial fixes* on all scale levels. The restructuring, rationalization and expansion processes are linked with a constant re-configuration of the spatial circumstances and relations.

Further research on the linkages between global production networks and their control mechanisms, respectively on balances of power, are needed (cf. Henderson, et al., 2001; Sturgeon, 2002). A special challenge remains to clarify how the logic of international restructuring at different scales is connected to the development of profitability in different sectors and regions.

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