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Horizontal diversification in the Danish national system of innovation: the case of pharmaceuticals [1]

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Abstract

The importance of advanced users in home markets as an inducement to technological innovation is now well recognised, thereby providing an explanation for important parts of international export specialisation. At the theoretical level upstream–downstream interaction has been made the generic micro-foundation of theories of national systems of innovation. However, this paper will argue that user–producer interaction is not the only (country-specific) inducement mechanism to innovation. Rather, the finding of this paper is in line with the proposition that when firms are science-based, linkages tend to be horizontal rather than vertical. The paper mobilises historical and bibliometric methods to trace the long-term development of technology at the Danish pharmaceutical company Novo Nordisk, and its links with the local (particularly university) environment. The paper demonstrates the importance of science-based competencies in moving from natural resource based technologies to those of greater sophistication, thereby influencing trade specialisation of advanced countries.

Keywords: National Systems of Innovation; Inducement mechanisms; Core technologies; Pharmaceuticals

1. Introduction

An important aim of the theory of national systems of innovation (Lundvall, 1992) is the attempt to assist in explaining the direction of technological development at the national level, by means of a combination of economic structure and national institutional set-up. Given that technology is an important, maybe the most important, determinant of comparative advantage in trade in more advanced sectors (Soete, 1981), theories of national systems of innovation have an important role to play in a trade specialisation context. This point has been elaborated from an empirical point of view by Fagerberg (1992), Fagerberg (1995).

A common denominator for this literature has been the focus on demand conditions as inducement mechanisms (cf. Hirschman, 1961) for technological innovation, thus to a large degree determining the pattern of comparative advantage among nations. In doing so, the authors have been influenced by the insights of Schmookler (1966) in his analysis of the effect of shifts in demand, influencing the allocation of resources to inventive activities and from project SAPPHO (Rothwell et al., 1974), showing that firms' attention to user needs is an important criterion for success in industrial innovation. However, this paper is going to argue that, while demand-induced innovation has been of central importance in many sectors,

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there are sectors where this inducement mechanism is not so important. Rather, it will be shown that supply side factors play an important role in this regard. Specifically, the paper aims at demonstrating that the cumulative mastery of core technologies has been a much more important inducement mechanism to innovation in the 'Danish insulin cluster' (cf. Porter, 1990, p. 150).

1.1. Inducements to technological innovation

It can be said that technological accumulation along country-specific technological trajectories (cf. Dosi, 1982, pp. 227–228), in developed countries, has led to the acquisition of personal, organisational and institutional competencies, which have enabled countries to adopt and develop product and process technologies of increasing sophistication. According to Bell and Pavitt (1992) such processes have evolved along with, and is increasingly a determinant of, international competitiveness.

Accordingly, Bell and Pavitt identify three types of mechanisms, which have been particularly important in influencing such trajectories in their rate and direction: (i) factor endowments; (ii) inter-sectoral linkages and (iii) the cumulative mastery of core technologies. The first mechanism has to do with the innovative response to alleviate for scarce factor endowments. The second mechanism has to do with inter-sectoral linkages, sometimes starting off with the exploitation of abundant raw materials, then later creating a base for competitiveness in downstream sectors. In turn (national) upstream sectors are reinforced through vertical linkages, making the sectors co-evolve. The third mechanism has to do with trajectories which are traced through horizontal technological diversification, and rooted in the R&D base.

The third mechanism is the focus of this paper. It has to do with the inherent characteristics of technology, namely that technology is firm-specific, cumulative and thus path-dependent. Given these characteristics, related diversification is feasible, as long as it is consistent with the underlying technological path dependency or/and imperatives of the individual firm (Teece, 1988). In other words, firms are not likely to survey all technological knowledge, before making a technological choice, rather firms will conduct searches which enable them to apply and enhance their existing technology base (Dosi, 1988). In this context, and based on data concerning the 500 largest corporations in the US 1949–1969, Rumelt (1974) has shown that in 1969 about 74% of all firms were diversified into related markets or into technologically related areas, whereas only 19% were diversified into technologically unrelated areas or markets, leaving about 6% as single product firms. In addition, Rumelt showed that related diversity is

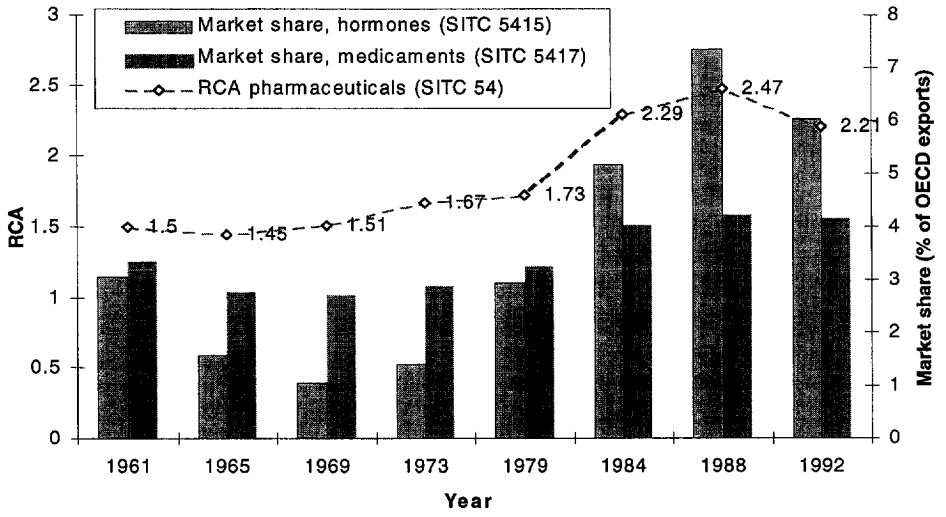

Fig. 1. Denmark's relative comparative advantage and market share of OECD exports to the world 1961–1992. Source: based on the IKE trade database.

associated with the financially best performance. Nevertheless, as stressed by Rumelt, one should be careful when determining the causation, since it makes no sense to diversify within the same product family if the firm is situated within a dying industry.

In the context of the latter type of inducement mechanism it is useful to distinguish between technological diversification and product diversification. As pointed out by Granstrand and Sjölander (1990) the product–technology relationship is not one-to-one, since the development, production and use of a product usually involve more than one technology and each technology can be applied in more than one product. Given the complexity of products, firms are therefore often 'multi-technology', i.e. are able to orchestrate several technologies.

Thus, given a certain amount of complexity, technology with multiple applications has in itself become a central inducement mechanism in technologically advanced countries. Therefore, such trajectories are traced through horizontal technological diversification, rooted in an R&D base, often connected to a university environment. Thus, this type of inducement mechanism might be relatively more important in science-based industries, as compared with production-intensive sectors.

Much attention has been paid to demand-led innovation in the Danish context, often focusing on production-intensive sectors, while less attention has been given to the localised rate and direction of innovation in science-based sectors (e.g. Andersen et al., 1981). Fig. 1 shows that Denmark has increasingly become specialised in pharmaceuticals, as measured by the revealed comparative advantage (RCA) index, [2] over the more than 30-year period from 1961 to 1992. If compared to other OECD countries, only Ireland (3.13) and Switzerland (5.01) display higher degrees of export specialisation in this area in 1992. Hence, it seems that a pharmaceutical trajectory can be identified in Denmark. If one takes a closer look at Denmark's export of pharmaceuticals, using OECD export data, classified according to standard international trade classification (SITC) revision 3, it can be shown that insulin export made up no less than 43% of Denmark's exports of commodity group 54 in 1992, thus being by far the single most important commodity in the commodity group labelled pharmaceuticals. Unfortunately, trade data according to the detailed five-digit SITC revision 3 is only available in the IKE trade database for the year 1992. However, insulin is included in two four-digit groups classified according to SITC revision 1. The development in terms of Danish market share of these two groups is displayed in Fig. 1. It can be seen that Denmark has a significant, and generally increasing, share of the OECD exports at the four-digit SITC levels (rev. 1) where insulin is contained. [3] The Danish stronghold in insulin export is underlined by the fact that Denmark's export market share, as a percentage of OECD exports to the world, in this group is about 72%. Nevertheless, this statistic also shows one of the limitations of using export specialisation, as a measure of comparative advantage, since it does not take into account commodities sold at the domestic market. According to observers, Eli Lilly of the US are nearly as large on the world market for insulin, when compared to the only Danish producer Novo Nordisk. However, the trade statistics only show a US market share of 12% of the world *export* market.

Given the importance of the insulin trajectory in Denmark, this paper will examine this trajectory from a historical perspective. Nonetheless, since there is only one single company developing and producing insulin today, Novo Nordisk, the focus will be upon this company. I shall therefore, in Section 2, begin with a chronological exposition of how tech-

[2] The RCA index is given as the share of a given commodity of the total export of a country, divided by the share of a commodity of the total export of the OECD countries to the world. Thus, if the index takes a value above one, a country is relatively advantaged in that commodity group; and if the index is below one, a country is comparatively disadvantaged in that commodity group. The RCA index can be described as:

$$\mathrm{RCA}_{ij} = \frac{X_{ij} / \sum_i X_{ij}}{\sum_j X_{ij} / \sum_i \sum_j X_{ij}}$$

where X_{ij} is OECD export to the world of commodity i, exported by country j.

[3] In 1992, the only year where insulin can be detected exactly in the database, insulin made up 49% of the Danish export of commodity group 'medicaments' (SITC 5415, rev. 1), while insulin made up 99% of the export of the group 'hormones' (SITC 5417, rev. 1).

nology was acquired by Novo. Section 2.1, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8 focus on specific product trajectories; on how they were created and influenced in their direction. It should emphasised that in conducting the case study, the focus will not be on why Novo has been particularly successful, compared with other firms (which would imply a focus on the innovation management aspect), rather the emphasis is on why Denmark is so successful in pharmaceuticals.

In order to identify particularly important inducement mechanisms, it is useful to start by identifying the possible sources of innovation among business firms. Therefore, it can be useful to discuss briefly what innovation theory has to say about the sources of innovation. One starting point can be von Hippel's (von Hippel, 1988) functional distinction, between the contribution of manufactures, suppliers and users, to the process of innovation. The functional distinction fits in with Pavitt (1984), who identifies differences in the importance of different sources of innovation according to which broad sector the individual firm belong. Four types of firms were identified accordingly; among these *science-based firms*. Science-based firms are found in the chemical and electronic sectors.

Given that Novo is a science-based firm, the literature on technological innovation suggests that one should look at sources of innovation among (i) *the manufacturer* (in this case Novo; its production engineering department and its R&D department), including technological links to former products or processes, (ii) *suppliers*, (iii) *users* and (iv) *universities*. In addition, a source of technology can be (v) *cooperation between rivals* (see von Hippel, 1988, Chapter 6), based on complementary assets. Furthermore, as suggested by Rosenberg (1976), when looking directly for inducement mechanisms, one has to look for (vi) *the importance of different resource constraints* to the process of innovation, in addition to abundance of particular inputs. Using the aforementioned entities as the units of analysis, the general focus will be on how the company acquired its technologies, enabling the company to produce new products, or improve old ones. Section 2.9 will focus on providing quantitative evidence (using patent data) for the 'technological relatedness' of products at Novo Nordisk. The relative importance of the sources of innovation, identified above, can then provide a framework for discussing the relative importance of inducement mechanisms, and their change over time. Section 3 will move back to the national level in focusing on the importance of a national science base for the pharmaceutical industry. A final section contains concluding remarks, based on a 'match' between the conceptual framework, presented above, and the case study which is to follow.

2. From calf's pancreases to biotechnology [4]

Novo Nordisk is today by far the largest Danish pharmaceutical company. This is illustrated by the fact that Novo's worldwide turnover in pharmaceuticals was as big as 78% of total Danish production [5] (1992). Similarly, Novo Nordisk's worldwide turnover in other chemicals was 16% of total Danish production. [6] Novo Nordisk's worldwide turnover in all chemicals was 36% of total Danish production in chemicals in 1992. Hence, Novo Nordisk is completely dominating in the Danish pharmaceutical sector, and prominent in the Danish chemical sector. The company had by the end of 1992, 10733 employees and has two main product areas: insulin and industrial enzymes. Insulin made up around 50% of total company turnover in 1992. The percentage for industrial enzymes was 29%. Novo Nordisk is the world's largest producer in both areas. Other important products are human growth hormones, haemophiliac medicine, hormones for the treatment of women, central nervous system drugs, semi-manufactured penicillin and plant protection. In 1992, 96% of total sales were sold outside Denmark. The company's R&D is located in four different countries and its production in six different countries.

[4] The case study draws on Richter-Friis (1991), as it provides very detailed descriptions on how the technologies were appropriated and developed at the company. Furthermore, the book seems reliable, since it is consistent with other sources, such as annual reports and newspaper articles.

[5] Defined as SITC (rev. 3) three-digit numbers 541 and 542.

[6] SITC commodity group 5** (three-digit), excluding pharmaceuticals (541 and 542).

2.1. The start-up of insulin production in Denmark

In 1921, the two Canadians *Frederick G. Banting* and *Charles H. Best* managed to isolate insulin, a hormone situated in the pancreas, which was known to determine sugar metabolism. This discovery made it possible to treat diabetes.

In the spring of 1922, a Danish biologist, August Krogh gave a series of lectures, at Yale University in the United States. August Krogh had, in 1920, been awarded the Nobel prize for his work on the intake of oxygen in animal muscles. Krogh knew that insulin had been successfully used in the treatment of diabetes in both the USA and Canada. In order to set up possible Danish production, Krogh went on to Canada, when his lectures were finished at Yale. In Canada, Krogh visited professor *J.J.R. Macleod*, the head of the institute in Toronto where the first extraction of insulin from animal pancreases took place.

This personal contact was a very important reason why insulin production was set up in Denmark. Another important factor was the abundant (at least in the beginning) availability of raw material in Denmark in the form of calf, ox and pig pancreases. These were all by-products from animal production in the predominantly agricultural country Denmark. Already, in 1923 the first Danish production of insulin was set up. In this way, Nordisk Insulin Laboratorium became the first Danish company producing insulin.

Nordisk Insulin Laboratorium was not, however, to become the leading insulin manufacturing company in Denmark. This role was to be played by *Novo*; a company set up in 1925 by the brothers *Harald* and *Thorvald Pedersen* – two brothers who had been working as an engineer and as a pharmacist at Nordisk Insulin Laboratorium from an early stage.

2.2. Diversifying into industrial enzymes

In early 1938, Novo had approximately 70 employees, the tasks within the company had become increasingly specialised and a more formal research laboratory was set up. Already in the 40s the laboratory came up with three major innovations: an improved insulin product, an improved production process and finally, based on knowledge accumulated in the laboratory about the raw material for manufacturing insulin (the pancreas), Novo diversified into industrial *enzymes*.

World War II broke out in September 1939, and Denmark was occupied April 9, 1940. This was of course to have a drastic impact on a company exporting 90% of its production. However, the main problem was not the lack of demand. Instead, the main problem was lack of pancreases, since the Danish stock of pigs was halved, mainly as a consequence of a lack of imported feedstuffs, due to the war. This problem was exacerbated by the fact that (industrial) chemical companies used the same scarce raw material input. The *trypsin* enzyme was also extracted from pancreases. These enzymes were used in the tanneries mainly for the purpose of softening leather.

According to conventional theory, insulin and enzymes could not be extracted from the *same* glands. Nonetheless, the scarcity induced Novo to research on this topic; perhaps the theory was wrong? In 1940, research aiming to solve this problem was initiated. A systematic investigation of what happened to the enzyme, when the insulin was extracted from the pancreas, was conducted. The researchers at Novo discovered that the enzymes were not destroyed in the process, rather they were precipitated. This meant that it would be theoretically possible to extract enzymes from the waste of insulin production.

Complex machinery, on an industrial scale, capable of extracting trypsin and another enzyme *chymotrypsin* from the 'waste' was accordingly developed by Novo. Initial problems were overcome, but more importantly, the experience with this first machinery could be used when a new trypsin plant was set up in 1943/44. The new production became an instant success on the marketplace; the demand, and hence production of insulin, determined the amount of enzymes produced.

2.3. Diversifying into fermentation and penicillin in 1950s

The Scottish bacteriologist *Alexander Fleming*, discovered penicillin in 1928, but he did not make any clinical products, and the discovery was more or less forgotten until shortly before World War II, when the two English scientists *Florey* and *Chain*

took an interest in Flemings' work, and developed clinical products. Florey took the discoveries to America in 1941, and production on a large scale was initiated.

At Novo, the Pedersen brothers and the head of research *Hallas-Møller* thought that fermentation (penicillin) production would fit into Novo's structure. Novo already had some experience in fermentation, manufacturing citric acid. This fermentation process had been possible due to the hiring of an Italian fermentation chemist, *B. Steinhardt*, in 1939. However, the citric acid was a commercial failure, and was given up when the war broke out. Nevertheless, without any knowledge of the technological advances that had been achieved in the States, the first experiments with penicillin fermentation were set up at Novo in 1943. The experiments did produce penicillin, but in too small amounts to form the basis of industrial production. After the war Hallas-Møller went to the States to visit leading public institutions heavily involved in the development and production of penicillin. During his stay, Hallas-Møller visited *Cornell University*, in New York, and became acquainted with crystalline penicillin. This product had the advantage of being non-perishable and could hence be stored for years, without loosing any effect, while the standard penicillin could be stored for only half a year only. Furthermore, the new drug did not need any (expensive) freeze-drying.

Hallas-Møller went to Copenhagen and set up a research team searching for a method of producing crystalline penicillin. Included in this team were Steinhardt who had fermentation production experience. Comprehensive fermentation experiments including trial and error tests were conducted. However, penicillin production is not only about fermentation, but also about purification. In this area the research team came up with new methods capable of making a very clean product. The intermediate product could now be manufactured (ammonium penicillin). But the final step crystallising the penicillin was extremely troublesome, and required months of trial and error. But in the summer of 1947 these problems were overcome.

The new penicillin trajectory was to become a very important part of the company, in the following years, both directly in terms of products, but also as a means of further diversification. In this latter context the fermentation capability became of utmost importance.

2.4. Microbiological enzymes

Novo's enzyme products were, until the early 50s, based on pancreas extracts only. However, as already noted the access to the raw material was the limiting factor. Furthermore, the demand for enzymes became more diverse. As a response to this situation, in the late 40s, Novo's fermentation expert Bruno Steinhardt suggested that enzymes could be produced by means of fermentation, utilising capabilities acquired in penicillin fermentation. By means of processing a culture of bacteria, he succeeded in making bacteria capable of producing the enzyme *amylase*. Subsequently, methods for concentration and purification were developed. These methods shared many similar characteristics with methods used in penicillin production. Consequently, experimental production was set up and the new product was put on the market in 1952. However, even though the product (with further improvements) became a relative success, its impact on total company turnover remained, for nearly a decade, very limited.

Nevertheless, markets for enzymes grew significantly when Novo, in 1960, managed to manufacture an enzyme (*alcalase*), which had an efficient impact in clothes washing. In 1965, the success was so evident that the multinational manufacturers could not leave this area unattended. Negotiations with multi-nationals such as Procter and Gamble, Unilever, Colgate-Palmolive and Henkel were initiated in 1965.

2.5. Other diversifications in the 1960s

Until the 1960s, Novo's products had been nearly only biology-based. But in the early 60s, Novo diversified into purely synthetic drugs. Products introduced in the early 60s included psycho-pharmaceuticals, sleeping medicine, gynaecological and contraceptive products. Even though diversification into these areas did not have as obvious links as in previous cases, a number of reasons for moving into synthetic drugs can be listed. First of all, the company had accumulated a general skill in biochemistry (from insulin and penicillin R&D and production).

In this context a closer inspection of Novo's patenting activity in the US shows that the 'synthetic'-based drugs (central nervous system drugs and hormones for women) involve one of the same patent classes (organic compounds series, class 532–570), as do the 'biology'-based drugs such as insulin, enzymes and blood products. Second, general skills in testing effects of drugs had been acquired from an early stage. These skills could also be utilised in the new areas.

2.6. Human insulin

Until 1982, all insulins manufactured had been bovine or porcine products. However, rapid scientific advances in the areas of molecular biology and peptide chemistry made it possible to make an insulin identical to the one produced by the human pancreas. The animal insulins are only slightly different from the human one, but these insulins are still alien proteins to the human body, so therapeutic advantages from such products could be expected.

Based on the advances in science, human insulin could (theoretically) be produced in two ways. It could be manufactured by means of fermentation, using genetic engineering, or by means of converting porcine insulin into human insulin, by means of (synthetic) biochemistry. Novo went both ways. But the first human insulin Novo put on the market was based on porcine insulin. It had been known since the 60s that both porcine and human insulin are made up of 51 amino acids. Only one of these acids differs between the two types of insulin. However small this difference might seem, it is an extremely complex biochemical process to get rid of the 'wrong' amino acid and replace it with the 'right' one, without damaging the complete molecule. It was well known that the enzyme trypsin could decompose the 'wrong' amino acid. So the problem was to fasten the 'right' amino acid to the molecule. In 1978, American researchers showed that enzymes could be used both in order to decompose and to link the amino acids. Progress was also made on this front in Japan.

As we have seen, knowledge concerning both enzymes and insulin had been accumulated at Novo. Based on this knowledge and the latest scientific advances abroad, researchers at the company managed to come up with a very elegant method, which could separate and link the amino acids in one single industrial process. The product was put on the market in 1982, and became the world's first human insulin. Clinical tests showed subsequently that the amount of antibodies produced were very low. In some instances allergic responses could be avoided as well.

In the US, Eli Lilly had high expectations of breaking into the European market, while defending its strong position in the US, based on its genetically engineered human insulin. Lilly's product was put on the market 3 months after Novo's. While Novo's human insulin was 'old fashioned', in terms of its biochemical production processes, the *products* were similar (Hall, 1988).

However, Novo did not ignore the progress within molecular genetics. The company had already gained experience in the field of biotechnology, since the mid-70s, due to the development of enzymes. Two benefits from producing enzymes can be identified in a biotechnological context. Firstly, enzymes are essential in rDNA techniques, since they are used to cut and splice genes. Hence, knowledge about the *artefact*, 'the enzyme', is very useful. Secondly, knowledge about how to *manufacture* enzymes is important, as fermentation technology is very important in this context, and fermentation is an essential part of biotechnological manufacturing.

Nevertheless, bacteria producing enzymes are found in nature (e.g. in soil) and can hence be changed incrementally, using biotechnological techniques, to produce enzymes with the desired characteristics. But there are no natural bacteria producing insulin; the bacteria have to be created (reprogrammed) synthetically. Hence, producing insulin by means of biotechnology is a more complex technology than producing enzymes using biotechnological techniques.

But even though Novo had biotechnological capabilities, it was not enough per se to make a genetically engineered insulin. External capabilities were bought in. In 1981, a contract was formed with *Biogen* in the US. Biogen is closely connected to Harvard University. Due to the very upstream nature (i.e. close to basic research) of the race to synthesise the human insulin, in which Genentech and Biogen took part (Hall, 1988), it was natural that Novo

wanted to acquire very upstream capabilities concerning the insulin gene. A more long-term relationship was developed with a smaller *dedicated biotechnology firm* (DBF), namely *ZymoGenetics* in Seattle. ZymoGenetics had, and still has, strong links with the University of Washington. A minority share was bought in this company in 1982. This company had know-how in the area of genetic engineering in yeast. In 1988 (when the collaboration had worked successfully), Novo bought the rest of the shares in the American company.

Based on a combination of these bought-in capabilities and in-house experience, Novo came up with new methods of making insulin by means of fermentation, in 1987. Experimentation targeted at optimising the yield of human insulin was conducted, and different yeast cells, producing different pre-stages to insulin, were made. Subsequently, new enzymatic methods of converting these pre-stages into human insulin were developed. In some cases this process of conversion could be conducted with methods very similar to the ones used when converting porcine insulin into human insulin.

2.7. A variety of enzymes

Whereas the 'enzyme boom' in the late 1960s had been based virtually on enzymes for detergents, the new expansion in the 1970s, in the area of industrial enzymes, was based on a broader variety of enzymes. Nevertheless, these areas were not technologically new to Novo, since a part of the development of these enzymes was conducted in the early 1960s. But the large-scale commercial exploitation of these products was not conducted before the mid-70s. Other areas where sales and product development have been expanded were enzymes for the textile industry, the brewing and alcohol industry, the paper industry, the dairy industry and the food and beverage industry, among others.

In the mid-1980s Novo had approximately 60% of the world market in enzymes. The success can partly be explained by the company's ability to tailor-make enzymes according to user needs. This responsiveness is indicated by the fact that Novo Nordisk's Bioindustrial Group, in 1992, had 40 basic fermentation products, but more than 500 different end-products. In contrast to innovations in insulin, innovations in enzymes have been induced, to a great extent, by means of interaction with the user. An example of such interaction is the recent co-development of the enzyme *Carezyme* with Procter and Gamble. In this case researchers from the two companies collaborated; Novo Nordisk's researchers primarily utilising the company's knowledge of the properties of enzymes, while Procter and Gamble's researchers could make contributions based on more general knowledge of detergents.

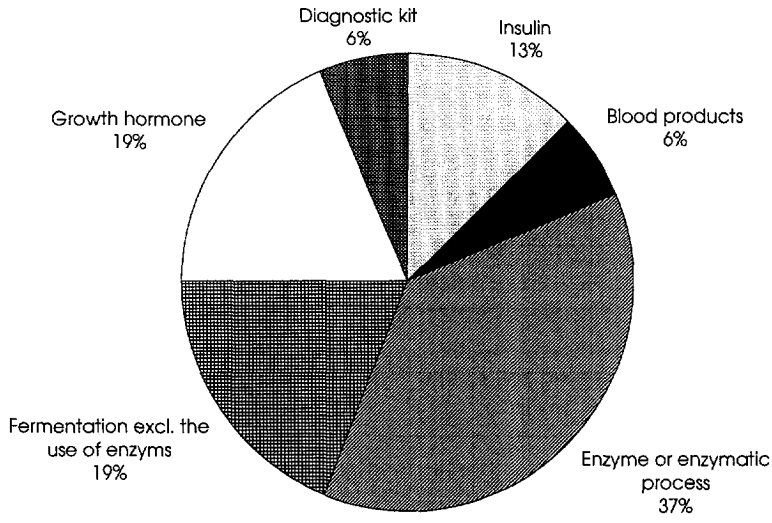

Fig. 2. Distribution of patents involving a biotechnological technique on product groups ($N = 16$). Source: based on data supplied to SPRU by the US Department of Commerce, Patent and Trademark Office.

2.8. The increasing importance of biotechnology

Novo Nordisk has strengthened research and sales in the areas of blood products and central nervous system drugs (*CNS*; psycho pharmaceuticals). Furthermore the company has diversified into growth hormones, diagnostic kits and biological pesticides. In the context of technology-based product diversification, biotechnology has become a very important basis for diversification at Novo, since biotechnological techniques are important to all the products mentioned above, except CNS.

Patent data show that biotechnological techniques are very important in the technological activity of Novo Nordisk A/S today, since 25% of all patents taken out by Novo in the period 1986–1990 have a biotechnological component. [7] Only 4.7% of the patents in the previous period (1980–1985) involved genetic engineering. The first 'biotechnological' patent was taken out in Denmark in 1981 (an enzyme). Fig. 2 shows in which 'old' product groups biotechnological activity was detected, and how much of total biotechnological patenting was done in the different areas. Thus, Fig. 2 demonstrates that biotechnology is a *generic process* technology, since it is present in many (and quite different) product areas. In this way the movement into biotechnology can be seen as technological diversification which provides a basis for product diversification (diagnostic kits, enzymes, growth hormones) or product/process improvements (insulin, enzymes, blood products).

2.9. Shared structural characteristics between products and processes

Table 1 is an attempt to classify Novo Nordisk's patents according to product groups. Given that the technology–product relationship is not one-to-one, it is not an easy task, since the US classification scheme relates to technological fields, rather than product fields. Nevertheless, the classification was attempted, drawing upon a knowledge of Novo's product portfolio and an interview with a Ph.D. student in molecular biology in addition to assistance from Novo Nordisk's own patent department. Table 1 shows a high degree of overlapping in terms of the same patent classes (as a proxy of structural characteristics) being present in different product/process groups. The two products that Novo Nordisk no longer does significant research on (penicillin and hormones for women) both belong to patent classes 532–570 ('organic compounds series'). However, these patent classes are present in six of today's products groups.

Such observed 'overlaps', in terms of several patent classes being present in a given product group, add to the understanding of why product diversification is possible when technology is cumulative and has a strong tacit dimension; some competencies (knowledge of structural characteristics of chemicals/materials) can be utilised in many different product groups. Hence, such cross-product capabilities provide a basis for product diversification.

Table 1 shows that technological diversification [8] does take place across product groups at Novo Nordisk A/S, since five out of six product groups (the six groups where data are available for both periods) display more patent classes involved (i.e. the product groups are more dispersed in terms of patent classes involved) in the period 1969–1979 than in the period 1980–1990. The table is inspired by similar calculations conducted by Granstrand et al. (1990).

Concerning Table 1, it should be noted that the indexes in two of these groups are very fragile, since they rely on only one observation in the first period (1969–1979). Another distinctive feature of Table 1 is that three of the 'new' product groups (growth hormone, diagnostic kits and pesticides) involve many technologies. Thus, the index is very low (< 0.40) in these areas. Since group 935 (genetic engineering) is a new one, it was excluded to test for sensitivity. However, even under these (for the hypothesis of technology diversification) unfavourable circumstances the *pattern* remains the same.

[7] Defined specifically as patent classes 435/70.1–75 and the complete patent class 935.

[8] The Herfindahls index expresses the concentration of certain technologies (measured as patent class) involved in a given product. Thus, an index value of one means that there is one technology (patent class) only involved in making the product.

Table 1
The depth and width of the technology base at Novo Nordisk, 1969–1990, measured by patent no. of classifications (no. of patents = 153, no. of patent classifications = 262)

Product group			Patent classes [a]									Technology diversification index [c]	
			424	426	435	436	514	530	532-570	935	Other (71/134/252) [b]	Unmod.	Mod. [d]
Insulin	(5.9%)	1969–1979			1		1		1			0.33	0.33
		1980–1990			4		3	2	1	1		0.26	0.30
Blood products		1969–1979	1		1			3				0.44	0.44
	(6.5%)	1980–1990	1		2		1	7	1	1		0.34	0.39
Other peptides/ polypeptides		1969-1979											
	(3.5%)	1980–1990	1				5	4				0.42	0.42
Enzyme or enzymatic process		1969-1979		2	16			1				0.72	0.72
	(34.3%)	1980–1990		12	38				1	5	9	0.40	0.46
Ferment. excl. the use of enzymes		1969–1979		1								1.00	1.00
	(6.5%)	1980–1990		7	8			1	1	2		0.33	0.40
Saccharides		1969-1979		1	5						1	0.55	0.55
	(6.5%)	1980–1990		1	6							0.76	0.76
CNS		1969–1979							1			1.00	1.00
	(13.6%)	1980–1990					20		22			0.50	0.50
Growth hormone		1969-1979											
	(4.1%)	1980–1990			5		4	3	1	3		0.23	0.30
Diagnostic kits		1969–1979											
	(1.8%)	1980–1990			3	3				1		0.39	0.39
Pesticides		1969–1979											
	(3.6%)	1980–1990	1		1		1				1	0.25	0.25
Antibiotics		1969–1979							19			1.00	1.00
	(3.0%)	1980–1990											
Hormones (for women)		1969–1979						12				1.00	1.00
	(5.3%)	1980–1990											
Number of patent-class references			4	24	90	3	35	22	28	13	12	262	2249

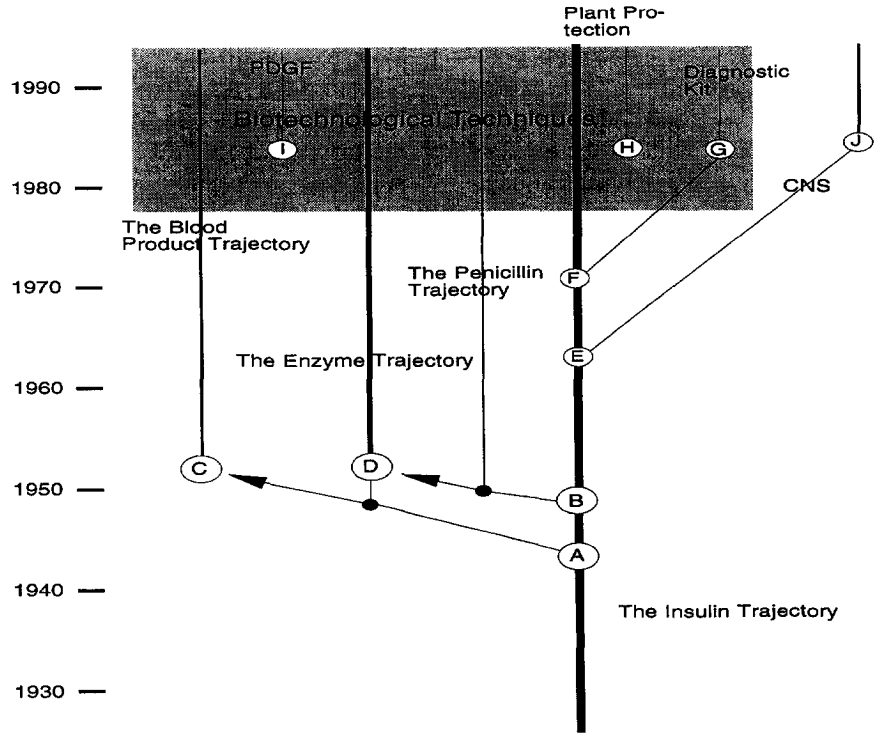

Fig. 3. Technological links between product trajectories at Novo 1925–1991.

2.10. Product and technological trajectories at Novo (Nordisk) 1925–1992

The case study has identified strong *internal* horizontal linkages between old and new products and core technologies, which were crucially important in the process of innovation. Fig. 3 summarises the product trajectories present at Novo Nordisk today, in which years they emerged and how these trajectories have been linked to one another. The first major product diversification (from insulin manufacturing) took place (A in Fig. 3) during and after the Second World War. The movement into the area of industrial enzymes was based on knowledge of the raw material (animal pancreases) used for manufacturing the two quite different products: insulin and enzymes. Knowledge concerning the pancreases had been accumulated while researching, developing and producing insulin, since 1925. Furthermore, knowledge concerning the extraction of insulin (mainly mechanical engineering) could be utilised in the new area.

The second main product diversification was the

Notes to Table 1:

[a] No. of patent classes is the number of *different* patent classifications at each individual patent times the total number of patents examined.

[b] The fact that 'other' includes more than one patent class does not affect the results, since they are only different across product groups (i.e. only one 'other' patent class is found in each product group).

[c] Technology diversification index = H, where H is Herfindahls index i.e. $H = \sum_{i=1}^{p}(n_i/N)^2$, and p is number of patent classes, n_i number of references in category i and N is total number of patent classifications.

[d] Modified by excluding patent class no. 935.

Source: calculations based on data supplied to Science Policy Research Unit (SPRU) by the US Department of Commerce, Patent and Trademark Office.

movement into penicillin (B) production. Even though the technology used for manufacturing penicillin (fermentation) was quite different from what the firm had been doing previously, the company could still build on its general skills in the areas of biology, biochemistry, testing and mechanical engineering. In addition to being a product diversification, it was also a technological diversification; future products could be based on the new capabilities acquired.

Further diversification into blood products (C) was based on the specific knowledge of the enzyme *trypsin*, an enzyme centrally important in extracting the blood product (*heparin*) from ox lungs. Heparin is capable of impeding blood coagulation, and is therefore useful in the treatment of patients with heart/vessel diseases. Also, Novo had more general capabilities in the purification and extraction from biological material (acquired in insulin and enzyme research and production).

As indicated above, the acquisition of fermentation skills was to become much more important for the company than the penicillin product itself. Based on the acquired fermentation capability in penicillin, Novo managed to diversify technologically into enzymes manufactured by means of fermentation (D) in the 1950s. The ability to make enzymes by means of fermentation made it possible to produce enzymes on a much larger scale; but also more diverse enzymes. Fermentation capabilities were also of utmost importance when Novo assimilated biotechnology (along with knowledge of enzymes) in the 1970s and 1980s.

Diversification into central nervous system drugs (E) was primarily based on a skill in the area of synthetic biochemistry, acquired through research and development in many different areas of pharmaceuticals. Nevertheless, the takeover of a Danish company (Ferrosan A/S) (J) has led to a significant enhancement of this technology within the company.

Furthermore, Novo Nordisk A/S has moved into new areas, such as growth hormones (PDGF) (I), plant protection (H) and diagnostic kits (G), primarily based on biotechnological competences. However, the diagnostic kit products also have backward horizontal linkages (F), based on in-house testing abilities. Besides the product diversification, innovation in existing products and processes has taken place; based on advances in science, the products have been improved. Most important have been improvements in the main business area, insulin. Most recently significant improvements have been made in the manufacture of a human insulin, first based on advances in peptide chemistry, later based on biotechnological techniques. In both these cases, knowledge accumulated in connection with another product trajectory (enzymes) was crucial in developing new products and methods in insulin. This is remarkable since enzymes originally spun off the insulin trajectory.

Nevertheless, one should be cautious in taking Fig. 3 as evidence of smooth technical change at Novo Nordisk, since the figure only involves the 'successes' in the sense of the product groups still being present at Novo. However, branches of Novo's 'product tree' have withered away as well. The descaling of activities in the area of penicillin and hormones for women has already been mentioned, but many more areas have 'been opened' and then later closed or sold off, when the company decided that resources were better spent elsewhere. Novo did, for instance, produce surgical threads based on sheep's intestines between 1938 and 1967 when the production was closed down. In 1990, Novo Nordisk sold its veterinary department off to a competitor. Very large research projects have also failed. One prominent 'failure' was the heavy investment in research on a drug containing an enzyme, in the early 1960s, which could theoretically dissolve thromboses. The expectations turned out to be too high, and the research did not produce any commercially useful products. The 'new' product groups at Novo Nordisk should be viewed in this light; because of fundamental technological uncertainty, new areas are opened up, of which some will 'survive' and grow, and others will be 'closed' again. New technology or product areas are invested in to increase option values (Mitchell and Hamilton, 1988). So even though R&D spending does not secure specific success in a product or technology area, high levels of R&D spending remain crucially important, since it increases option values in a complex and uncertain world. If technological capabilities are present, *some* of the projects will be successful.

In spite of substantial technological uncertainty, some of the product diversifications have brought

about technological diversifications (i.e. new core technologies have been created), which in turn have provided a basis for further product diversification in the future.

3. Back to the national level

So far, the case study has primarily dealt with technical change at the firm level. In this section the focus will shift to Denmark's specialisation in a science-based sector, and the quality and impact of the local science base will be analysed. Even though basic research has a strong public good element to it, this is not the full agenda. Recent research by Hicks et al. (1994) has showed that publications produced by Japanese companies (basic research) tend to over-cite the national science system by approximately 30%, which in turn suggests that the economic benefits are geographically and linguistically localised, since they are embodied in persons and institutions, and mainly transmitted through personal contacts. Similar findings have been made by Narin and Olivastro (1992) showing that national patents cite national science and vice-versa. A strong position in basic research at the national level is therefore economically important, because it provides research training, state-of-the-art development and use of research techniques and instrumentation, and access to high-quality international networks (Gibbons and Johnston, 1974; Pavitt, 1993). In addition basic research provides an important country-specific incentive to science-based firms, providing recent results from national as well as international state-of-the-art research as an input to commercial research.

The main source used in this analysis is Schubert et al. (1989), which provides a comprehensive dataset based on 2649 journals, in the period 1981–1985. The journal set was fixed in the sense that all journals were cited in all years. In all science fields Denmark ranked fifth in terms of mean citation per paper, which can be applied as an imperfect proxy for the quality of the general science base. Additionally, Denmark ranked third in terms of numbers of papers published as a percentage of world publications, adjusted for population size. It can be seen from Fig. 4 that Denmark publishes more papers in relation to population size (except from the field of chemistry) and has got a higher mean citation ratio than the 'rest EU' in all science fields. The number

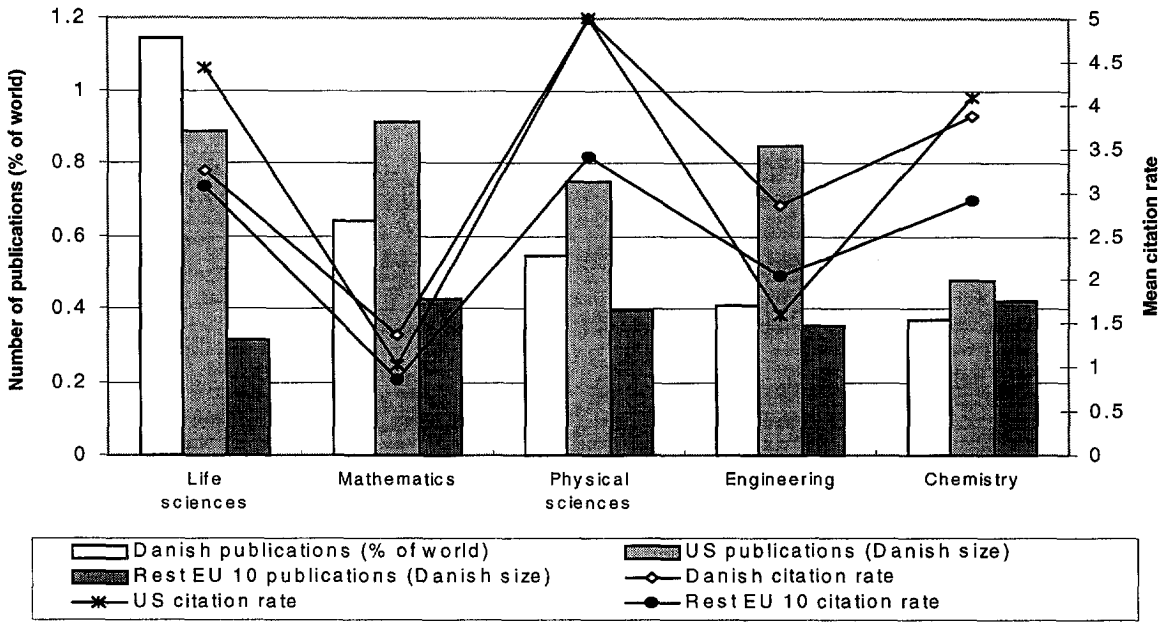

Fig. 4. Number of publications and citations per paper in major scientific fields, 1981–1985. Denmark versus rest EU 10 and the USA. Source: Schubert et al. (1989).

of Danish papers published in life sciences is significantly above the number of papers published by the rest EU.

Bibliometric data of this kind may be misleading, however. Martin (1994) argues that since these measures take into account all scientific output, they might be biased, due to many relatively small and trivial contributions. Furthermore, scientific progress might to some extent rely on major breakthroughs (Kuhnian 'scientific revolutions'). In this context Martin suggests that a possible measure of such breakthroughs can be the number of Nobel prizes a country has won. In the period 1957–1992, Danish scientists were awarded three Nobel prizes in the areas of Physics, Chemistry and Medicine or Physiology, which makes Denmark rank third in the world, when looking at Nobel prizes won per citizen. Even though these figures should be taken with a pinch of salt, given the small number of observations, the numbers do indicate that Danish science has the ability to produce some major breakthroughs. Another measure of contributions to scientific breakthroughs is papers among the 1000 most cited papers in the world. Based on data supplied by the Institute for Scientific Information (ISI), Nørretranders and Haaland (1990) have shown that Denmark ranks sixth in the world, when such a measure is applied and adjusted for population size.

The importance of a strong science base as an incentive to innovation in science-based sectors can also be examined in more quantitative terms. The relationship between the trade specialisation in pharmaceuticals and the quality of the science base can be examined by means of cross-country regression analysis. However, the RCA index has got the disadvantage of having a skew distribution with a long tail to the right. A skew distribution violates the assumption of normality of the error term in regression analysis, thus not producing reliable t-statistics. In addition, the use of the RCA in regression analysis gives much more weight to values above one, when compared with observations below one. Given these observations the RSCA ('revealed symmetric comparative advantage') transformation of the RCA index was preferred (see Table 2). Based on numbers of references on patents to scientific papers, Narin and Olivastro (1992) showed that the linkage between science and technology is by far the strongest in pharmaceuticals, when compared with other product groups. Table 2 supports these results in showing that there is a significant and positive relationship between national trade specialisation in pharmaceuticals and the quality of the national science base, measured as mean citation per academic paper. There is also a positive and significant relationship between the quality of national life sciences (which are supposed to be the sciences most closely linked to pharmaceuticals) and trade specialisation, however significant only at the 5% level. Nevertheless, Patel and Pavitt (1993) show that national citation rates are correlated with GDP per head. Therefore, one would suspect that specialisation in pharmaceuticals is a simple function of GDP per capita. Nevertheless, this is not the case, as displayed in Table 2. Overall, the regressions in Table 2 point to a high-quality science base as being a necessary condition for being specialised in pharmaceuticals.

Table 2
Relationships between country specialisation in pharmaceuticals and bibliometric variables

RSCA54 = −88.5 + 24.7ASF (26.7)* (8.8)*	$R^2 = 0.31$
	$n = 23$
RSCA54 = −80.6 + 23.5LS (25.6)* (9.1)**	$R^2 = 0.24$
	$n = 23$
RSCA54 = −42.5 + 0.0022RGDP92(46.1) (0.0034)	$R^2 = 0.02$
	$n = 23$

Standard error in brackets. *, ** denote significant at the 1% and at the 5% levels, respectively.
Variables: RSCA54 is the 'revealed symmetric comparative advantage' for pharmaceuticals, 1992, defined as (RCA − 1)/(RCA + 1). Source: IKE trade database. ASF is the citation rate for 'all science fields' and LS is the citation rate for 'life sciences', 1981–85. Source: Schubert et al. (1989). RGDP92 is the real GDP per capita 1992, expressed in international prices, with base 1985. Source: Penn World Tables mark. 5.6.

4. Conclusion and implications

As pointed out in Section 1, three types of localised inducement mechanisms seem to have been particularly important in determining the direction of technological trajectories at the national level strongly influencing the trade specialisation pattern of advanced countries. They were: (i) factor endowments; (ii) inter-sectoral linkages and (iii) the cumulative

mastery of core technologies. However, in order to identify the relative importance of these mechanisms, a number of sources of innovation were identified according to the literature on technological innovation. They were *suppliers*, *users*, *the manufacturer* and *universities*. I shall deal with these in turn.

This paper has stressed the crucial importance of technology and product diversification, based on mastery of in-house core technologies, as inducers of technological innovation at Novo Nordisk A/S. However, interaction with upstream capital good *suppliers* does take place. Novo Nordisk does not build its highly complex fermentation factories on its own. The highly advanced electronic control equipment is, for example, developed together with suppliers. Nevertheless, there is no 'semi-turnkey' fermentation factory available on the market; different parts are developed together with different suppliers, since it is Novo Nordisk which has the overall fermentation competence (the overall design of the plants is conducted by Novo Nordisk). In this context the company has a big engineering department, with the single function of setting up new production capacity worldwide. But this is somehow beside the point, since the opening question of this paper asked about important 'inducement mechanisms' to innovation. So even though suppliers play a part in the process of innovation, they cannot be said to have played an important part in *inducing* innovation at Novo Nordisk. This is so because the breakthroughs in product and process innovations have always been pioneered in the research laboratories and internal production engineering departments; suppliers have only been brought in at much later stages. These findings are in line with the results of Klevorick et al. (1995) who, based on attitudinal data, show that suppliers are not creating important technological opportunities in pharmaceuticals, whereas university research does.

When it comes to downstream *users*, they cannot be said to have played any significant part in inducing innovation in pharmaceuticals. In the area of biochemicals, the situation is different, since the enzymes are intermediate (capital) goods, which have a variety of uses across sectors. Hence, the enzymes are incrementally adapted according to specific user needs. The products are often developed jointly with the user. Nonetheless, it should be stressed that the major breakthroughs in the field of biochemicals did not have any users involved.

The central source of innovation has been a combination of *the manufacturer* and related university activities. In Section 2, the path-dependent nature of technological development was demonstrated, since technology-based diversification (based on competencies developed in the context of previous products) was shown to be present and very important in the movement into enzymes, penicillin, blood products and a number of new biotechnology-based products. In this context an interaction between the movement into new product areas and the adoption of new core technologies can be observed. In other words the (few) movements into new core technologies were often motivated by a wish to strengthen existing products, or by a wish to move into new product areas, which required an additional technology. The new technology could then be the basis for future product diversification. Such product diversification can take place because firms are often 'multi-technology'. Furthermore, external horizontal linkages to other firms or to science were strongest, while assimilating new core technologies.

As mentioned in Section 3, the economic benefits from basic research (conducted at universities) includes research training, state-of-the-art development and use of research techniques and instrumentation, and access to international professional networks. These economic benefits accrue, not only because of the research conducted by the scientists of a given country, but (mainly at least in a small country case) because of the ability to assimilate the results of basic research conducted by other countries, an ability which in turn partly depends on the home country's ability to perform high quality basic research itself. In the Novo case, major breakthroughs were nearly always conducted at foreign universities. In this context, the *research skills* developed at Danish universities have been of utmost importance in assimilating and commercialising inventions made abroad. Another potential impact of basic research was found in many cases, through the entire history of Novo, namely the *ready access to high-quality international scientific networks*, a story which began with Krogh himself, ending up with contacts to 'centres of excellence' in biotechnology situated in California. These more indirect impacts from na-

tional science to national technology might also assist in explaining why the correlation is stronger between the general quality of the science base (all science fields) and the degree of trade specialisation in pharmaceuticals, when compared with the more specific quality of the science bases (life sciences) and their correlation with specialisation in pharmaceuticals.

Based on the relative importance of the *manufacturer* and *universities* as the sources of innovation, compared with the importance of *users* and *suppliers*, it has to be concluded that the relatively most important inducement mechanism identified in the Novo case was the *cumulative mastery of core technologies* with multiple applications, together with related assimilation of new core technologies. In addition, the study has presented two instances where *factor endowments* constituted an inducement of innovation. The start-up of insulin production was based on the abundant availability of the raw material (animal pancreases). In addition, the initial acquisition of enzyme technology was spurred by a scarce supply of pancreases during the Second World War. However, as indicated above, the case study has also demonstrated that the importance of inducement mechanisms may change over time. Initially, factor endowments, in terms of availability of raw materials, were necessary for insulin production in Denmark, while today's more sophisticated production has lost its direct connection to the factor endowment.

But why does the importance of users and producers differ among industries? More specifically, why is user–producer interaction not so important in pharmaceuticals? One explanation is of course that technological opportunities emerge from science in the pharmaceutical industry, mainly. The research and development of e.g. capital goods can be viewed as a by-product of opportunities created by up-to-date science. In this context a distinction between directly providing technological opportunity and science which creates technological opportunity by adding to a pool of (not necessarily new) knowledge (Klevorick et al., 1995) is to be kept in mind. Whereas both the pharmaceutical industry and e.g. the industry for electronic components can be said to be science-based, since they are both heavily dependent on science in the latter sense, only *new* scientific advances are highly relevant for the pharmaceutical industry (ibid). In addition, technological leads in making capital goods for the production of pharmaceuticals were, at least in the Novo case, important for appropriating returns from innovation, thus not being in the interest of the company to out-source the production of crucial parts of capital equipment.

An innovation system can be defined in terms of a common knowledge base, and it is therefore more than just the sum of its parts. Previous studies (e.g. Andersen et al., 1981; Lundvall et al., 1984) of the Danish innovation system have shown that this knowledge base often consists of a national user–producer interaction. Nevertheless, this study has found that the most important knowledge base can in some cases reside inside large firms and in related university activities.

The story of Novo's initial acquisition of insulin technology is to some extent the story of the importance of small events in determining the direction of technological change (Arthur, 1989). However, as contrasted with Krugman (1987) this paper maintains that nations matter in a technological context, by showing that two country-specific factors were necessary conditions for the insulin production in Denmark, namely the availability of the raw material and the presence of high quality science. The explanation of trade-specialisation is richer than just chance and scale economies.

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