INDUSTRIAL CHANGE AND REGIONAL DEVELOPMENT: THE CASE OF THE US BIOTECHNOLOGY AND PHARMACEUTICAL INDUSTRIES

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Abstract

This paper examines the arguments surrounding the location and organization of innovative firms and examines the prospects for industry renewal and regional rejuvenation. We examine the effect of technological breakthroughs in the US biotechnology industry on the organization and location of production with respect to mature and emergent regions. We find that despite losing much of their preeminence in R&D, traditional firms in mature regions of the USA have managed to "capture" a substantial amount of manufacturing and marketing. The drug development experience, manufacturing capabilities, and marketing channels of more established companies in mature regions are turning out to be major sources of competitive advantage.

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Introduction

One of the most absorbing puzzles in economic geography is the apparent resurgence of regional economies amidst the virtual dissolution of national economies. Intensified global competition and rapid technological change have eroded the foundations of the postwar keynesian welfare state. A rapidly changing economic environment continues to exert tremendous pressure for industrial restructuring among all high wage countries. Simultaneous trends towards regional specialization and geographic dispersion raise questions about the conditions under which urban industrial areas might thrive in the new world economy.

Since the mid 1970s, the advanced industrial economies have experienced massive economic restructuring in response to increased international competition and falling rates of productivity (Bluestone and Bluestone, 1992). Technological innovation is widely regarded as the propulsive engine for new growth in the most developed countries in the global economy. Such innovation may involve new product development based on research and development, or new process development based on the application of new technologies to continuous incremental improvements in the production process. Innovative industries may therefore include the emergence of "high tech" industries, such as semiconductors, advanced materials, and biotechnology, and the revitalization of mature design-oriented industries, such as textiles and ceramics of Northeast Italy (Storper and Harrison, 1991; Best, 1990; Scott, 1988a, 1988b). With some exceptions, most of the interest in the revival of craft-based industries is associated with Europe more than the US. Scholars of the American economy have focused more on the high technology industries that seem to better characterize American innovative growth. This study

combines the two by looking at the impact of product innovation on a mature industry in the US.

Scholars' preoccupation with high tech industries stems from their potential for exceptional growth. Compared to more traditional industries, high tech industries are thought to agglomerate and become anchored in a region. Innovative firms are regarded as being more dependent upon social, institutional and economic factors that are interwoven at the regional level into a local "world of production" (Storper, 1993). Thus, the regional development, structure, location, organization and competitive strategies of high tech industries have received much attention.

There are two contending visions of how and where innovative firm growth occurs. One dominant line of reasoning assumes that firms in emerging industries must locate in new regions, without a strong industrial history, in order to innovate. From this viewpoint, innovative firms need a region where they can experiment with the organization of production, and so avoid regions with previously constructed industrial culture. This perspective views innovative firms as prone to vertical disintegration, agglomeration, and localization economies which result in the new region hosting the entire production complex. The competing view is that firms in emerging industries are likely to originate from the rich economic mix provided by established firms in mature regions, or existing centers of industry. This argument holds that innovative firms thrive from the urbanization economies found in mature economic centers. This results in firms keeping their production in mature regions, at least until a product is standardized.

This paper examines the theoretical arguments surrounding the location and organization of innovative firms and examines the prospects for industrial renewal and regional rejuvenation. Do emerging high tech firms need to locate in new regions in order to innovate? Or are they likely to originate in mature regions? Wherever they locate, how tightly

linked are research, manufacturing, and commercialization functions? Can other regions, not hosting research, share in the economic growth resulting from the innovation? Or will they be locked out of the economic benefits of innovation altogether? The evidence we analyze comes from the impact of technological breakthroughs, in molecular biology in this case, on the organization and location of production with respect to mature and emergent host regions.

Theories of Industrial and Regional Change

A fundamental part of this argument involves our conception of emergent and mature regional economic identities. The social relations arising from the socioeconomic, political, and cultural milieu can make one region distinct from another (Massey, 1984; Markusen, 1987). In fact, the homogeneity of a region is only significant in its differentiation from other places or regions. This is particularly true in the literature on new and mature regions, in which such regions are continuously defined in relation to each other by academic, policy-oriented, and popular observers (Allen et al. 1998). Within this context, the emergent region consciously constructs its identity as a new norm that embodies the social relations desired by emerging industries.

Although not as explicit in the past, the construction of regional economic roles is not new. Theories of the relationship between industrial change and regional outcomes have evolved over the last thirty years to explain new developments in the spatial distribution of growth. Running throughout the discussions of these trends are actually two distinctive dimensions of change. The first is whether innovative firms in emerging industries require a region relatively unshaped by previous rounds of accumulation. The second dimension is whether or not industrial change is understood as a progression from invention and innovation through maturation and dispersion. The intersection between these dimensions has been understood in sharply contrasting ways.

Product cycle theory was developed towards the end of the postwar boom by economists studying high wage economies (Thompson, 1965; Vernon, 1966; Wells, 1972). The basic argument is that the most advanced regional economies generate new industries as they shed mature ones. The evolution of industries from innovation to standardization to decline requires corresponding changes in the organization and location of production.

New product development is associated with flexible organizations requiring a skilled workforce and supplier base to avoid locking into a specific design too early. As products become more standardized for higher volume, firms begin to establish routine production systems. This process leads firms to become increasingly footloose as their product and process technologies mature which enables them to locate new branches in lower cost business environments. This standardization and dispersion, together with the constant downward pressure on prices, means that firms may eventually exit the industry or the region altogether as lower cost rivals successfully imitate them.

But the regional development process often contains the seeds of economic renewal within it. Emerging industries attract and augment productive resources and establish sophisticated markets for subsequent rounds of innovation. These resources are redeployable to new and higher uses either within existing firms or in new start-ups, and the whole process may begin all over again. In this way, the most advanced regions are likely to remain dynamic and prosperous relative to those following in their wake.

The economic restructuring of the 1970s and early 1980s, however, raised disturbing doubts concerning the dynamism of mature regions. A large number of urban industrial areas in the US, the UK, and other European nations suffered catastrophic job losses in manufacturing without compensating growth in new industries (Bluestone and Harrison, 1982; Massey and Meegan, 1982). Job growth in the service sector offered limited opportunities for reemployment at comparable

wages, while emerging high technology industries were commonly located away from the traditional manufacturing belt. Responses to these trends by the mid-1980s led to two very different revisions of product cycle theory.

The first response accepted that regional economic prosperity ultimately depends upon the continual development of new industries, but that *mature* regions are unlikely to generate or attract innovative industries as traditional ones decline (Markusen, 1985). The reason is that established industries in mature regions block innovations. As firms in emerging industries struggle to standardize their products, the resulting scale economies drive out rivals and create entry barriers. Firms in the dominant industry try to maintain a stable environment, since they have a vested interest in the existing firm structure, production processes and infrastructure. Where oligopolistic structure characterizes these industries, market power enables the remaining firms to prolong the stream of economic rents which originally flowed from the product and process innovations of their start-up phase.

The dominance of spatially clustered, mass-production, oligopolistic industries may prolong regional prosperity at the expense of adaptability, since local labor, finance, business services, politics, and culture are all structured to fulfill the demand of the dominant sector (Chinitz, 1960; Checkland, 1975). Oligopolies lose their dynamism in a somewhat sheltered business environment and undermine the diversification of the regional economic base. Firms in emerging industries, repelled by the business climate and business culture of mature industrial areas, are likely to set up shop in entirely new regions, unsullied by previous industrial traditions. When firms in the dominant industry eventually suffer a profit squeeze, the reversal of regional fortunes is likely to occur with little apparent warning and with few apparent options. This approach provided an explanation for the simultaneous decline of urban industrial areas in the rustbelt and the growth of new ones in the sunbelt.

A second response maintained that mature industrial areas are not without prospects for prosperity after all. Unlike the original product cycle theory, however, the emphasis was on innovation in networks of small firms in traditional industries (Piore and Sabel, 1984; Best, 1990). The reason is that intensified rivalry, technological change, and market segmentation drives firms to constantly innovate and to remain as flexible as possible to avoid being rigidly locked into a particular technology, process, or product. Uncertainties in the market and in new technologies can compel firms in established industries to constantly revert back to their earlier phase of innovation. The mass production of standardized products by large oligopolistic firms is replaced by the flexible production of specialized products by networks of small firms. Adjustment to the acceleration or even disintegration of product life cycles entails the reintegration of design and manufacturing both within firms and between firms and results in sectoral agglomeration. This line of thought is based on observations of new industrial districts in Italy and other European countries (Becattini, 1978; Brusco, 1982; Schmitz, 1992; Zeitlin, 1992), but vertical disintegration and customer-supplier linkages amounted to the functional equivalent of small firm networks in industries with significant entry barriers. Both cases suggest an alternative for mature industries could be found in the way regional governments and secondary associations supplied collective inputs that small firms are unable to provide on their own.

These theories of profit cycles and flexible specialization converged in a distinctive way among economic geographers by the end of the 1980s (Scott, 1988a; Storper and Walker; 1989; Storper and Scott, 1992; Storper, 1993). The "new industrial spaces" school shares the flexible specialization view that profit cycles were contingent upon the prevailing economic and technological conditions of an earlier industrial era (Storper, 1985). Drawing heavily upon regulation theory, they argue that the Fordist/Keynesian system of production and regulation has disintegrated and is being replaced by a new regime of flexible accumulation characterized by flexible production

ensembles. These theorists argue that fragmented demand undermines mass production, that changing technology allows firms to respond to uncertain demand, and new organizational forms of production and innovation decrease the importance of industry cycles.

However, despite the rejection of industry cycles, the new industrial spaces theorists share in common with the profit cycle theorists the view that mature regional economies offer an inhospitable environment to innovative industrial practices. New industrial spaces are not expected to emerge in the declining regions of the rustbelt, but are found instead in the high-tech regions of the sunbelt. The vertical integration, centralized control, and rigid labor/management relations exhibited by dominant firms in mature regions precludes effective responses to the increasing volatility of markets and changing technologies. Instead, most innovative industries choose areas without any significant prior industrial development (Scott, 1988a). These new regions were "marginal areas which had been greatly overshadowed by the main centers of industrial production" in the 1950s and 1960 - regions with malleable resources and social relations. This allowed the formation of regional network-based industrial systems that promote collective learning and flexible adjustment among small enterprises with complementary specialties required for industrial innovation.

Variation in Industrial Restructuring and Regional Development

Studies of industrial restructuring and regional development in the new global economy suggest a variety of possible outcomes. One possibility is that international differences in the organization of capital and labor markets mean that advanced industry practices may emerge in mature sectors in Japan and Europe but only in emerging sectors in the United States. This possibility is intimated by an intriguing international comparison of prosperous regions with alternative paths to the same destination (Sabel et al., 1987). Although Baden-Wurttemberg and Massachusetts both hosted leading clusters

of textile machinery in the postwar era, the sector fared very differently in the two regions. German firms, specializing in the continuous development of better products to meet unique customer needs, continued to prosper in the new world economy. Machine-builders in Massachusetts, however, were ultimately decimated by the quality-competitiveness of their international rivals.

There is even variation in industrial organization within the high tech industry in the US. One intriguing study supporting the new industrial spaces hypothesis is an interregional comparison of similar industry complexes with sharply divergent outcomes. The contrasting fates of Route 128 and Silicon Valley present a unique opportunity for analysis, since their industries were similar, they both enjoyed the largesse of defense expenditures, and both were widely regarded as models of the high-tech future throughout much of the 1980s (Saxenian, 1994). While firms in Silicon Valley thrived, firms in the Route 128 corridor lost their market share and their innovative edge. Saxenian argues that the difference in outcomes is attributable to the cultural and institutional legacy of the mature surroundings of Route 128. In contrast, Silicon Valley suggests a much closer approximation of a high-tech industrial district built upon collaborative business and professional relationships. The industry in the region is marked by continuous innovation which depends upon the construction of new institutional arrangements for the production of collective inputs to avoid the descent into ruinous competition and destructive conflict.

Scott also provides empirical evidence that points to the development of new industrial spaces in the US. He analyzes the growth of the semiconductors industry in Silicon Valley, the aerospace industry and electronic system houses in Southern California as American high tech examples of the new industrial spaces phenomena (Scott and Angel, 1987; Scott; 1988b; Scott and Mattingly, 1989; Scott, 1992). In these cases, he and his co-authors argue that the vertically disintegrated structure of these industries, strong agglomeration

economies, and the need for flexibility in production led firms to locate where labor markets and local arrangements were fluid.

Other studies have bolstered the view that new industries locate in new regions or at least in the "new" periphery of smaller cities. Industries such as biotechnology (Willoughby, 1993a; 1993b), the film industry (Storper, 1994), and software (Schweikhardt, 1993) have been put forward as industries that have created their own flexible accumulation ensembles.

However, this interpretation has been challenged by others who see greater variation in industrial restructuring and regional development in the new global economy than the new industrial spaces literature allows. Research on technology districts in the United States, which are defined in terms of specialization in successful export-oriented industries, indicates these are located in both mature and emergent regions (Storper, 1992). Comparative research on the organization of production in high growth regions demonstrates considerable variation in business, labor, and government relations with a variety of types found in the United States and internationally (Markusen, 1996; DiGiovanna, 1996). At the same time, there is growing evidence that certain durable goods plants and foreign transplants are altering their internal operations and external relations in order to implement advanced production systems in the American and Canadian industrial heartland (Schoenberger, 1997; Florida, 1996; Gertler, 1995; Parker and Rogers, 1995).

Furthermore, it is clear that unionized labor, representing as it does Fordist labor/management relations, *can* work effectively in advanced production systems. High profile plants such as NUMMI, the GM-Toyota joint venture in California, and Saturn, GM's experiment in rural Tennessee, suggest that mass production firms, working with a unionized workforce, can successfully institute an advanced production system - while operating in new industrial spaces (Brown and Reich, 1989; Bluestone and Bluestone, 1992).

This variation suggests that some regional economies have more malleable identities than others. The creation, dissolution, and re-creation of regional identity is a fluid process, rather than a permanent appellation (Allen et al., 1998). For example, a city such as Seattle, that was once viewed as a strong union town, a center of Fordist aerospace production and shipbuilding, within a decade became regarded as a high-tech "hothouse," home to a myriad of software and biotech firms, and attracts firms wanting to share in this image of success, even though Fordist aerospace remains the region's largest employer (Gray et al., 1996). In fact, a region can be, and usually is, simultaneously new and mature, since factions of regional resources are easily reconfigured for new needs, while others may be more rigid or ossified.

The Pharmaceutical Industry

An emerging industry based on a technological breakthrough that challenges an older industry concentrated in a mature region presents an ideal research opportunity. Such an opportunity is found in the pharmaceutical industry where there are now traditional and emerging sectors that are spatially concentrated in more than one locale. The traditional industry has a strong presence in New Jersey/New York region and the Upper Midwest (Figure 1) and firms in the industry tend to locate in close proximity to each other (Fineberg et al., 1993; Howells, 1992; Feldman and Schreuder, 1995). Much of the traditional industry remains highly concentrated along the New York-New Jersey-Philadelphia corridor. Most of the world's leading traditional pharmaceutical firms have either their world headquarters or their US headquarters (in the case of foreign-based multinationals) in the region (Table 1). These firms generally locate their principal research laboratories and product launching plants in the country either on-site or nearby. As new products achieve commercial scale and production processes become routine, they are increasingly sourced out to branch plants in lower wage regions. Special tax incentives favored Puerto Rico as the location of choice in the 1970s

and 1980s, but the Carolinas or other southern states would have served almost as well.

The emergence of biotechnology in the 1970s posed a challenge to the core technology base of the traditional pharmaceutical industry in organic chemistry. A trial and error approach to drug discovery and development was effectively superseded by the biotechnology industry's genetically engineered, targeted approach. Therefore, for the first time in a generation, major start-ups entered the field due to the combination of the new technology found *outside* the pharmaceutical industry and new sources of industry funding from venture capital (Kenney, 1986; Powell and Brantley, 1992).

As in the microelectronics revolution, the new biotech firms were clustered around leading research universities in the Boston and San Francisco Bay areas. The data on publicly traded companies (Table 2) show more than half of all biotech employment is concentrated in California. By contrast, the concentration of employment in the New York-New Jersey-Philadelphia area is less than one-third of that of the traditional pharmaceutical industry. It is unclear whether or not this signals a change in the industry's typical location pattern. As with many other high-tech products, academics have suggested that successful innovation in biotechnology requires a renewed link between research and production (Pisano, 1997; Callan, 1996). Biotechnology research also requires a large ensemble of specialized scientists, and thus tends to cluster around research universities (Feldman, 1985; Kenney, 1986; Blakely and Nishikawa, 1992; Haug and Ness, 1993; Prevezer, 1997). If the research-production link is strong, production facilities are also likely to cluster in the same regions (Schoenberger, 1988; Dore, 1986), while commercialization functions are likely to remain tied to the innovating firms' headquarters.

The development of new product-based technologies has fueled considerable speculation about the future of the pharmaceutical industry.

Some observers predicted that the new biotech start-ups based in new regions would quickly surpass the old industry giants, much as the automobile superseded the horse and buggy. The original business model of first movers in the biopharmaceutical field demonstrated a propensity for becoming fully integrated organizations. Yet the traditional pharmaceutical sector continues to show remarkable strength and remains one of the most profitable industries in the US (Standard and Poor, 1997). Both sectors have undergone fundamental changes that have transformed their relationship with one another and resulted in a complex locational pattern for the industry as a whole.

The business environment of the pharmaceutical industry changed drastically over the last fifteen years as the first genetically engineered products hit the market. The transition to managed care in the health care sector sharply increased bargaining power on the demand side of the market, while federal legislation accelerated generic product introductions after patent expiration on the supply side. The resulting squeeze on profits and panic over the health care debate culminated in a sharp decline in stock prices from their peak in 1992. The simultaneous failure of high profile products in clinical trials virtually sealed the window for biopharmaceutical firms on Wall Street. As consolidation and restructuring finally gripped the industry, traditional pharmaceutical firms were looking to improve their product pipelines, while biotech companies were looking for external resources and expertise. The emerging pattern thus seems to be one of increasing interdependence where the biotech firms increasingly focus exclusively on R&D, while traditional industry giants supply bring the new products to market.

Methods and Data

This study tracks the geography of the entire industry, including the location of research and development, pilot production, production of active bulk ingredients, formulation and packaging, and domestic and foreign marketing. This allows us to investigate *who* performs different functions, *where* these functions are located, and *why* they are located there. The focus

is on the biotechnology therapeutic drugs that have already been approved by the Food and Drug Administration. Although there are over 500 biotech products in some stage of development, most of these will never make it to the market (Lee and Burrill, 1995). The location of downstream functions remains unknown until later stages of the development cycle when the probability of success begins to improve and plans can be made for full scale production and marketing. The sample of 32 products represents the entire universe of therapeutic products based on biotechnology that have been successfully commercialized.

Most studies of the drug-producing industry, and especially of the biotechnology subsector, focus exclusively on the location of headquarters and research (or on regional biotechnology clusters) and ignore the role played by downstream functions (Holmes and Dunning, 1994; Haug and Ness, 1993; Howells, 1990a; Howells, 1990b). However, the omission of downstream functions, such as manufacturing and marketing, ignores the fact that they can contribute *more* to a region's economic well-being than does R&D. Although less glamorous, downstream functions can provide growth in regional incomes, maintain a relatively good income distribution, foster strong trade unions, and contribute to a quality living environment.

Despite the image of research as the engine behind regional prosperity, in reality, production workers still constitute the largest occupation in the industry followed by those in marketing (Table 3). Production workers comprise almost 32% and marketing workers represent almost 30% of the industry. The industry is partially unionized (almost exclusively in the mature regions) and production workers are relatively well-paid (Gray and Parker, forthcoming).

The lack of academic attention to post-R&D functions perhaps reflects past industry concerns. Historically, production costs and manufacturing strategies have not been very important to pharmaceuticals or biotech firms (Feldman, 1985; Fineberg et al., 1993). The traditional focus of drug manufacturing was on providing

sufficient capacity and developing better sourcing strategies. However, an intriguing study of Eli Lilly suggests that this may now be changing. Rising manufacturing costs (they climbed from 10% of sales in 1980 to 20% in 1990) encouraged Eli Lilly to invest heavily in reengineering their production process. As part of this they moved from dedicated to flexible plants and, in so doing, they increased facility usage, reduced cycle time, improved yields, and lowered production costs (Hayes et al., 1996). The move towards advanced production systems seems to be a part of a broader restructuring within the industry (Gray and Parker, forthcoming). This restructuring is also apparent in the out-sourcing of commercialization functions, although little work has been done to explore the spatial effects of this change in the industry.

The list of approved products was obtained directly from the Food and Drug Administration and from the biotechnology sector's industry group, The Biotechnology Industry Organization (BIO). The secretive nature of the industry and the complex relationship between firms meant that following each drug through each function often required following the product as it moved between firms and between regions. There was a plethora of inter-firm alliances and agreements around these products. Thus, two interlocking phenomena appeared: 1) locational changes, not of the firm itself, but of product realization, and 2) organizational changes due to inter-firm agreements affecting firm structure and strategy.

The locational information came from published information and telephone interviews. One major published source was each firm's 1995 Security and Exchange Commission's 10-K reports, in which firms are legally required to disclose information that affects profitability. Annual reports sometimes also reported on location, although it was unusual to find product-specific information. Another important source was *Bioscan*, a directory published by an independent industrial reporting service. *Bioscan* tracks information on each firm's licensing agreements and joint ventures by product. Other industry sources provided scraps of locational information. Between these sources, we gathered roughly

three-quarters of the information. However, firms consider much of the location information "sensitive," especially in pilot production and high-end manufacturing, so we conducted short telephone interviews to obtain the unpublished information.

Organizational Restructuring

The realignment between the two sectors is reflected in the flood of agreements between firms and institutions that has characterized the industry in the last five years (Powell and Brantley, 1992). These agreements not only shape a firm's organization and strategies (its scale, scope, and geographical reach), but also determine which firm controls the decision over where to locate research, production, and commercialization functions. These deals vary tremendously in structure and scope, but most arrangements involve joint R&D, product/technology licensing, or marketing rights.

The two sectors come to the negotiating table with different needs and firm strategies. Pharmaceutical firms are often looking for new products to supplement their own pipelines, while the smaller biotechs are usually searching for research funds, the ability to quickly scale-up production, and global marketing capabilities. Both sectors also want to share risk and lower the cost of research. Both pharmaceutical and biotechnology firms have come to rely upon such agreements and the partners involved and the items negotiated vary enormously. Deals are struck among and between large pharmaceutical firms, small biotech start-ups, and public institutions.

Some clear patterns in these agreements emerge in our sample of firms with approved products (Table 4). One finding is the strong relationship between the innovative biotech and established pharmaceutical sectors. A majority of the pharmaceutical firms' agreements (69%) are negotiated with biotech firms rather than other pharmaceuticals. Likewise, the average biotechnology firm in our sample is more likely to be linked with pharmaceuticals (49%) than other biotechs, although the latter is not

uncommon (34% of agreements). Biotech firms are also twice as likely to have agreements with public institutions, such as universities and the National Institute of Health. These numbers lend credence to industry analysts' predictions that some biotechnology firms have decided to not become fully integrated drug-producing firms, but to concentrate solely on the R&D function (Lee and Burrill, 1995).

Highlighting the importance of agreements and the growing reliance between firms should not obscure the intense rivalry and competition between the firms or romanticize the relationship between the sectors. Despite some claims to the contrary (Willoughby, 1993b), the tangled connections between firms and their proclivity to cluster spatially show little resemblance to either new industrial districts or Japanese-style networks (Fineberg et al., 1993; Powell and Brantley, 1992). In fact, their relationship is marked by a high degree of litigousness. A full 7 of the 32 drugs in this study are currently enmeshed in legal proceedings, most often involving patent infringement.

Spatial Restructuring

The restructuring of the industry and the massive realignment of the two sectors reflected by the interfirm agreements has also changed the geography of the entire industry. The amount of outsourcing or vertical disintegration is always tempered in the drug-producing industry by concerns regarding proprietary product and process knowledge (Lee and Burrill, 1995). This has caused some firms to keep the entire process in-house, but more often than not, bringing a pharmaceutical drug to market is split among different establishments, different locations, and even different firms.

The data on the approved biotechnology drugs highlights the changing spatial patterns of both the research and manufacturing functions, as well as the commercialization functions (Table 4). As, expected, firms in the San Francisco Bay Area, the largest and most buoyant of the "new" regions for biotechnology, conducted research

on 16 of the 32 products. However, these firms only ran the pilot production for 10 of the products. Continuing the pattern of loss, firms in the region manufactured 8 of the products, marketed 4 products for the domestic market, and did not market any of the products for foreign markets. The same pattern is seen in the other "new spaces" of biotechnology: although firms in these regions conducted much of the R&D, they were much less likely to perform the post-R&D functions. Interestingly, firms in mature pharmaceutical regions, such as New York/New Jersey and Illinois/Indiana, conducted a relatively small amount of the R&D, and yet they controlled much of the pilot production, some of the manufacturing, and most of the marketing functions. Likewise, firms in high-cost regions of Europe controlled a significant amount of advanced manufacturing. As expected, high volume manufacturing for 15 of the 32 products occurred in the Puerto Rico or southern states in the US.

Another way to view the data is by explicit regional type (Table 5 and Chart 1). We have collapsed the regions hosting biotechnology into distinct, if stylized and simplified, regional types in order to allow us to differentiate between regional type and firm function. The first regional type is the mature drug-producing region, which is a region that historically hosted drug production before the advent of biotechnology. This category includes New Jersey, New York, Pennsylvania, Delaware, Illinois, and Indiana. Another category is the emerging drug-producing region, which is a region that has not hosted a previous round of drug-production, before hosting the biotechnology industry. This category includes San Francisco, San Diego, Los Angeles, Seattle, and Boston. A third regional type is the low-cost periphery region, which is typified by low wage rates and/or low rates of unionization. This category includes Puerto Rico, the Southern states of the US, and other scattered isolated rural locations. The final regional type is a high-cost European location, which epitomizes locations in the core manufacturing regions of Europe. These regions include cities in Switzerland, Belgium, and the Netherlands. These regions can be seen as a European variant of the

mature industrial region with a strong base in pharmaceuticals. The "high-cost" designation differentiates these regions from low-cost periphery European locations, such as Ireland, Spain, or Portugal.

Research is the primary focus of most biotech companies and remains an important function in the traditional sector as well. R&D budgets often range from 10% to 15% of sales in the pharmaceutical industry to 20% to 50% of sales in the biotech industry (Lee and Burrill, 1995). Our findings show that firms in new regions dominated the research on the innovative drugs, conducting research on 82% of the new drugs, while firms in mature regions conducted the remaining 18%. Interestingly, the R&D activity in mature regions came almost exclusively from *biotech* firms located in the older regions. In fact, only one of the approved products originated from an established *pharmaceutical* firm. Although firms in mature regions performed some of the R&D, it seems the main focus of innovative activity occurred in emerging regions.

However, conducting research does not translate into controlling all of the post-R&D functions. It is clear that despite losing much of the research, firms in mature regions still retain some of the manufacturing, usually the highest end (pilot and advanced manufacturing). Firms in mature regions conducted pilot manufacturing on 53% of the drugs, while firms in new regions retained 47% of the pilot manufacturing. Pilot manufacturing, where drugs are produced in relatively large batches for the first time, is particularly significant in biotechnology since the newer, biotechnology-based drugs are increasingly complex and difficult to produce and require a set of highly skilled scientific and production workers (Pisano, 1997; Lee and Burrill, 1995). In an excellent and unusual study that contrasts the production process of chemically-synthesized and biotechnology-based drugs, Gary Pisano (1997) argues that the science underlying biotechnology remains poorly understood, and therefore, profitable production is harder to attain. Scale-up issues often arise, since production in the laboratory and the

plant are very different. Thus, scaling up to commercial production is not yet a routine function for biotechnology-based drugs. This may help to explain why mature pharmaceutical regions, with their process engineering and skilled manufacturing workforce, have "captured" so much pilot production.

Production usually shifts from the pilot plant to the commercial plant just before FDA approval so that large volumes of the product are ready for the product launch. Commercial production consists of two parts: a high-value added stage in which intermediate active ingredients are produced and a lower value-added stage in which the drug is formulated and packaged in its final form. We refer to the two parts as advanced and high volume manufacturing, respectively. Firms in new regions kept 43% of the advanced manufacturing, and 34% of the high volume manufacturing. Firms in mature regions produced 26% of the active ingredients. Firms in Europe also conducted some of these processes, particularly the advanced manufacturing, producing drugs for both the European and American markets and exploiting existing manufacturing capacity in these nations. Overall, only 19% of the products have their active ingredients manufactured in low cost "periphery" locations in the US and Puerto Rico. In fact, almost three-quarters of the products' active ingredients are manufactured in the high-cost emerging or mature regions. This suggests that the link between engineering and manufacturing is still important, or is gaining in importance, for the higher end manufacturing functions. Its also suggests that the engineering expertise acquired through manufacturing traditional, chemically-based, drugs can be equally useful when producing biologically-based drugs.

The high volume, low value-added, manufacturing process conforms more closely to the expected pattern of dispersion. The reduced need for skilled labor gives this segment of the industry great mobility and permits a more decentralized pattern of location, away from high cost regions. We followed each drug's formulation/packaging location for

the domestic US market. More generally, the formulation and packaging plants tend to be geographically dispersed around the world to achieve local market presence and because the filling and packaging specifications have traditionally varied by country (Hayes et al., 1996). Despite more dispersion in packaging and formulation, both the emerging regions, such as the San Francisco Bay Area and Los Angeles, and mature regions, such as New Jersey-New York-Pennsylvania and Illinois-Indiana, have managed to retain some formulation and packaging plants (34% and 16% respectively).

Marketing prescription drugs, whether to doctors or to benefits managers, is an extremely labor-intensive function that employed almost 60,000 workers in 1995 (PhRMA, 1996). The marketing and sales component of the drug industry has grown steadily over the years until it is almost as large as manufacturing and larger than research and development. Marketing has both a large centralized component and an extensive local component. Although large corporate marketing departments are clustered, there are dispersed marketing operations in almost every country in which a firm sells its products. Although exact numbers are difficult to find (the industry is even more secretive about, and has been more severely criticized over, its marketing practices than its research), one study from the Massachusetts Institute of Technology estimates that in the early 1990s, the drug industry spent approximately $4.5 billion on marketing (Berndt, et al., 1994).

We tracked the main corporate marketing department (or marketing firm, if the product was outsourced) in charge of marketing each product. Table 5 shows that firms in mature regions marketed the great majority of products, for domestic and foreign markets (72% and 63% respectively). Emerging regions retained a good portion of domestic marketing (25%), but very little foreign marketing (only 9%). This suggests that the large marketing networks and distribution channels necessary to market nationally, no less internationally, are too expensive or difficult for the newer market entrants to replicate.

The minimum scale needed to set up a global network of distribution channels poses large entry barriers and this has encouraged many smaller firms to license marketing rights to larger firms.

Multi-Centered Industry

The implications of these new industry patterns is that mature and emerging regions play an important role. Firms in the emerging biotechnology regions have conducted a striking amount of research on the new products and created brand new centers of R&D excellence, far removed from the traditional centers. In addition, they have retained a large amount of manufacturing. However, many biotech firms have chosen not to become fully integrated firms, and have negotiated away manufacturing and marketing rights.

The traditional pharmaceutical regions clearly have lost some of their long-standing prominence in drug-oriented R&D in the last 15 years to new firm clusters on the West Coast. However, despite an assumption that firms will locate manufacturing close to R&D to ensure production problems are quickly resolved, manufacturing in the industry displays a variety of responses. Firms in mature industrial regions have managed to "capture" a substantial amount of manufacturing. Even firms in mature areas that had no successful biotech product research, such as the Illinois-Indiana region, still managed to host biotech manufacturing. This suggests that the pharmaceutical-engineering/biotechnology-manufacturing tie can substitute for the biotechnology-engineering/biotechnology-manufacturing tie. One reason for this may be that the new centers of drug discovery lack product development and manufacturing expertise which, in turn, may contribute to manufacturing's continued strength in the older pharmaceutical centers. This is especially likely with some of the newer biotech products with complex production processes that make scaling up production difficult. Ultimately, the older pharmaceutical regions are benefiting from their pre-existing agglomeration of expertise and skilled engineering and manufacturing labor.

It seems that scale economies and expertise in manufacturing have allowed the mature pharmaceutical regions to maintain their position in the new business environment. The barriers to new product approvals and the complexity of the new production processes reinforce the position of traditional firms. Some of them at least have begun to upgrade their historically neglected manufacturing functions and view manufacturing more strategically as a mechanism for reducing production costs and retaining competitive advantage. Anecdotal evidence suggests some companies in the traditional pharmaceutical regions are reinvesting in pilot and commercial production facilities in the region.

Domestic and foreign marketing is the other area of strength for the traditional pharmaceutical regions. The concentration of headquarter facilities and the depth of the specialized business services found in the mature regions, particularly the New Jersey/New York region, makes it likely these regions will retain the function. Proximity to New York City, the world center of advertising and marketing, may also anchor the marketing function in the Mid-Atlantic region.

Conclusion

Traditional product cycle theory of regional growth might have predicted the progression of the pharmaceutical industry based in the New York-New Jersey-Philadelphia corridor towards genetic engineering. But the emergence of biotechnology start-ups in California, Massachusetts, and elsewhere is apparently more consistent with predictions derived from the profit cycle and new spaces literatures. The technology base and available capital generated outside of the pharmaceutical industry led to the formation of new firms clustered around premier universities and government laboratories. It has become increasingly clear, however, that few of these new entrants will emerge as large integrated pharmaceutical companies to seriously challenge the position of industry leaders anytime soon.

The drug development experience, manufacturing capabilities, and marketing channels of more established companies are turning out to be major sources of competitive advantage in the new business environment. They are reorienting their own research and development efforts, consolidating and reorganizing production systems, and realigning their marketing channels. These manoeuvres strengthen their position to negotiate strategic alliances, joint ventures, mergers and acquisitions with biopharmaceutical firms specializing in basic research and development. Recent deals suggest a reorientation of competitive strategies among new entrants towards a variety of business models, including extensive partnerships, virtual enterprises, research consortia and the like.

The future of pharmaceutical firms in mature drug-producing regions still remains an open question at this point. Some of these companies in these regions are reinvesting in drug development and pilot production facilities in the region. Conversion to advanced work systems and human resource practices could minimize lead times and cycle times, boost yield rates, and reduce scrap, inventory and handling costs. Such advanced manufacturing capabilities may facilitate rapid product introductions and greater savings of revenues for further research and development. This would support the view that firms in mature industrial regions can adopt a strategy of flexible specialization as an alternative to relocation or decline. In terms of profit cycle theory, this would mean significant portions of older industries may experience a "dematuration process" in the face of shifting market signals and technological frontiers. In either case, this would entail a transformation of relationships between firms, between firms and employees, and the industry and surrounding institutions. Whether this is better interpreted as the end of industry cycles as we knew them or a natural extension of profit cycle theory is open to further discussion. But whatever the case may be, the experience of the bio-pharmaceutical industry recommends further attention to economies of scale across business functions, the sector-specific

conditions of competition and technology, and the potential for large firms to become innovative once again.

This study suggests that firms in emerging industries follow a complex location pattern that involves both new and mature industrial spaces. Innovative firms will use the "clean slate" offered by new industrial spaces for some functions. However, firms not only do not avoid, but positively seek out, mature regions for other functions, *because* of their pre-existing economic legacy.

TABLES, FIGURES AND CHARTS

Table 1 The Pharmaceutical Industry by State, 1993

	Employment (000)	Percent of National	Location Quotient
New Jersey	50.7	19%	6.30
New York	25.2	10%	1.39
Pennsylvania	21.4	8%	1.77
Illinois	18.2	7%	1.48
Total	262.1	100%	

Source: US Department of Labor, Bureau of Labor Statistics, Current Employment.

Table 2 The Biotechnology Industry by Selected Region, 1994

	Total Firms	Public Firms	Employment	% of National
San Francisco	207	50	13,900	23%
LA/Orange County	71	12	13,000	22%
Boston	177	44	8,700	15%
San Diego	98	24	4,100	7%
New Jersey/New York	149	33	4,500	8%
Philadelphia/Delaware	60	8	1,600	3%
Total	1,308	260	60,000	100%

Source: Lee and Burrill, 1995

Table 3 US Domestic Employment, by Function: PhRMA Member Firms 1990, 1995

Employment Function	1990	Percent of Total	1995	Percent of Total
Production & Quality Control	59,546	31.5%	64,078	31.7%
Medical R&D	43,952	23.3%	48,887	24.2%
Marketing	56,014	29.7%	59,889	29.6%
Administration	21,915	11.6%	24,254	12.0%
Distribution and Others	7,384	3.9%	5,285	2.6%
Total US Employment	188,811	100.0%	202,393	100.0%

Source: Pharmaceutical Research and Manufacturers of America, 1996.
N.B. PhRMA includes many of the larger biotechnology firms as well as the pharmaceutical firms.

Table 4 Research, Manufacturing and Commercialization Functions, by Region: Number of Approved Biotechnology Products, 1996

Region	Research in Region	Pilot Mfg in Region	Advanced Mfg in Region	High Vol Mfg in Region	Domestic Marketing	Foreign Marketing
San Francisco	16	10	8	8	4	0
Boston	4	2	2	2	2	2
New York/New Jersey	6	12	5	3	16	15
San Diego/LA	3	2	3	1	1	1
Seattle	3	1	1	0	1	0
Illinois/Indiana	0	5	3	2	7	5
Europe	0	0	4	1	1	0
South/Puerto Rico	0	0	6	15	0	9
Total	32	32	32	32	32	32

Source: Telephone Interviews, Security and Exchange Commission's 10-K reports

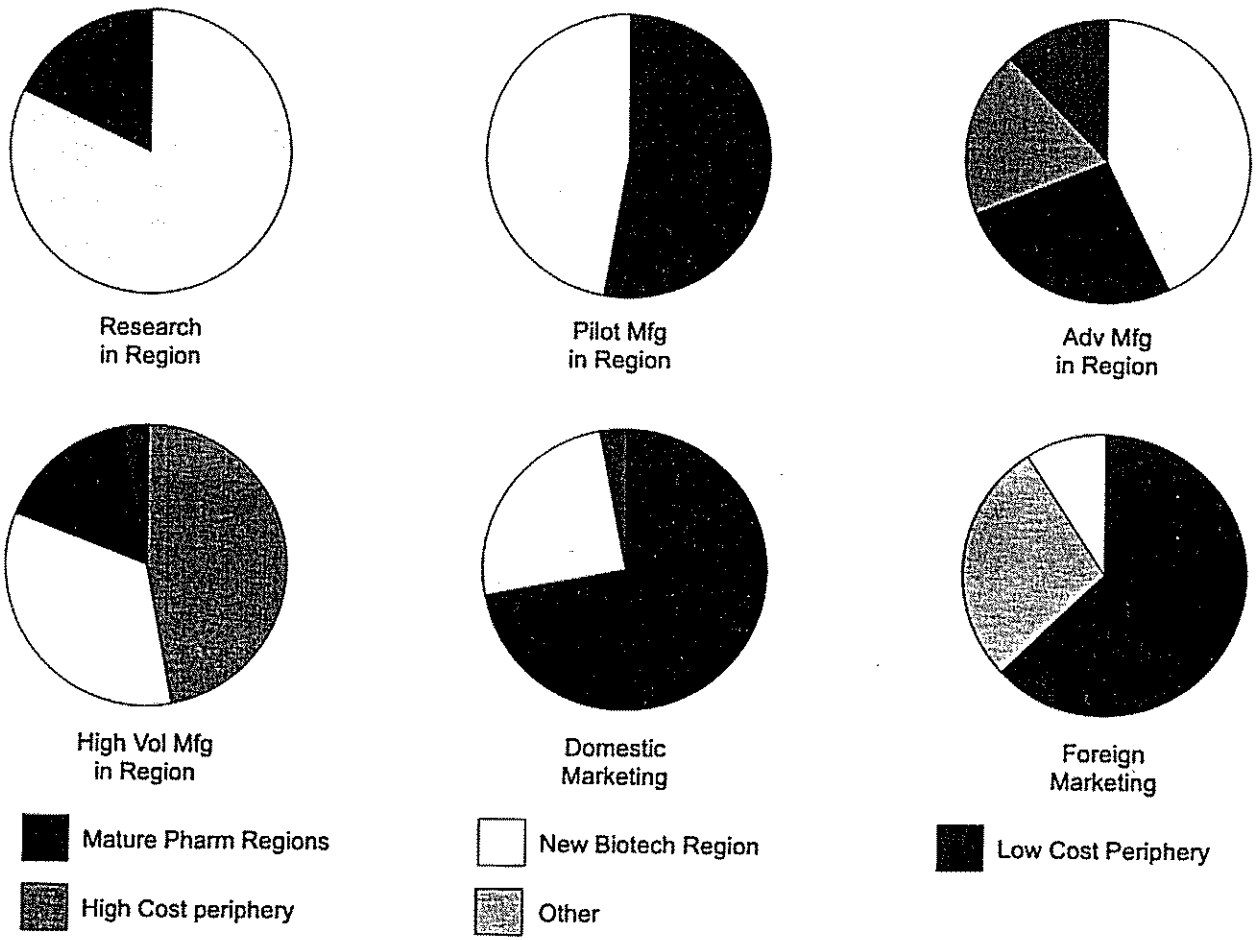
Table 5 Research, Manufacturing and Commercialization Functions, by Regional Type: Percent of Approved Biotechnology Products, 1996

	Research in Region	Pilot Mfg in Region	Advanced Mfg in Region	High Vol Mfg in Region	Domestic Marketing	Foreign Marketing
Mature Pharm Regior	18%	53%	26%	16%	72%	63%
New Biotech Region	82%	47%	43%	34%	25%	9%
Low Cost Periphery	0%	0%	19%	47%	0%	0%
High Cost Europe	0%	0%	12%	3%	3%	0%
Other	0%	0%	0%	0%	0%	28%
Total	100%	100%	100%	100%	100%	100%

Source: Telephone Interviews, Security and Exchange Commission's 10-K reprots

Figure 1: Employment Patterns of
Pharmaceutical (1993) and Biotechnology (1994) Industries

Chart 1: Location of Research, Manufacturing and Commercialization Functions



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