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The Drivers of Transnational Subsidiary Evolution: the Upgrading of Process R&D in the Irish Pharmaceutical Industry

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The drivers of transnational subsidiary evolution: the upgrading of process R&D in the Irish pharmaceutical industry.

Chris van Egeraat and Proinnsias Breathnach

Abstract

This paper contributes to the theory of subsidiary evolution in large corporations through an examination of the driving forces behind recent upgrading of process R&D activities in the Irish pharmaceutical industry. It is based on a survey of 80 pharmaceutical establishments in Ireland and a follow-up set of 52 semi-structured, face-to-face interviews with senior staff at 12 of the surveyed establishments carried out in 2006. We show that vigorous growth is occurring in the incidence of process R&D activity among manufacturing subsidiaries of transnational pharmaceutical firms located in Ireland. The paper supports the utility of a multi-level systems perspective on subsidiary evolution as proposed by Tavares (2001). The external environment, internal (corporate) environment and subsidiary drivers are seen to drive upgrading in a systemic way, whereby various drivers mutually interact, co-evolve and operate through each other. In further support of Tavares, the primary drivers for the subsidiaries' enhanced role lie in the (global) external environment, notably in the industrial competitive structure and technological change.

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1. Introduction

This paper contributes to the theory of subsidiary evolution in large corporations through an examination of the driving forces behind recent upgrading of process R&D activities in the Irish pharmaceutical industry. The paper begins with a review of recent literature relating to subsidiary evolution, paying particular attention to the multi-level systems framework for analysing the evolutionary process proposed by Tavares (2001). This is followed by an account of the evolution and current structure of the organisation of R&D within large pharmaceutical firms. This leads into a description of the traditional spatial configuration of process R&D functions in large corporations and an examination of the recent growth in process R&D activities in Irish pharmaceutical subsidiaries based on a comprehensive survey of these subsidiaries supplemented by detailed follow-up interviews with corporate personnel in the industry. The key drivers accounting for this growth are then identified and explored, utilising Tavares's analytical framework. Finally, some conclusions are drawn from the foregoing analysis.

2. Theorising subsidiary evolution in transnational companies (TNCs)

A considerable literature has developed in recent years concerning the extent to which subsidiary plants of large corporations have experienced upgrading in the range and sophistication of functions which they perform and the factors underpinning this upgrading (Young et al. (1994), Birkinshaw and Hood, 1998; Hood and Taggart, 1999; Tavares, 2001). Early models of TNC organisational structures saw technology and other capabilities (e.g. managerial competence) being developed centrally and then transferred to subsidiaries, initially as multidomestic miniature replicas (Pearce, 1992), some of which may have also been allocated the function of adapting the parent company technology to local market conditions. Subsequently, supranational regional integration and globalisation, accompanied by major advances in transport and communications, engendered a shift from a multidomestic structure to international/global production systems, wherein different specialised functions in the overall production chain are performed in different countries (Gereffi, 1995). This reorganisation involved some subsidiaries (usually small-scale operations in smaller markets) being closed down altogether with others being given specialised functions within these global production systems (Birkinshaw and Hood, 1998). Such specialised subsidiaries, not being focused any longer on particular national markets, generally lost their process/product adaptation functions, while continuing to be dependent on the parent firm for executive decision-making, basic R&D and marketing, although they may have attracted an R&D function focused on their specialised area of production (Pearce, 1999).

More recently, there has been some evidence of TNCs in certain sectors upgrading the functional capabilities of overseas subsidiaries. In this respect, much of the literature on subsidiary evolution has focused on how subsidiaries – especially those which have developed a high level of production, innovative or entrepreneurial capability - have been either earning or wresting autonomy, functional upgrading and product mandates from their parent companies (Birkinshaw and Hood 1998; Birkinshaw, Hood and Jonsson 1998; Pearce 1999). However, there is also considerable evidence of TNC head offices themselves taking a proactive role in upgrading or broadening the functional base of overseas subsidiaries. In some cases this reflects a desire on the part of TNCs to tap into local technology knowledge bases, which usually requires

local subsidiaries to themselves be significant centres of technological development and know-how (Cantwell and Mudambi, 1998; Cantwell and Piscitello 2005; Schmidt and Schurig, 2003; Zanfei, 2000). The movement towards less hierarchical and more flexible corporate network structures and new forms of inter-firm co-operation is also seen as providing impetus for the granting of greater autonomy (sometimes involving the awarding of regional or global product mandates) to overseas subsidiaries (Zanfei 2000).

While much of the subsidiary upgrading which has taken place has been concentrated on units located in major markets and centres of technological innovation, there is also evidence of a parallel trend to move significant product and especially process development functions to overseas manufacturing sites which are not located in such areas. To an extent, this is attributable to measures implemented by local and national economic development agencies with a view to attracting such functions. These may include specific measures to attract these functions, such as tax credits, grants and subsidies, or general measures to enhance local technological infrastructures such as investment in scientific research and technological training (Cantwell and Mudambi, 1998). However, it is likely that a more important factor in the relocation of product and (especially) process development functions to peripherally-located branch plants is corporate reorganisation in response to growing competitive pressures arising from globalisation, changing regulatory regimes and shortening product life cycles resulting from the accelerating pace of technological innovation (Dunning 1995). The nature and role of these pressures are discussed further with respect to the pharmaceutical industry in section 6.1 below.

The role of external pressures in influencing TNC subsidiary evolution is a central element in Tavares's (2001) analytical framework for analysing subsidiary evolution. Tavares proposes an elaborate multi-level systems perspective built around three sets of what she terms subsidiary evolution "drivers": firstly, those emanating from within subsidiaries themselves (e.g. desire on the part of subsidiary managements to enhance the functions which they perform); secondly, those deriving from the "internal" environment of the TNC of which the subsidiary is a component (e.g. supports for, and blockages to, subsidiary development emanating from the parent firm and "sister" subsidiaries); and, thirdly, those deriving from the "external" environment (Figure 1). Tavares's analytical framework is particularly useful in terms of her treatment of the external environment. Firstly, unlike earlier analyses (such as Birkinshaw and Hood, 1998) which have tended to equate the subsidiary's external environment with the host country in which it is located, Tavares sees the external environment as operating at four different spatial scales: the subnational (the micro-region), the national (the host country), the supranational (the macro-region), and the global. She highlights the role which institutions (e.g. inward investment agencies) can play in influencing subsidiary evolution at all levels in this spatial hierarchy. Tavares also usefully incorporates a non-territorial element (e.g. industrial competitive structure and technological change) into her conception of the external environment. Overall, according to Tavares, the external environment has impacted on the process of subsidiary evolution to a much greater extent than has been acknowledged in the existing literature.

A further key element in Tavares's analytical framework is its systemic approach which provides for two-way "dialectical" interactions between the various elements of

the subsidiary evolution system, leading to evolution over time in the nature of these interactions. Not only do subsidiaries interact directly with both the internal (parent firm) and external (territorial and industrial) environments, but the internal and external environments interact themselves in ways which can impinge indirectly on subsidiaries. This can give rise to very complex systems of interaction, the unpacking of which can be a daunting task.

This paper utilises Tavares's framework to analyse the extent of, and drivers underpinning, the incorporation of process R&D activities into the subsidiaries of transnational pharmaceutical firms operating in Ireland. However, before addressing the empirical case study, the paper next provides a description of the configuration of the R&D cycle in the pharmaceutical industry, with particular reference to the role of process R&D in this overall cycle, followed by a general account of early locational trends in R&D activities in transnational pharmaceutical firms.

[Insert figure 1 about here]

3. The R&D cycle of the pharmaceutical industry[i]

Pharmaceutical drugs can be derived through both chemical synthesis and biotechnological processes. While the development of the two types of drugs involves quite different activities, in both cases the same broad stages can be identified. This section focuses on the research and development (R&D) cycle of chemical-synthesis drugs.[ii] This cycle entails two largely parallel but quite distinct sets of activities i.e. "product" and "process" R&D (See Figure 2). Product R&D includes both the development of new "active ingredients" - also referred to as drug substances - and the development of related finished drug "formulations" (the actual tablet, capsule or injection through which the active ingredient is delivered to patients). The function of process R&D is to develop methods for bulk production of both active ingredients and drug formulations. In the pharmaceutical industry, product and process R&D are strongly integrated. However, in the following subsections the two cycles are described separately.

[Insert Figure 2 about here]

3.2.1 The pharmaceutical product R&D cycle

The product R&D cycle of a chemical-synthesis drug can be divided into four stages: initial drug discovery, pre-clinical development, clinical development and regulatory approval (Figure 2). The discovery stage is concerned with research into the causes of diseases and the identification of compounds ("active ingredients") that could be active in relation to the treatment of certain diseases. The discovery stage ends with the selection of one or a small number of drug "candidates" which offer prospects of effective disease treatment. These are then tested on animals in the pre-clinical development stage, with any candidate which emerges successfully from this stage entering the clinical development stage, during which the candidate drug is tested on humans. This stage generally involves three phases, during which the drug is tested on increasingly large groups of human subjects. Successful Phase II trials can lead to the drug candidate achieving what is termed "proof of concept" status which sanctions the commencement of the costly Phase III trials, where the drug is tested on thousands of patients. If successful, the drug then enters the regulatory approval stage of the R&D

cycle during which an application to sell the drug will be prepared and filed with the regulatory authorities.

The R&D of the finished drug formulation moves in tandem with that of the active ingredient and starts in the pre-clinical stage with pre-formulation studies. The responsible unit investigates the physical and chemical properties of a drug substance and prepares a number of model formulations for toxicity studies and early clinical trials. The findings of this stage guide the choice of inactive ingredients (excipients) which can be combined with the active ingredient in order to facilitate delivery to patients, the selection of possible formulation recipes and dosage forms, and the identification of a manufacturing process for the finished product. The formulation development group subsequently further refines a number of formulations. Companies generally aim to complete the development and testing of the formulation recipes and dosage forms in advance of the large-scale testing involved in Phase III clinical trials.

3.2.2 The pharmaceutical process R&D cycle

In parallel with drug *product* R&D, and strongly integrated with it, runs drug *process* R&D. The tasks of process R&D are to develop an effective process for the large scale manufacturing a new drug product and to supply material for the clinical trial stages of the product R&D cycle. As in the case of product R&D, process R&D involves two parallel cycles – one for the active ingredient and one for the drug formulation.

Process R&D for active ingredients involves three overlapping phases: process research, process development and transfer to commercial manufacturing. Process research usually starts immediately after candidate selection, and involves developing a deeper understanding of the chemistry of the candidate drug and exploring alternative methods of synthesis (synthetic routes). Promising routes are then progressively evaluated and scaled up via “paper experiments”, computer simulation, small-scale laboratory experiments and experiments in the ‘kilo lab’ (a larger laboratory scale). In the process development phase R&D activities move to the pilot plant where the process is further scaled up, with the research focus now on optimising flow rates and equipment design and developing process mechanics. Apart from developing a manufacturing process, a second important function of the pilot plant is to produce material for large-scale clinical trials.

Companies generally aim to ‘lock down’ the essential drug production process at the point where large-scale clinical trials begin in the product development cycle. From here on, process development focuses on the final details of the process. The process R&D cycle concludes with the transfer of drug production to commercial-scale plants which involves the documentation of standard operating procedures and the training of operating staff. Process development continues during the entire life cycle of a drug substance in the form of continuous improvement activities conducted by technical staff at the commercial plant. This typically involves small, incremental, changes that do not require refiling with the regulatory authorities. In addition, many companies will now start a new cycle of process R&D for the same compound, generally referred to as ‘second generation’. Such redevelopment activities, although requiring refilling, tend not to involve a fundamental route change.

Process R&D of the drug formulation also starts with pre-formulation studies which assess the "manufacturability" of the candidate drug formulation. Subsequently, a formulation process development group identifies a potential manufacturing process which is then identified, evaluated and scaled up, as with the process R&D cycle for the active ingredient. As in the active ingredient process R&D cycle, an important function of the drug formulation pilot plant is to produce material for large-scale clinical trials. The manufacturing process R&D cycle for the drug formulation then continues with the transfer to a commercial manufacturing plant, validation and regulatory filing and continuous improvement.

The various stages in the process R&D cycle require different numbers of researchers with different skill sets. Although all stages can involve skilled and highly educated staff, these are mainly concentrated in the early stages in the cycle.

4. The early spatial configuration of process R&D in the pharmaceuticals industry

The transnational pharmaceutical firms which emerged in the 1950s and 1960s were models of Fordist industrial organisation involving a very distinctive geography of both R&D and manufacturing production. The latter was generally located away from the headquarters regions and was frequently moved overseas, either to major markets (especially those protected by trade barriers) or to low-tax countries such as Ireland and Puerto Rico where profits could be concentrated via intra-corporate transfer price manipulation, a particularly important consideration for the highly-profitable pharmaceutical industry (Lall, 1979). By contrast, the R&D functions of transnational companies, particularly the more strategic activities, remained firmly located in their home countries, and usually in the same regions as the head offices and main production plants. Some decentralisation of R&D did occur, but such units were typically small and limited to short-run adaptations of mature products (Hayter, 1998)

Until the 1980s, the pharmaceuticals sector followed this locational model closely. Branch plants frequently housed small technical/development units, but the scope of their activities was limited (Howells, 1984). Even in the case of process R&D, typically, the manufacturing process was for the most part developed in the central R&D laboratories with the technology then being transferred to the manufacturing division and manufacturing sites. However, there are indications that this geographical configuration of process R&D is undergoing profound change, characterised by a decentralisation of process R&D functions to the manufacturing subsidiaries of transnational pharmaceutical companies. This tendency is examined further in the following section, which focuses on the development of process R&D in the Irish pharmaceutical industry.

5. Process R&D in the Irish pharmaceutical industry

This section of the paper examines the extent to which the purported trend towards decentralisation of process R&D activities in the global networks of transnational pharmaceutical companies is apparent among the branch plants of transnational

pharmaceutical firms located in Ireland. The section begins with a general overview of the pharmaceutical industry in Ireland.

5.1 The pharmaceutical industry in Ireland

Foreign investment in the Irish pharmaceuticals industry commenced in the 1960s following the adoption by the Irish government of an inward investment promotion policy (based on the availability of tax incentives, capital grants and a plentiful supply of cheap labour) in the late 1950s (van Egeraat and Breathnach, 2007). Inward investment in the industry accelerated in the 1970s, following Ireland's entry into the European Economic Community and the implementation by the Industrial Development Authority (IDA) of an aggressive marketing strategy which targeted the leading companies in emerging growth sectors, including pharmaceuticals (White, 2000a). This decade therefore saw a number of major investments, mainly by US firms, in the production of active ingredients and drug formulations.

Following a brief period of stagnation in the early 1980s, strong growth in the industry re-emerged in the second half of the decade and has continued more or less ever since, with employment rising from less than 5,000 in 1985 to 19,500 in 2003 (Van Egeraat and Breathnach, 2007). By far the strongest growth occurred in formulation, although the active ingredient sub-sector experienced strong growth as well, particularly in the second half of the 1990s.

Table 1 shows the configuration of the Irish pharmaceutical industry in 2003. The production of active ingredients and formulations, either separately or in combined plants, accounted for 93 per cent of employment in the industry. The same proportion of employment in the industry is accounted for by foreign firms which represent almost all active ingredient and formulation activity, while indigenous companies are mainly active in the formulation of human and veterinary pharmaceuticals and, to a lesser extent, diagnostics products. Foreign operations are, for the most part, relatively large-scale (mean plant employment 244) compared with the more modest scale of the indigenous sector (mean plant employment 67, with most below 50).

[Insert Table 1 here]

5.2 Process R&D activities in pharmaceutical firms in Ireland

5.2.1 Data sources

The analysis which follows of Ireland's changing role in corporate process R&D in the pharmaceutical industry, and of the drivers underpinning this changing role, is based on data collected from two sources: a mail survey of all 80 pharmaceutical establishments in Ireland engaged in the production of active ingredients and/or in drug formulation and a follow-up set of 53 semi-structured, face-to-face interviews with senior staff at 12 of the surveyed establishments. The questionnaire used in the mail survey worked with generic names for the various process R&D categories that suited plants in the active ingredient and drug formulation sub-sectors and the analysis in this section combines both sub-sectors.[iii] The mail survey generated a response rate of 95 per cent, covering 92 per cent of all employees in the target population, according to data supplied by Forfás (the Irish government's National Policy and

Advisory Board for Enterprise, Trade, Science, Technology and Innovation). The profile of the respondent firms accorded closely with the characteristics of the industry as shown in Table 1.

5.2.2 The scale and scope of process R&D in Ireland

The survey confirms the rapid recent expansion of process R&D activities in Ireland. In the six-year period between 2000-2006, the number of people involved in process R&D in the responding companies nearly doubled, from 408 to 800, compared with a 36 per cent growth rate in total employment in the companies in the same period. Three quarters of responding establishments expanded their process R&D staff in this period. At the end of 2006, all but one of the 76 respondent companies employed staff who were involved at least to some extent in process R&D. However, as much of the process R&D involvement was on a part-time basis, the total of 800 converted to 580 full-time equivalents based on information contained in the survey returns. The number of staff involved in process R&D varied considerably between establishments: 30 employed less than five, 32 between 5-14, eight between 15-29 and five thirty or more. As regards future intentions, 31 of the respondent companies had concrete plans to expand their process R&D activities in Ireland over the next five years. Of these, 27 provided an estimate of the additional process R&D staff requirements over this period, amounting to a total of 311 additional staff.

The interviews showed that the technology staff in the Irish operations were generally involved in process R&D as members of global project teams made up of staff from the R&D and manufacturing divisions of the parent firms drawn from different locations around the world. Such teams are normally set up at an early stage of the process R&D cycle to facilitate early involvement in the cycle of all the relevant functions, including manufacturing, and to streamline the transition between the various stages and locations.

To get an insight into the relative role of the Irish plants in the global networks of their parent firms, survey respondents were asked to rate the input of the local staff in various process R&D activities of the parent firm on a seven-point Likert scale (where a score of 1 indicated that the Irish plant had no input in the activity and a score of 7 indicated that the Irish plant had sole ownership of the activity in question). This question did not apply to the 14 respondent establishments which were single-site operations. In addition, not all of the categories of R&D activity included in the question applied to all respondent establishments. As a result, the individual activity categories in the question applied to different numbers of establishments ranging between 58-62.[iv] The findings of this question are presented in Table 2, with process R&D activities listed in the order in which they were presented in the survey. In Table 2, the columns represent the proportion of relevant establishments falling into each Likert scale score category while the “mean” column indicates the mean score obtained for all respondent establishments for the relevant R&D activity.

[Insert Table 2 here]

The results show that the great majority of Irish establishments (with a small number of exceptions) have little or no involvement in the early stages of the process R&D cycle (activities 1-4 in Table 2). Involvement rises somewhat for activities 5-6

(production for Phase II clinical trials and pilot plant evaluation & optimisation prior to Phase III clinical trials) but still remains generally low. The involvement of the Irish establishments only becomes substantial at phase III clinical trials but the mean score for the involvement in production (activity 7) is higher than for involvement in evaluation and optimisation (activity 8). This pattern suggests, and the interviews confirm, that in a substantial number of cases the main function of the staff involved in process development in Irish pilot plants is the manufacture of material to support clinical trials. A large part of the evaluation/optimisation is carried out by staff from the process R&D groups in the core global research locations, both at these core locations and/or at the site in Ireland. In many cases, staff from the Irish units, as members of the global project teams, have some involvement in evaluation/optimisation, even if not involved in the production of the evaluation batches. However, in most cases the involvement is very limited, particularly at the early stages.

There is a very significant upward shift in the level of Irish plant participation in the technology transfer phase of the process R&D cycle - optimisation in the commercial plant (activity 10) and the running of validation batches (activity 11). Technology transfer essentially involves taking a process from the pilot plant scale and replicating it with, preferably, minor changes at the commercial manufacturing plant. This activity is typically organised through commissioning teams that include staff from the transferring location and, on the receiving end, local staff with responsibility for new product introductions. Once the commercial manufacturing plant is up and running, continuous improvement activities (activity 12) tend to be carried out almost entirely by local staff. At this stage staff from the core research locations tend to have a very limited, more consultative, role.

Overall the data clearly show that the involvement of the Irish staff in process R&D only becomes substantial after the proof-of-concept point, at the start of phase III clinical trials. As pointed out in the outline of the process R&D cycles, this is the point at which companies generally want to have locked down the process parameters. From here on process R&D activities focus on the final details of the process and technology transfer.

The fact that the Irish establishments tend to concentrate their involvement in process R&D activities in the later stages of the cycle does not mean that they are involved in low-skilled or mundane activities. The education profile of staff involved in process R&D can be used as an indicator of the quality or sophistication of the activities carried out in the Irish subsidiaries. The survey shows that the process R&D activities in the Irish pharmaceutical industry employ a substantial number of highly skilled people, with 30 per cent of the 800 people involved holding a PhD degree as their highest level of academic attainment, with 19 per cent having a Masters degree, and a further 46 per cent a primary degree.

6. The drivers of process development upgrading in Irish pharmaceutical subsidiaries

This section of the paper seeks to identify the main drivers underlying the upgrading in process R&D activities which has occurred in the Irish subsidiaries of

pharmaceutical TNCs in recent years, as elicited from the survey data. It employs the analytical framework proposed by Tavares (2001) which distinguishes between drivers operating in the external environment, those operating in the internal environment (i.e. within the parent corporation) and those emanating from within the Irish subsidiaries themselves, while at the same time emphasising the fact that the different drivers act in a systemic way, involving processes of mutual interaction, reinforcement and co-evolution.

6.1 External and internal environment drivers

Tavares (2001) sees external drivers as operating at four spatial scales: the global/industrial, the (supranational) macro-regional, the national (host country) and the (subnational) micro-regional. The last of these is inapplicable in the Irish case because of Ireland's small size and the absence of the kind of Porterian local clustering which Tavares highlights in this context. As regards the others, the research suggests that it is drivers operating at the global/industrial scale which have been most influential in stimulating upgrading in Irish pharmaceutical subsidiaries. Two such drivers have been of particular importance: a growing cost/revenue squeeze arising from changes in the competitive and technological environments and significant changes in the tax treatment of costs and revenues relating to intellectual property on the part of the government of the USA, by far the main source of pharmaceuticals investment in Ireland. A third (host-country level) external driver - the efforts of the Irish government to promote up-grading - has been of secondary importance. Most external drivers have been operating through the internal environment (the parent firm) to influence subsidiary evolution, while in some instances the external environment has influenced by developments in the internal environment, clearly illustrating the systemic nature of the processes involved.

6.1.1 The changing competitive, regulatory and technological environment

Since the 1980s pharmaceutical companies have been increasingly confronted with important changes in their regulatory, competitive and technological environments. Across the world, regulatory authorities have imposed increasingly stringent requirements on the pharmaceutical sector, which means that it is taking companies longer to develop new products and gain regulatory approval. This has substantially increased the costs of developing new drugs and bringing them to market. The costs have also increased due to the greater complexity of new product and process technology, notably in the realm of biotechnology. At the same time, pharmaceutical companies have experienced a reduction in their rate of revenue growth. The emergence of new biotechnology firms have led to higher levels of competition and downward pressure on prices (Pisano, 1997). In addition, in an effort to curb expanding health expenditures, some important markets have introduced stringent price controls while buyer bargaining power has increased due, for example, to the rapid expansion of Managed Care Networks in the USA. (Agrawal, 1999). Finally, the more demanding regulatory procedures have also reduced significantly the effective period in which a product enjoys patent protection (Howells et al., 2005; Pisano, 1997).

Co-location of process R&D and manufacturing

These developments in their external environment have spurred pharmaceutical companies to review their corporate strategies and organisational configurations (i.e.

the internal environment in which subsidiaries operate, in Tavares's terminology). A key target of this review process has been the inefficiencies in the organisation of R&D and production which had developed in the industry in the 1950s and 1960s. The transnational pharmaceutical firms which emerged in this period were structured along classic Fordist lines, with R&D being typically organised as a linear process (Malecki, 1997; Hayter, 1998; Dicken, 2007). There existed a high degree of compartmentalisation of specialised R&D functions and of separation between R&D and manufacturing. Planned interaction between departments was one-way and largely confined to the moments of transfer of finished tasks. This organisation involved a lot of wastage, high costs and long development times (Hayter, 1998). In particular, because of the lack of participation of manufacturing staff in the R&D process and the poor provision for feedback from manufacturing to the R&D offices, problems and inefficiencies in the manufacturing process were frequently identified at a very late stage in the process R&D cycle. This tended to delay the launch of products and/or led to significant post-launch changes to the manufacturing process that involved time-consuming regulatory re-filing procedures

One consequence of the review by pharmaceutical companies of their strategies and organisational structures has been widespread restructuring of the way these firms configure their global process R&D operations. This reorganisation is designed to reduce not only the cost of developing and manufacturing new products but, more importantly, the time it takes to bring new products to the market, thereby increasing the effective patent protection period (Pisano, 1997). One of the key themes in the reorganisation of process R&D is "co-ordination integration", involving better integration between both the various stages of the process R&D cycle and the product discovery, process development and manufacturing functions. Ideally, the manufacturing plant becomes an integral part of the process development cycle at an early stage of projects.

This increase in the degree of co-ordination integration and the concomitant requirement for improved communication flows can explain, at least in part, the rise in the level of process development activities in Irish pharmaceutical manufacturing subsidiaries in recent years. Pisano (1997) suggests that co-ordination between process R&D and manufacturing is best facilitated through the co-location of these functions, which previously tended to be separated. Such co-location facilitates not only the transfer of technology to manufacturing plants but also the flow of feedback information from these plants to R&D departments.

Zanfei (2000) has identified a series of reasons why the co-location of product and process development with manufacturing enhances overall operational efficiencies. Communication between scientific, engineering and production personnel is effected more easily and rapidly where they are all located on the same site. This refers not only to spatial proximity, but to commonality of language and other cultural symbol systems, and shared background and tacit knowledge. Also, information flows between development and production personnel will receive top priority by recipients where both are co-located on the same site, whereas remote production sites seeking information from centralised R&D units have to take their place in the queue. Problems of national/local pride and managerial jealousies will also be minimised where information flows are localised rather than moving between spatially separated units of the same firm.

However, the idea of co-location of process R&D and manufacturing is complicated by the fact that transnational firms generally operate multiple manufacturing plants around the world. In such cases co-location can lead to fragmentation of the process R&D function, and the impairment of information flow within the overall corporate R&D organisation (Malecki, 1997). Location decisions regarding (individual) process development functions relative to other functions necessarily involve a trade-off between these conflicting considerations.

This trade-off is reflected in the organisation and spatial configuration of the process development activities of the pharmaceutical companies which were the focus of the empirical research for this paper. The interviews all confirmed a strong emphasis on co-ordination between the process development and manufacturing functions. Process development project teams involve members from various organisations, including discovery, process R&D and commercial manufacturing. The co-ordination involves a large amount of information exchange, including face-to-face exchange. In relation to the pilot plants, the interviewees generally confirmed that co-location with the commercial manufacturing plants in Ireland did facilitate information exchange, particularly when technology was being transferred to the latter plants. At the same time, invariably, the discovery and the early stage process R&D functions remain strongly centralised in the core global research locations. In fact, a large part of the actual process R&D work in the Irish pilot plants is carried out by staff from central process development groups. Strongly developed organisational links and advanced ICT infrastructure between the core process development locations and the staff at the pilot plants reduces the requirement for travel to an extent. As one pilot plant manager mentioned:

> We have learned that telecommunications are extremely effective. Once you establish a relationship face-to-face, you can maintain that very effectively. […] We don't even use the video anymore. Telephone is fine. We use the video system for data display. We find that to be hugely valuable. We can edit documents on line. (Manager AI pilot plant, 2006)

Still, centrally-located staff need to travel regularly to Ireland and often stay there for extended periods to carry out the process development and technology transfer work in conjunction with staff based at the local facilities. Hence, at least some of the gain in efficiency in face-to-face information exchange between the pilot plant and the commercial plant comes at the expense of a higher amount of travel between the pilot plant in Ireland and the process development groups in the core locations.

Co-locating pilot plants at commercial plants in Ireland streamlines the technology transfer to the commercial plant in other important ways as well. Firstly, it can significantly speed up the regulatory process. In order to register a production process, scale-up batches and stability batches produced at the pilot plant need to be inspected by the regulatory authorities. If this pilot plant is located at the same site as the commercial plant, registration of the process will qualify the entire site, including the commercial plant. This significantly shortens the length of the overall registration process. A further benefit of simultaneous registration of commercial and pilot plants is the greater flexibility it gives firms in the timing of major capital investment in

commercial manufacturing plant, strongly reducing the risk involved with such investment. For example, firms can decide, at a relatively late stage, to delay investment in refitting or expanding the commercial plant and continue to manufacture the launch stock out of the pilot facility until the moment they have more clarity regarding the product's success in the market. Co-location also reduces the chance that technology transfer might be complicated by a change in the physical environment that a change of site might bring, a particularly pertinent issue in bio-pharmaceutical process development (see also Pisano, 1997).

Finally, co-location of the pilot and commercial plants also facilitates post-launch continuous improvement and process re-development (second generation) activities. Typically, a large part of these activities is carried out by the manufacturing organisation and its staff located at the commercial plants. Since their work can require experimentation in pilot plants, co-location provides obvious efficiencies.

Increasing size of Irish pharmaceutical subsidiaries

Changes in the global competitive and technological regime have also stimulated process development activities by changing the relative size of Irish pharmaceutical manufacturing operations. This was driven by two factors. The first of these was a wave of merger and acquisition activity which occurred in the global pharmaceutical industry in the 1990s – itself a response to the growing competitive pressures being experienced in the industry at the time (Agrawal, 1999). A common consequence of these mergers and acquisitions was the rationalisation of excess manufacturing capacity (Schofield 2001). Secondly the Single European Market and the ongoing World Trade Organisation negotiations have greatly reduced the necessity to operate duplicate drug product plants in different national markets, as had previously been the norm in the pharmaceutical industry (Schweitzer, 1997; Gambardella et al., 2000). Rationalisation, in turn, has led to growing concentration of manufacturing capacity in fewer and larger plants (ICSTI, 1999).

For reasons mainly related to its prevailing corporate taxation regime, Ireland has been a very attractive location for these consolidated facilities, with the result that many pharmaceutical subsidiaries in Ireland have developed into the largest manufacturing sites in their corporate networks. An increasing number of these plants now act as "strategic sites", responsible for global new product launches. As a result, these sites became prime targets for the relocation of process development activity arising from the new organisational structures described above.

6.1.2 Changes in tax treatment of intellectual property in the USA

Another example of how changes in the external environment can operate via the internal corporate environment to influence subsidiary evolution relates to the tax regime within which pharmaceutical TNCs operate. At first glance, Ireland's low corporation tax should work against TNCs carrying out R&D activities in Ireland, as TNCs generally prefer to undertake R&D in high-tax regimes so that R&D expenditure can be written off against higher rates of corporation tax, thereby reducing the global tax bill (ICSTI 1999; 2003). The attraction of the U.S. as a location for R&D is further enhanced by relatively generous tax allowances for R&D expenses. However, there have been developments regarding other aspects of

international and national taxation regimes, notably those related to intellectual property, which have actively encouraged the location of process R&D in Ireland.

An important development in this respect was the introduction in the mid 1990s of U.S. legislation for Cost-Sharing Arrangements (CSAs) which permit companies in different jurisdictions to share the R&D costs involved in developing intellectual property. Because the costs are shared, the revenues and profits arising from the development of intellectual property may also be shared. This provides an instrument which allows TNCs to shift some profits to subsidiaries (registered as separate companies) in jurisdictions with lower tax rates than the USA (e.g. Ireland), thereby facilitating significant reductions in the effective global tax rate for the TNCs in question (Simpson, 2005; Heinze, 2005). Typically a CSA involves a buy-in payment where the Irish subsidiary pays the parent company for the value of the pre-existing intellectual property. In theory this buy-in payment should be a fair reflection of the value of the IP transferred. But the system is susceptible to abuse and pharmaceutical firms are widely believed to under-value the buy-in payments. This is supported by the creation of complex global structures and the location of functions additional to manufacturing, including R&D, in low tax jurisdictions such as Ireland. The presence of such R&D facilities can be used to justify inflated levels of value added and profits being attributed to the Irish subsidiaries. A common justification device is the involvement of Irish subsidiaries in the development of second generations of existing products (Simpson, 2005; Heinze, 2005; *Irish Times*, 12 September 2006).

These developments illustrate the systemic nature of the processes and the co-evolution of the drivers involved in subsidiary evolution. On the one hand these developments can be interpreted as "the multinational shifting governance modes and structures in response to environmental shocks" (Tavares, 2001: 146). On the other hand, the environmental shock was, to an extent, encouraged by the lobbying of the transnational companies. They also illustrate how developments in one environment can radically change the operation of drivers in another environment. Initially Ireland's low corporation tax rate had the effect of further exacerbating the host country's existing disadvantages (i.e. small market size and absence of an advanced technological base) as a site for the location of TNC R&D activities). However, the changes in US fiscal arrangements described above had the effect of turning Ireland's low tax rate into an attraction for, rather than a deterrent to, R&D activities.

6.1.3 Irish government measures to promote upgrading

While the changes in corporate organisational structures and tax arrangements described in the previous two subsections were the key external drivers of the incorporation of process R&D functions in Irish pharmaceutical subsidiaries, a number of measures implemented by the Irish government in recent years have also served to enhance Ireland's attractiveness as a base for these functions. These include rapid growth in the supply of science and technology graduates in the 1990s (partly arising from increased government investment in education) and, more recently, major expansion in state funding of scientific research which has placed considerable emphasis on research collaboration between research institutions and industry. Several measures have also been introduced with the specific objective of promoting R&D activities in foreign-owned branch plants, including tax credits for R&D

expenditures incurred in Ireland and grant schemes to support R&D and innovation initiatives.

A large share of the new resources has been used to support the pharmaceutical/biotechnology sector, which has been identified as possessing considerable potential for future growth. In the pharmaceutical industry, following from the changes in the global 'external' environment and corporate 'internal' environments as described above, recent Irish industrial policy documents specifically promote process research and development as an important area for higher value-added activity (ICSTI, 2003; Enterprise Strategy Group, 2004). In line with this, in 2006 the technology infrastructure for pharmaceutical process research and development was significantly expanded with the establishment of the government funded National Institute for Bioprocessing Research and Training – a centre of excellence for the Irish bioprocessing industry.

The company interviewees indicated that all of these measures have exerted a limited positive influence on the disposition of pharmaceutical TNCs towards locating R&D activities in Ireland. At the same interviewees pointed out that, while Ireland scores better than other countries in relation to the availability of graduates with basic skills, the really high-end skills are in short supply. Several interviewees expressed that the Irish education system is still focussing too much on supplying graduates that can work in manufacturing or technology transfer functions. There is insufficient focus on scientific synthetic chemistry skills required to work in the up-stream process R&D functions. For these types of skills companies often have to recruit abroad. "We don't have an oversupply of suitable employees. So when we recruited for the [process development] unit, day one we brought in a lot of people from France and the UK". (manager process development centre, 2006).

This suggests that, in educational terms, the Irish national environment is trailing the growing requirements of pharmaceutical subsidiaries located in Ireland. This in turn suggests that, although the expansion and upgrading of the skills pool has contributed to the greater role of subsidiaries in process R&D, the instigating drivers for the greater involvement of Irish subsidiaries in process R&D lies in the global and macro-regional external environment and the related corporate response (internal environment).

6.2 Subsidiary drivers of evolution

The highly regulated nature of process development in the pharmaceutical industry strongly restricts the room for autonomous development of initiatives by 'entrepreneurial' local subsidiary management. The majority of plans for major expansions of process research and development units originate in the "internal environment" whereby large corporations follow a very systematic tender process to allocate units to particular subsidiaries. This is not to say that local subsidiaries play no role in their own evolutionary process. The company interviews identified several projects that started on the initiative of the Irish subsidiary. Such projects depended very strongly on the quality and energy of local staff. A number of companies gave clear evidence of the need to overcome 'structural inertia' (Tavares, 2001) at the parent company level and the need to 'sell' upgrading proposals to corporate headquarters. In the words of one interviewee: "It took quite a while to convince people [to establish a local pilot plant]…A huge personal energy goes into making

this happen. It will not come to Ireland unless there is somebody out here constantly knocking at their door".

The interviews suggest several factors driving subsidiary staff. One of these is that local process development activity facilitates greater efficiency of the manufacturing operations. Another reason lies in the desire of local management/staff to enhance the profile of the Irish subsidiary within the corporation, which is seen as being important for the long-term survival of the subsidiary in the face of corporate consolidation activities and rising factor costs in Ireland. Local technology staff are also driven by the desire to be involved in more advanced and challenging activities.

7 Conclusions

This paper has found that vigorous growth is occurring in the incidence of process R&D activity among manufacturing subsidiaries of transnational pharmaceutical firms located in Ireland. While this activity is concentrated in the less skill-intensive later stages in the process R&D cycle, it has nevertheless involved a substantial upgrading in skill levels in the plants concerned. In examining the factors or drivers responsible for this functional upgrading, the analytical framework proposed by Tavares (2001) proved to be quite fruitful. All three categories of drivers identified by Tavares were found to be influential in the Irish case, with Irish subsidiary upgrading arising from a combination of impulses deriving from the external environment, the internal corporate environment of the parent firms of Irish subsidiaries, and the subsidiaries themselves. Furthermore, the external drivers were seen to operate at different spatial scales, as proposed by Tavares, including the global/industrial (new regulatory, technological and competitive contexts), the macro-regional (in the form of rationalisation processes resulting from the creation of the Single European Market) and the host-country (Irish government measures to stimulate industrial development in general and functional upgrading in particular) levels. The findings show that the primary drivers for the subsidiaries' enhanced role in process R&D lie in the external environment, notably at the global/industrial level. This supports Tavares's contention that greater weight needs to be given to these environmental drivers of subsidiary evolution.

A particularly insightful element of Tavares's framework for subsidiary evolution – its systemic nature, whereby various drivers mutually interact, co-evolve and operate through each other to influence subsidiary upgrading – was seen to work to particular effect in the Irish case. For example, the changes in the internal organisation of R&D within pharmaceutical firms which favoured the transfer of process R&D functions to Irish subsidiaries were themselves driven by the need on the part of these firms to respond to key developments in their external environments. At the same time, some of the changes in the external environment were partly influenced by actions in the internal environment, as in the case of the introduction of U.S. legislation for cost-sharing arrangements. The latter development illustrates how changes in one environment can radically change the operation of drivers in another environment. The host country's long-established low-tax regime – previously a deterrent to the location of R&D activities in Irish subsidiaries – was converted overnight into an important incentive for locating such activities in Ireland due to its fortuitously beneficial interaction with changes wrought in the fiscal regime relating to intellectual property in the USA.

Ultimately, the significant upgrading which has occurred in the functionality of Irish pharmaceutical subsidiaries has arisen largely from developments in the global external environment which have proved serendipitous for Ireland; initiatives undertaken by the Irish government and the Irish subsidiaries themselves have only been of secondary significance in this context. This points to the contingent nature and inherent fragility of the Irish industrial structure, dominated as it is by subsidiary operations of transnational firms.

The findings highlight opportunities and challenges for Ireland in its pursuit of process R&D functions in the pharmaceutical industry. On the one hand there is great opportunity for expansion of activities in the final stages of the process R&D cycle, either through the establishment of new process R&D units or in the form of expansion of staff numbers at existing units. The findings suggest that this, in itself, requires further efforts to expand and upgrade the national pool of workers with relevant process development skills. On the other hand, serious challenges remain in relation to the up-stream phases of the process R&D cycle. In the short term the Irish government's latitude to stimulate these up-stream phases is limited. Corporations will prove very reluctant to move such activities away from their core product R&D units and it is questionable whether such up-stream process R&D activities can be developed in Ireland without the parallel development of a product R&D infrastructure. These product R&D functions of TNCs are even more locationally inert than the upstream process R&D functions.

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Table 1. Number of operations and employees in pharmaceutical industry - 2003

	Foreign		Indigenous		Total	
	Operations	**Employees**	**Operations**	**Employees**	**Operations**	**Employees**
Active ingredient	29	6367	1	26	30	6393
Formulation	31	8784	13	886	44	9670
Both active ingredient and formulation.	7	2082	1	20	8	2102
Other intermediates	2	109	2	58	4	167
Diagnostics	5	732	4	411	9	1143
Total	74	18074	21	1401	95	19475

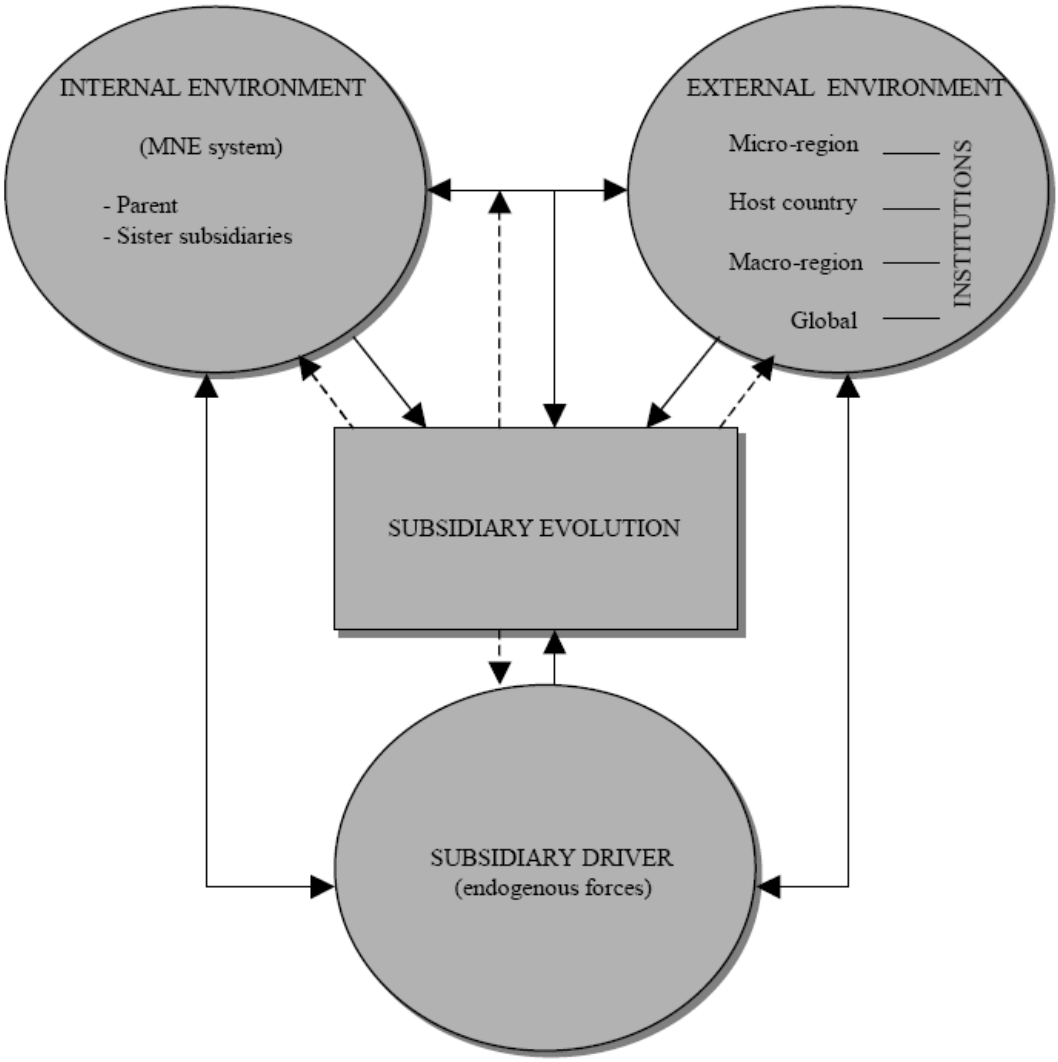
Source: Van Egeraat (2006), based on Forfás Employment Survey

Table 2. Involvement of Irish establishments in process R&D activities

		*Likert scale score (% of establishments)**							
	Process R&D activities	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*mean*
1	Pre-formulation studies.	74.6	6.8	0.0	1.7	5.1	3.4	8.5	2.0
2	Derivation of initial route / process options and preliminary evaluation	71.0	11.3	1.6	3.2	6.5	1.6	4.8	1.9
3	Evaluation in small scale experiments	63.9	13.1	3.3	3.3	4.9	1.6	9.8	2.2
4	Evaluation in kilo lab	62.1	10.3	5.2	1.7	5.2	6.9	8.6	2.3
5	Production for Phase II clinical trials	52.8	13.2	5.7	5.7	7.5	1.9	13.2	2.6
6	Evaluation and optimisation in pilot plant prior to Phase III clinical trials	39.6	17.0	17.0	7.5	5.7	5.7	7.5	2.7
7	Production for Phase III clinical trials	25.9	5.6	9.3	9.3	14.8	16.7	18.5	4.1
8	Evaluation and optimisation in pilot plant during Phase III clinical trials	27.8	9.3	14.8	7.4	16.7	13.0	11.1	3.6
9	Equipment design	9.7	9.7	11.3	14.5	19.4	19.4	16.1	4.5
10	Optimisation in commercial plant (pre filing)	4.8	3.2	3.2	6.5	16.1	21.0	45.2	5.7
11	Validation	0.0	0.0	3.2	4.8	6.5	22.6	62.9	6.4
12	Continuous improvement	0.0	1.6	0.0	1.6	9.7	21.0	66.1	6.5
13	Development of second generation process (outside filing parameters)	9.8	8.2	14.8	4.9	14.8	11.5	36.1	4.9

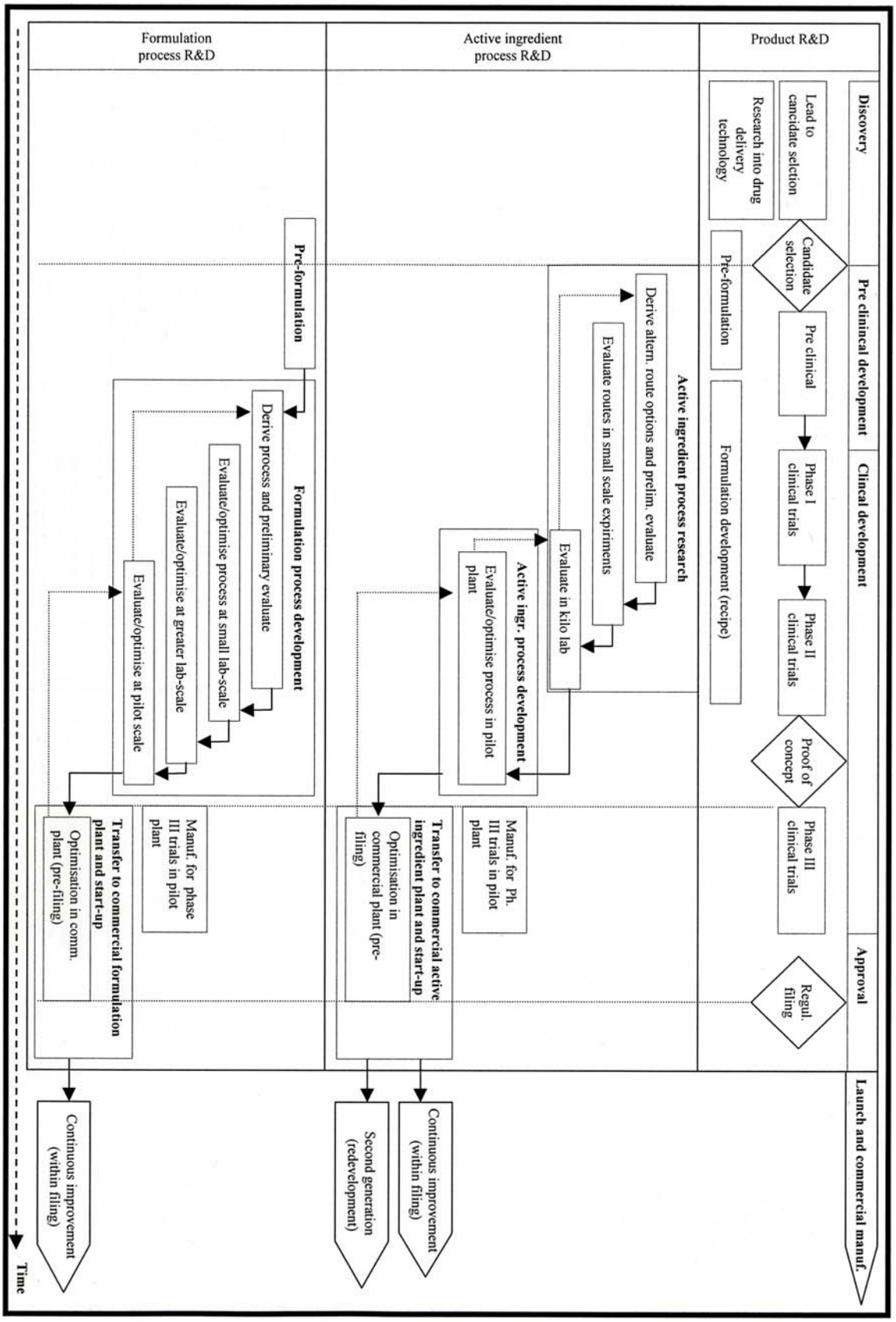
*Note: 1 = no input in activity by Irish plant; 7 = Irish plant has sole ownership of activity

Fig. 1. Drivers of Subsidiary Evolution.



Source: Tavares, 2001

Fig. 2. Process R&D cycle for chemically synthesised drugs



[i] The R&D cycle of the pharmaceutical industry is very complex. This section of the paper confines itself to presenting a concise overview of this cycle, and to highlighting certain aspects of the cycle which are particularly germane to the empirical part of the paper and the associated arguments regarding the drivers of subsidiary evolution. For a more detailed description of the pharmaceutical R&D cycle, see Van Egeraat (2007).

[ii] This section is partly based on Pisano (1997) supplemented with information obtained during company interviews

[iii] The survey and interviews were conducted in 2005-06. For more detail regarding the survey methodology see Van Egeraat (2007).

[iv] For further detail on the methodological considerations relating to this question, see van Egeraat (2007).