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The Scale and Scope of Process R&D in the Irish Pharmaceutical Industry

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Abstract

Manufacturing Process R&D activities are one of the target areas of Irish industrial development agencies in their quest towards embedding pharmaceutical companies in Ireland. This paper analyses the changing role of Ireland in the global process R&D networks of the pharmaceutical companies. The paper is based on data collected in an email survey of all pharmaceutical establishments in Ireland and face-to-face interviews with 13 companies. The article outlines the various stages of the process R&D cycle and assesses the involvement of the Irish establishments at each stage. Far from a uniform undifferentiated activity, process R&D comprises a range of activities. The results show that although Irish plants are increasing their involvement in process R&D, this involvement tends to be concentrated in the last stages of the cycle.

1. Introduction

Since its relatively late introduction at the end of the 1950s, the pharmaceutical sector in Ireland has experienced strong and virtually continuous growth. The implementation of outward-looking economic policies (focused strongly on the stimulation of exports through the attraction of inward investment) from the end of the 1950s (O'Malley, 1989) led quickly to the arrival of the first foreign manufacturing plants. Initially the companies in question were primarily attracted by the zero rate of corporation tax on profits derived from exports. The pharmaceutical industry in Ireland really took off in the 1970s after the Industrial Development Authority (IDA) identified the industry as one of its target sectors (Childs, 1996; White, 2000a). Additional attractions for inward investment now included access to the European market (following entry to the European Union in 1973) and an increasingly skilled labour force.

By 2003 the pharmaceutical industry had developed into one of the main industrial sectors in Ireland, employing nearly 19,500 people (see Figure 1), over eight per cent of total manufacturing employment (Van Egeraat, 2006). Foreign companies account for 93 per cent of total employment. Employment in the industry more than doubled in the period 1993-2003. Exports of the broader pharmaceutical/chemical industry have grown from about €2 billion in 1990 to €39 billion in 2002 making it the largest export sector in Ireland, accounting for 42 per cent of the value of all manufactured goods exported in that year. Since 2001 the sector has been the largest contributor of corporation tax to the Irish exchequer (ICSTI, 2003).

For a long time the pharmaceutical industry in Ireland, like most other industries, had a strongly truncated form, involving foreign branch plants focussing on production with little or no R&D activity. In the context of rising factor costs and the perceived associated threat of plant closures during the second half of the 1990s, Irish industrial policy began prioritising the upgrading and enhanced embedding of firms through, inter alia, encouraging the incorporation of R&D activities into their operations (Industrial Policy Review Group, 1992) Recent policy documents specifically promote process R&D as an important opportunity for higher value-added activities in the Irish pharmaceuticals industry (ICSTI, 2003; Enterprise Strategy Group, 2004).

This policy is inspired by a perceived changing spatial configuration of process R&D activities within the global networks of pharmaceutical firms. Breaking a tradition of concentrating process R&D activities at the central R&D sites in the home countries of multinational enterprises, anecdotal evidence suggests that process R&D activities are increasingly being dispersed to branch plants in the global production networks of these firms (Pisano, 1997; Chiesa 1996; Howels 1984). Although some studies address the changing spatial configuration of pharmaceutical product R&D or pharmaceutical innovation in general (Howells, 1983, 1984, 1990) little detailed work has been done on process R&D and no information exists about the situation in Ireland. The purpose of this article is to provide a detailed account of the evolving nature and spatial configuration of process R&D in the global pharmaceutical industry and how these are reflected in the changing profile of the activities of pharmaceutical enterprises operating in Ireland. R&D may be carried out either inside the multinational firm, in the form of 'internalised R&D' (Dicken, 2003), or through

external networks. Process R&D is still largely organised internally and this article deals exclusively with this internalised R&D.

This paper draws on research conducted in the context of a broader research project looking into Ireland's changing role in Global Production Networks in the pharmaceutical industry. The analysis of Ireland's role in process R&D is based on data collected from two sources: an email survey among all pharmaceutical establishments and multiple face-to-face interviews in 13 selected pharmaceutical companies.

The paper begins with an account of how the influences of globalisation and increasing competition have prompted pharmaceutical companies to restructure the spatial organisation of their process R&D activities. The next section provides a detailed outline of the R&D cycle in the industry today. Far from a uniform undifferentiated activity, process R&D consists of a range of activities, potentially involving different tendencies of decentralisation. This provides the necessary background for the following section which contains a detailed discussion of the scale, growth, scope, sophistication and evolution of process R&D activities in the Irish pharmaceuticals industry. The final section presents conclusions and raises some policy issues arising from the findings.

[Insert Figure 1 here]

2. The changing spatial configuration of process R&D in the pharmaceutical industry

The origins of the pharmaceutical industry date back to the last quarter of the 19th century as a spin-off from the bulk organic chemistry industry in Germany and Switzerland (Schofield, 2001; MacGarvie and Furman, 2005). Until this point medicines had been extracted from organic material by small firms or the practitioners themselves, using simple processes. Over the next decades an increasing number of companies dedicated themselves to the systematic discovery and mass manufacture of organic medicines. The technological sophistication and scale of the industry increased steadily. Yet, the real chemo-therapeutic revolution did not occur until WW II which instigated a focussed effort to develop mass-produced medicines. After the war US companies emerged as the dominant players. The next 20 years, the period of Europe's post-was recovery, saw the development of a global pharmaceutical industry concentrated in the US, Germany, France, Switzerland, Italy and the UK. With US companies dominating, a large part of the industry developed under Fordist principles.

Under Fordism, R&D had developed as a linear process (Malecki, 1997; Hayter, 1998; Dicken, 2007) involving a continuum of activities leading from basic research through applied research and product/process development to technology transfer to the commercial manufacturing plants. Within large corporations, ideas were progressively researched, developed and transferred to the production plants. Functions were highly specialised and compartmentalised. There was a strong distinction between the individual R&D functions and between the R&D and manufacturing functions. Each R&D group constituted its own compartmentalised speciality responsible for a particular task in the linear process. Planned interactions between departments were constrained to the moments of transfer of a finished task.

The Fordist method of work organisation was associated with a distinct geography of production and R&D. The geography of production was characterised by a decentralisation of manufacturing functions. In the post-war period many pharmaceutical companies rapidly expanded their manufacturing networks both inside their home countries and abroad. Companies established branch plants in numerous markets to overcome trade-barriers and, in countries such as Ireland and Puerto Rico, to avail of local tax incentives.

The Fordist geography of R&D was different from that of production. On a national scale, large firms typically established large-scale specialised R&D laboratories locationally separate from the factories, in suburban areas in the same metropolitan area as the corporate head office. Concentrating R&D staff was believed to bring efficiency and productivity gains. The tendency to locational separation of R&D from manufacturing was related to the fact that R&D and manufacturing operations have different labour requirements (scientists and engineers vs. operators) that are satisfied in different locations. Location separation was also thought to provide a more favourable working environment for the R&D staff, less interrupted by daily troubleshooting requests from the manufacturing units. On an international level, the R&D functions of multinational companies, particularly the more strategic activities, remained firmly located in the home countries. Some decentralisation of R&D occurred, 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, with basic research functions being conducted in the central research units located near the head-offices and main production sites of the companies. Branch plants frequently housed small technical and development units, but the scope of the activities was limited (Howells, 1984). Even in the case of process R&D, typically, the manufacturing process was for the most part developed by the central R&D group located near the head-office before the technology was transferred to the manufacturing function and manufacturing sites.

The Fordist, linear approach to R&D involved inherent inefficiencies. The linear approach and highly specialised and compartmentalised organisation of functions are unsuitable for the realities of research projects where decisions taken during the early stages of the cycle strongly influence the possibilities and parameters for the later stages, and vice versa. The lack of integration and communication between the various R&D functions and between the R&D and manufacturing plants led to a lot of wastage, high costs and long development times (Hayter, 1998). In pharmaceutical process R&D, because of the late involvement of the manufacturing function, problems and inefficiencies in the manufacturing process were identified at a very late stage in the process R&D cycle. This tended to delay the product launch and/or led to significant post-launch changes to the process that involved time-consuming regulatory re-filing procedures.

These inherent deficiencies in the Fordist innovation model didn't really matter in the 1950s and 1960s, especially in the US, as strong and sustained growth delivered high profits despite high costs and as the US economy remained largely immune from foreign competition. However, things changed drastically with the economic

downturn of the 1970s and the increasing opening up of the American economy to competition as the globalisation process accelerated. Many companies were forced to increase the efficiency of product and process R&D. This typically involved a shift towards an R&D organisation that explicitly incorporated the 'loopy' nature of the R&D process (Hayter, 1998). The traditional compartmentalised structures were increasingly replaced by cross-functional product/process development teams that embraced the different R&D functions as well as non-R&D functions such as manufacturing and sales and marketing.

Likewise, since the 1980s, confronted with important global changes in the competitive and technological environment, pharmaceutical companies have come under pressure to increase efficiency in product and process R&D. As regards process R&D, in many cases companies sought the solution in earlier involvement of the manufacturing function in the process R&D cycle. (Pisano, 1997; van Egeraat, 2007).

Post-Fordist forms of work organisation are changing the relative strength of spatial concentration and dispersal forces in determining the geography of R&D. On the one hand there is some evidence of increasing geographical dispersal of R&D activities on a national and international scale. On the other hand, multinational companies retain the majority of their R&D in their home countries while foreign R&D laboratories are concentrated in the core regions of a small number of core countries (Dicken, 2007). The tendency for concentration/dispersal is not the same for all R&D activities. While firms still tend to concentrate their high-level and innovative research at central laboratories, there is some evidence that the less technically-complex activities, especially process R&D, are being located at some, but not all, branch plants (Malecki, 1997). In relation to process R&D, the idea is that decentralisation or dispersal will facilitate integration of, and communication between, the process R&D function and the manufacturing operations.

This article examines the extent to which the trend of decentralisation of process R&D activities in the global networks of multinational pharmaceutical companies is affecting Ireland. In the conventional classification, process R&D is typically treated as a uniform category. However, process R&D in the pharmaceutical industry is far from being a uniform, undifferentiated, function. Instead, it comprises a wide range of activities, some of which cross the boundary with applied research. The individual activities may involve different tendencies of decentralisation. Therefore, the next section first provides a detailed outline of the R&D cycle in the industry today.

3. The R&D cycle of the pharmaceutical industry

Conventional classifications typically treat process R&D as a uniform category. This section aims to open the "black-box" of process R&D activities in pharmaceutical companies. Pharmaceuticals can be derived through chemical synthesis ("chemical pharma") and through biotechnological processes ("bio pharma"). The two types of drugs involve different product and process R&D activities, although the same broad stages can be identified (see below). This section focuses mainly on the R&D cycle of chemical synthesis drugs but includes a concise treatment of the R&D cycle of biotechnology-derived drugs, outlining the main differences with chemical synthesis R&D cycle.[i]

In the pharmaceutical industry, product and manufacturing process R&D are strongly integrated, with product R&D strongly influencing the organisation of process R&D. For this reason the core discussion of process R&D will be preceded by an outline of the product R&D activities. The process R&D cycle of pharmaceuticals involves two cycles – one for the active ingredient (the drug substance) and one for the finished drug formulation (the actual tablet, capsule or injection). Although the two cycles are strongly integrated and, as will be discussed, share certain activities/functions, they will be described separately here, starting with the process R&D cycle for the active ingredient.[ii]

3.1 Product R&D for (chemically synthesised) drugs

Product R&D entails both R&D into new active ingredients (AIs) and R&D into related finished drug formulations (DFs) (the actual tablet, capsule or injection). The product R&D cycle of a chemical synthesis drug can be divided into four stages: discovery, pre-clinical development, clinical development and regulatory approval (see Figure 2). The discovery stage is concerned with research into the causes of diseases and the identification of compounds (AIs) that could be active in relation to certain diseases – commonly referred to as 'leads'. A large number of these leads are assessed for their biological activity. The discovery stage ends with the selection of one or a small number of drug candidates that are believed to have potential for further development.

The product now enters the pre-clinical development stage, during which the candidates are subjected to animal testing to further determine their therapeutic effect and, importantly, their toxicity and side effects, before being tested in humans. After this, the drug enters the clinical development stage, during which the drugs are tested in humans. Clinical development can broadly be divided into three clinical trial phases. Phase I clinical trials are usually small trials during which the drug is administered to healthy volunteers to establish possible adverse side effects. In Phase II trials the drug is administered to a somewhat larger group of persons who have the target disease to investigate the drug's efficacy and side effects. Successful Phase II trials can lead to what the industry refers to as "proof of concept" This sanctions the commencement of the costly Phase III trials, where the drug is tested for efficacy and safety on thousands of patients. If successful, the product 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. After being granted a product licence, a company can start the product launch and commercial manufacturing.

Product R&D into the finished DF starts in the pre-clinical stage with 'pre-formulation studies'.[iii] The responsible unit investigates the physical and chemical properties of a drug substance e.g. particle size, solubility, stability etc. Analytical chemists and pharmacists prepare a number of model formulations for toxicity studies and early clinical trials. The findings guide the choice of inactive ingredients (excipients), the selection of possible formulation recipes and dosage forms (as well as the manufacturing process – see below).[iv] The 'formulation development group' subsequently further refines a number of formulations. This involves further drug-excipient compatibility studies, tests to determine both physical and chemical stability and additional animal tests. Companies generally aim to complete the development

and testing of the formulation recipes and dosage forms by the end of Phase II clinical trials.

[Insert Figure 2 about here]

3.2 Process R&D cycle for (chemically synthesised) active ingredients

In parallel with product R&D, and strongly integrated with it, runs process R&D for the active ingredient. The task of process R&D is to develop a manufacturing process for the active ingredient. Any given molecule or compound can be synthesised through a number of 'synthetic routes'. During the discovery phase, medicinal chemists will have synthesised the drug candidate for test purposes. This 'discovery route' is a very inefficient process. During process R&D, process chemists will search for a large scale, efficient and robust process. At the same time process R&D has the task of supplying product to feed the clinical trials.

Process R&D for the AI involves three overlapping phases: process research, pilot development and transfer to commercial manufacturing. Process research usually starts immediately after candidate selection. Process chemists will start by exploring alternative synthetic routes. These are then evaluated, first in "paper experiments" and computer simulation and, after narrowing down the options, in small-scale laboratory experiments. Since the scale of the process can have a strong influence on the process parameters, the process needs to be 'scaled up' in a number of stages. The first step in this scale-up is the evaluation of promising routes at a larger laboratory scale, the 'kilo lab'. This scale increase is also required to produce sufficient material to supply the early clinical trials and the DF R&D function (see below).

In the process development phase the process moves to the pilot plant. The pilot plant scale is more representative of the eventual commercial plant scale. Using the knowledge gained in process research, the process is scaled-up and process parameters are selected. The nature of the activities is changing. Whereas in the process research phase the focus is on understanding the chemistry and developing new synthetic routes, during the development phase the focus shifts to optimising flow rates, equipment design and developing process mechanics – chemists hand over to chemical engineers. An important function of the pilot plant is to produce material for large-scale clinical trials.

Although the boundaries are vague, the process development phase continues to the proof-of-concept point and the start of Phase III clinical trials. Companies generally aim to 'lock down' the process at this point. Major changes after this point mean that the eventual process may not be representative for the process used for the production of clinical trial material, which may lead to additional clinical work. From here on, process development focuses on the final details of the process.

The AI now enters the final phase of the process R&D cycle – the transfer to the commercial-scale AI plant. Technology transfer is generally carried out by 'commissioning teams' made up of staff from process development and staff from the commercial plant. The actual design and engineering of the commercial facilities and some of the equipment usually will already have started during the process development phase. The documented process is now transferred to the commercial plant, operators are trained and standard operating procedures are written up. Apart

from transferring the process, this phase can still involve an element of development in terms of adapting the process to the plant and resolving unforeseen problems. A successful run of validation batches completes the technology transfer. A detailed description of the process will be included in regulatory filing documents.

Technology transfer and regulatory filing are sometimes seen as the end of the process R&D cycle. This is partly because at this point accountability for the process is often handed over to a different section within the company i.e. manufacturing or operations. Yet, process development activities for a particular substance do not come to a complete stop here. During the entire life cycle of the product, technical staff at the plant often continue to carry out continuous improvement. This involves small, incremental, changes to the process that do not require refiling with the regulatory authorities. In addition, under the pressure of supplying clinical trial material and bringing a product to launch as quickly as possible, companies may not have been able to fully explore the possibility of more efficient synthetic routes or processes. Less constrained by time-pressure, 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 encompassing more than continuous improvement, often do not involve a fundamental route change. It is often more about changing one or two parts of the process.

Although described as a linear process, in reality there is a strong overlap between the phases of the process R&D cycle and the cycle includes many feedback loops. Thus, while evaluating a particular synthetic route in the kilo lab, process research chemists may start exploring new synthetic routes and difficulties encountered in the pilot plant may result in the evaluation of new routes in the process research environment.

3.3 Process R&D cycle for (chemically synthesised) drug formulation

In parallel with product R&D for the DF (determining the dosage form and recipe) the company needs to develop a manufacturing process for the formulation. The manufacturing process of a DF differs strongly from that of an AI. In the chemical synthesis of an AI, raw materials are transformed through chemical reaction into a final compound – a chemical transformation. In DF manufacturing the AI is combined with other, inactive ingredients (excipients) in a physical transformation process, involving processes such as granulation, drying, blending, compressing, etc. This is arguably a less complex process but can nevertheless involve a substantial development effort.

The distinction between DF process R&D and DF product R&D is not always clear-cut, with certain activities/functions playing a role in both areas. Manufacturing process R&D of the DF starts with the 'pre-formulation studies'. Apart from guiding the selection of a formulation recipe and dosage form (product R&D), the findings of the pre-formulation studies also inform the development of the manufacturing process. For example, the physical structural character of an AI can influence the manufacturability of certain dosage forms. The 'formulation process development' group subsequently identifies a potential manufacturing process which is then evaluated and scaled up from a small laboratory scale to an intermediate laboratory scale and finally to a pilot scale in the pilot plant, akin to the process R&D cycle of an AI. As in the AI process R&D cycle, an important function of the DF pilot plant is to produce material for Phase III clinical trials. Very much along the lines of the AI

process R&D cycle, the manufacturing process R&D cycle for the DF ends with the transfer to the commercial manufacturing plant, validation and regulatory filing, although continuous improvement will continue throughout the life cycle.

The above subsections present a stylised picture of the process R&D cycle. In reality the process R&D cycles can differ from product to product. Depending on the technology involved, the scale of the eventual process and the requirements for regulatory approval, the cycle may not include all of the described stages. For example, in the case of niche products that require relatively small quantities of product, one of the scale-up steps may be omitted.

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, the early stages in the cycle require a greater number of highly educated and skilled researchers than the later stages.

3.4 Product and process R&D for bio-pharmaceuticals

Process R&D in bio-pharmaceuticals differs in many ways from that in chemical pharmaceuticals. The differences are due to the nature of the product and the technologies involved. Many physiological processes and diseases involve proteins that are naturally produced by cells in the human body. These proteins are too large and complex to synthesise chemically. However, advances in biotechnology have made it possible to genetically manipulate specific bacterial or mammalian cells that produce the required proteins. The manufacturing process of the active ingredient involves two steps: the growing of cells in bioreactors (upstream process) and the subsequent separation/purification of the protein (downstream process).

Although product and process R&D for biopharmaceuticals is very different from that for chemical pharmaceuticals, it involves the same broad stages (but named differently). Product R&D again involves the four stages of discovery, pre-clinical and clinical development and regulatory approval. But here discovery is not occupied with a search for molecules or ‘leads’ that may be active in certain diseases - there is only one protein that performs the specific function. Instead, discovery is occupied with isolating the gene that is responsible for the production of the particular protein and the insertion of this gene into a bacterial or mammalian host cell. The end product of the discovery phase is a cell-line or a set of cell-lines that produce the required specific protein and a method for isolating or purifying the protein. In a sense, there are no candidates in biopharmaceuticals - there is only one protein[v].

Process R&D for bio-pharmaceutical AIs involves the three overlapping phases of process research, process development and transfer to the commercial plant. Process research and process development involve the exploration and evaluation of promising cell line options and experimentation with upstream and downstream process parameters, first at a small scale (shake flasks), followed by bench-top reactor scale and subsequently at intermediate scale. The process R&D cycle for the AI ends with the transfer to the commercial manufacturing plant, validation and regulatory filing, similar to the AI cycle of chemically-derived AIs. The process R&D cycle of bio-pharmaceutical DFs is in principle not different from that of chemically derived pharmaceuticals.

4. Process R&D activities in pharmaceutical firms in Ireland

4.1 Data sources

The analysis of Ireland's role in process R&D which follows is based on data collected from two sources: multiple interviews at 13 selected pharmaceutical companies and a mail survey of all pharmaceutical companies in Ireland. Semi-structured, face-to-face, interviews were conducted with senior staff at twelve major pharmaceutical plants in the period 2005-2006. A total of 53 staff members were interviewed, including general managers, materials managers, personnel managers and process development managers. The material presented in this paper is based mainly on information obtained during the interviews with the process development managers. In one case interviews were conducted with global process development managers located at global headquarters. These interviews were used, *inter alia*, to obtain detailed micro-level data about the dynamics of the global organisation and spatial configuration of process R&D activities in the pharmaceutical companies, with particular reference to the relative role played by the Irish subsidiaries in these activities. The selection process ensured that the sample included companies in different sub-sectors (drug product and drug formulation), from different nationalities (US, UK, Swiss, French, Japanese and Irish), with different levels of involvement in process R&D and with different locations in Ireland.

In addition, a mail-survey was conducted of all pharmaceutical establishments in Ireland in the period 2006-2007. A list of pharmaceutical companies was obtained from the annual Employment Survey of manufacturing operations in Ireland, conducted by Forfás (the National Policy Advisory Board for Enterprise, Trade, Science, Technology and Innovation). This list was thoroughly checked and amended on the basis of information obtained through Internet-based research combined with short telephone interviews.[vi] Establishments with only a marketing or distribution function were excluded. In addition, a small number of establishments were excluded because they were still in the construction phase. The final list included 80 establishments.

Process development managers or managers of technical services were personally approached and asked to complete a two-page questionnaire. Following an intensive survey administration process, 76 useable questionnaires were returned - a response rate of 95 per cent. The Forfás Employment Survey shows that the 76 respondent companies represent 92 per cent of all employees employed by the listed pharmaceutical companies. The survey therefore covers nearly the entire Pharmaceutical industry. Table 1 presents the characteristics of the sample of 76 respondent companies. About a third of the establishments were exclusively involved in the production of active ingredients, 58 percent in drug formulation and the remaining 8 percent manufactured both active ingredients and drug formulations. Foreign companies made up 84% of the sample and 95% of employment. Nearly all (10 out of 12) indigenous companies were exclusively involved in the production of drug formulations. Four of the 76 establishments produced biopharmaceutical active ingredients in fermentation plants

Table 1: Characteristics of the 76 respondent companies

	Number of companies	Percentage of companies	Percentage of employees
Irish companies	12	16%	5%
Foreign companies	64	84%	95%
Active ingredients	26	34%	32%
Drug formulation	14	58%	57%
Both active ingredients and drug formulations	6	8%	11%
Chemical pharmaceuticals and bio pharmaceutical drug formulation	72	95%	89%
Bio pharmaceuticals (active ingredients)	4	5%	11%

The questionnaire sought information on, *inter alia*, the age of the establishment, the product, the number of employees involved in process R&D and their education level, and the role of the local units in the global process R&D networks of the companies. As regards the latter, it was recognised that the post-Fordist organisation of process R&D tends to involve global project teams made up of staff of different R&D functions as well as manufacturing and marketing. In such structures, local units tend to have at least some input in most process R&D activities and it is often not possible to characterise the location of the various activities in terms of "here or there". To get an insight into the relative role of the local units in the overall network, in this research respondents were asked to rate the relative input of the local staff in various process R&D activities on a seven-point Likert scale (1 = no input; 7 = sole ownership).

The same questionnaires were used for drug substance and drug product plants. The questionnaire worked with generic names for the various process R&D categories that suited plants in both the drug substance and drug products sub-sectors. Categories at the same stage in the process R&D cycle were combined. For example the category "derive initial routes and preliminary evaluation" of the drug substance cycle was combined with "derive initial process options and preliminary evaluation" of the drug formulation cycle into the generic category "derive initial route/process options and preliminary evaluation (paper experiments)". For clarity reasons, the questionnaire sent to the four biopharmaceutical active ingredients (fermentation) plants included a slightly different categorisation.[vii]

Follow-up phone calls to some of the respondent firms were made in order to clarify answers and obtain supplementary information. These phone calls often provided valuable qualitative information on process R&D activities that informed the analysis

The results of the company interviews and mail survey are used in a complementary way to analyse the process R&D activities in the Irish pharmaceutical industry. The quantitative data from the mail survey are used to construct a broad overview of process R&D in the Irish pharmaceutical industry and the relative role of Irish establishments in the various process R&D activities. The interview data serve to obtain a more detailed and nuanced understanding of the relative role of Irish establishments, notably the changing nature of this role.

4.2 The scale of process R&D in Ireland

The survey of pharmaceutical firms in Ireland shows that, at the end of 2006, the 76 respondent companies employed a total of 800 staff involved in process R&D, irrespective of the proportion of their time spend on these activities. These people were either part of dedicated process R&D units or were employed in other functions such as production, technical support, quality control, etc. Most people spent only part of their time on process R&D activities. Respondents were asked to estimate the average of the proportion of their time that the people involved spent on process R&D activities. Based on this information it is estimated that process R&D employed the equivalent of 580 full-time people.

The average number of people involved in process R&D per firm was 10.5 but the distribution is strongly skewed (see Figure 3). More than 40 percent of the companies had less then 5 staff involved in process R&D while in two thirds of the companies less then 10 people were involved. Four companies had over 50 people involved. In one case the high figure was related to the fact that the establishment was still partly in the ramp-up phase. A large part of the staff was therefore involved in process R&D activities as defined in this research but the majority would have subsequently been transferred into manufacturing after the start-up phase.

[Insert Figure 3 here]

The survey confirms the rapid recent expansion of process R&D activities in Ireland. In the six-year period between 2000 and end-2006, the number of people involved in process R&D in the responding companies nearly doubled, from 408 to 800.[viii] To put this growth in perspective, total employment in the 76 respondent companies grew by 36 per cent over the same period. On average the plants that existed in 2000 had an additional three staff involved in process R&D in 2006. Figure 4 shows that 22 per cent of these plants experienced no change in the number of persons involved, while eight per cent increased their process R&D staff numbers by more than 10 people. Six per cent of the incumbent operations experienced a reduction in process R&D staff. The twelve operations that entered the sector since 2000 employed an average of 17 people involved in process R&D activities in 2006. Apart from the fact that some of these companies engaged a greater number of staff in process R&D during the ramp-up phase, this greater growth in employment of process R&D staff is partly explained by the relative size of some of the new operations in question.

[Insert Figure 4 here]

As for the future, 38 per cent of the respondent companies had concrete plans to expand their process R&D activities in Ireland over the next five years. Out of the 31 companies with concrete expansion plans, 27 provided an estimate of the additional process R&D staff requirements over this period, amounting to a total of 311 additional staff. The total increase in the sector will most likely be far greater than this since the question only referred to concrete plans. Almost half of the 311 staff are accounted for by just three companies which were planning major expansions. Staff numbers involved in the other planned expansions ranged from one to 20.

4.3 The scope of process R&D in Ireland

Although impressive in their own right, the above figures tell us little about Ireland's relative role in the global process R&D networks of the respondent firms. To get an insight into this role, respondents were asked to rate the relative input of the local staff in various process R&D activities on a seven-point Likert scale (1 = no input; 7 = sole ownership). This section first discusses the results of the drug substance and drug products sub-sectors combined, followed by a discussion of the differences between the sub-sectors.

Most indigenous companies and a small number of foreign-owned companies were single-site operations. In these cases the question regarding the relative input of local staff is not relevant since the local establishments had full ownership of all activities that were relevant to the companies in question. Because of this, the following discussion only pertains to the 62 multi-site companies (companies with manufacturing or research operations in more than one country) in the survey. Not all research categories were relevant to all companies. For example, some companies producing over-the-counter and generic pharmaceuticals did not have to go through elaborate phase I and phase II clinical trials. Therefore the results for the various research activities pertain to different numbers of companies (ranging from 58 to 62).

Table 2 Involvement of local staff in process R&D activities

	1	*2*	*3*	*4*	*5*	*6*	*7*		*mean*
Pre-formulation studies.	74.6	6.8	0.0	1.7	5.1	3.4	8.5	100	2.0
Derive initial route / process options and preliminary evaluation	71.0	11.3	1.6	3.2	6.5	1.6	4.8	100	1.9
Evaluate in small scale experiments	63.9	13.1	3.3	3.3	4.9	1.6	9.8	100	2.2
Evaluate in kilo lab	62.1	10.3	5.2	1.7	5.2	6.9	8.6	100	2.3
Production for phase II clinical trials	52.8	13.2	5.7	5.7	7.5	1.9	13.2	100	2.6
Evaluate and optimise process in pilot plant prior to phase III clinical trials	39.6	17.0	17.0	7.5	5.7	5.7	7.5	100	2.7
Production for phase III clinical trials	25.9	5.6	9.3	9.3	14.8	16.7	18.5	100	4.1
Evaluate and optimise process in pilot plant during phase III clinical trials	27.8	9.3	14.8	7.4	16.7	13.0	11.1	100	3.6
Equipment design	9.7	9.7	11.3	14.5	19.4	19.4	16.1	100	4.5
Optimisation in commercial plant (pre filing)	4.8	3.2	3.2	6.5	16.1	21.0	45.2	100	5.7
Validation	0.0	0.0	3.2	4.8	6.5	22.6	62.9	100	6.4
Continuous improvement	0.0	1.6	0.0	1.6	9.7	21.0	66.1	100	6.5
Development of second generation process (outside filing parameters)	9.8	8.2	14.8	4.9	14.8	11.5	36.1	100	4.9

Note: scores on a 7-point Likert scale (1 = no input; 7 = sole ownership)

Table 2 and Figure 5 present the average scores accorded by the respondents to the various research activities. The column with the title "1" states the percentage of relevant companies that accorded a score of 1 to their involvement in a particular research category, and so forth. The final column lists the mean scores for involvement of the local companies in the various research categories. The results show that the Irish companies tend to have very little involvement in the early stages of the process R&D cycle. The mean score for involvement in 'pre-formulation studies' (2.0) indicates a very low level of involvement. Threequarters of the establishments for which this activity was relevant had no input in it while only 5 per

cent had sole ownership. The mean score for 'deriving initial route/process options and preliminary evaluation through paper experiments' was even lower (1.9). Here again, a large proportion of the relevant establishments had no input whatsoever while only 5 per cent had sole ownership. The mean scores for 'evaluation in small-scale experiments' and 'evaluation in kilo lab' were only marginally higher and the percentage of establishments having full ownership remained below 10 per cent.

[Insert Figure 5 about here]

The interviews confirmed that local technology staff were generally involved in process R&D as members of global project teams made up of staff from R&D and the manufacturing organisations from various geographies. Such teams are set up at an early stage of the process R&D cycle to facilitate an early involvement of all the relevant functions, including manufacturing, and to streamline the transition between the various stages and locations.

The involvement of the Irish establishments rose at the phase II clinical trials stage. The mean score for involvement in "production for phase II clinical trials" was 2.6 while the mean score for involvement in 'evaluation and optimisation of the process' at this stage was 2.7. However the mean scores conceal significant differences between the Irish involvement in the two activities. Of the establishments for which production for phase II clinical trials was a relevant category, only 47 per cent had at least some input (scoring 2 to 7) in this activity. Sixty per cent of the same group of establishments had at least some input in the evaluation of the process at this stage. Although a greater proportion of companies had some involvement in evaluation/optimisation, this involvement tended to be very limited, with over one-third of the respondents scoring either two or three. At the other end of the scale, a substantially larger proportion of establishments in the same group had full ownership of production for phase II clinical trials (13.2%) than of the evaluation/optimisation of the process (7.5%).

The pattern is even more pronounced in the context of phase III clinical trials. The involvement of the local establishments at this stage was substantially greater, with a mean score of 4.1 for 'production' and 3.6 for 'evaluation/optimisation'. Again the proportion of relevant establishments with no input in 'production' was somewhat smaller than the proportion that had no input in the 'evaluation/optimisation'. At the same time, 35 per cent of the relevant companies rated their involvement in production of phase III batches at a score of six or seven compared with only 24 per cent in relation to evaluation/optimisation activities.

This pattern reflects the fact that the staff involved in process R&D in Irish pilot plants and commercial plants are focussing on the production aspect of process R&D activities. As shown in Section 3, apart from developing the manufacturing process, a second important function of pilot plants is to produce material for large-scale clinical trials. The survey data suggest, and the interviews confirm, that in a substantial number of cases the main function of the staff involved in process development was 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. In some cases local staff have a strong input in the evaluation of the batches and subsequent optimisation of the process. However, more often the involvement is very limited, particularly at the early stages. One respondent who gave a rating of three to his establishment's involvement in evaluation/optimisation during phase III clinical trials commented: "We do produce for clinical trials but the scope of our activities is clearly defined by the guys in the US and therefore our involvement in optimisation is limited as well. But we acquire in-depth knowledge and are involved in discussions."

The mean score for involvement in equipment design wais 4.5. Although more than half the companies scored 5 or higher, a substantial group of companies (31 per cent) had either a rather limited involvement in this activity or none at all. As expected, the involvement of the Irish establishments tends to rise significantly at the stage of 'optimisation in the commercial plant (pre-filing)'. This optimisation is part of the broader technology transfer phase. Technology transfer essentially involves taking a process from the pilot plant scale and replicating it with, preferably, minor changes (optimisation) 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.

The data indicate that local staff have a high level of involvement in the actual optimisation activities (mean score of 5.7). In 45 per cent of the cases local staff had full ownership while 37 per cent of the respondents indicated a high level of involvement (scoring a 5 or a 6). These figures pertain to situations where no major process changes are necessary. Significant changes require a strong involvement of the transferring location but such changes tend to be avoided at this stage. Instead companies prefer to divert the making of major changes to the development of second generation processes. Local staff tend to have an even greater involvement in the running of 'validation' batches, with 63 per cent of the respondents indicating full ownership.

'Continuous improvement activities after filing' tend to be carried out almost entirely by the local staff. The mean score for this activity is 6.5 with two thirds of the respondents stating they had full ownership. At this stage staff from the core research locations tend to have a very limited, more consultative, role. In many cases there is not even a requirement to formally communicate improvements to the central research locations. However, information on process improvements continues to be shared and discussed with the central research locations and other functional units through the global project teams and technology networks.

Finally, the mean score for the level of involvement drops to 4.9 with respect to the 'development of second generation processes (outside filing)'. 36 per cent of the respondents stated that they had total ownership of this activity. It is important to appreciate that this category does not involve a single activity but can involve all the previous ones. In addition, the development of second-generation processes entails very different activities from company to company. In many companies it involves relatively minor changes, requiring limited technological resources, while in other

companies it involves the development of an entirely different chemical route, basically repeating the process R&D cycle. Many of the companies which stated that they had total ownership of the development of the second generation process were likely to be part of the first group. At the same time, the substantial number of companies giving evidence of more limited involvement included companies from the second group. One establishment that included a global dedicated second-generation process development group reported how, even in this case, a substantial part of the activities was carried out by staff of the central research groups:

> Basically, the way it actually works is that we are responsible for finding the second-generation products. We would identify where the needs are, because we work for manufacturing and then we find out what the solution is and we don't care where the solution is. […] It could be a research unit in [head quarters], or it could be ourselves. It depends on the complexity. […] We have done some [second generation process R&D]. (Manager global process development unit, AI plant, firm 5, 2006)

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.

Figure 6 breaks down the data between drug substance and drug formulation establishments. Five multi-location companies which produced both substances and formulations were excluded from the analysis. The data suggest that there is no strong link between sub-sector and level of involvement. For most categories, the differences in the average level of involvement of the two groups of establishments were relatively small. The largest differences occur in the areas of 'equipment design' (0.9 points) and 'evaluation of route/process options in the kilo lab' (0.8 points), with drug substance establishments scoring higher in both cases. However, there is no obvious pattern in the differences, with the drug substance companies having a greater involvement in eight of the categories and drug formulation companies having a greater involvement in five.

[Insert Figure 6 about here]

4.4 The sophistication of the process R&D in Ireland

The education profile of staff involved in process R&D can be used as an indicator of the quality or sophistication of the process R&D activities being carried out in Ireland. The survey shows that the process R&D activities in the Irish pharmaceutical industry employ a substantial number of highly skilled people. Overall, 30 per cent of the 800 people involved held a PhD as their highest level of academic attainment, 19 per cent held a Masters degree, while a further 46 per cent held a third-level degree.

The number of PhDs varied considerably between companies. One third of the companies did not employ a single PhD in process R&D while another third employed more then 3 PhDs, including one company which employed 40. The number of PhDs employed is partly a reflection of the size of the overall operations.

But even when we control for overall establishment size, the numbers vary substantially. Figure 7 presents the numbers of PhDs as a percentage of all staff employed per establishment in 2006. In the great majority of cases the number of PhDs in process R&D accounted for less then 3 per cent of all staff. In 11 per cent of the companies PhDs accounted for between 5 and 10 per cent of staff while in two companies they made up as much as 13 per cent of staff.

[Insert Figure 7 about here]

[Insert Figure 8 about here]

The number of PhDs involved in process R&D varied strongly by sub-sector, with drug formulation plants tending to employ fewer numbers than active ingredient plants. Figure 8 shows that half of the drug formulation plants did not employ a single PhD in process R&D, compared to only four per cent of the active ingredient plants. At the other end of the scale, two thirds of the active ingredient plants employed 3 or more PhDs in process R&D compared to only 14 per cent of the drug formulation plants. Thus, although the previous section showed that the two sub-sectors tend to be involved in the same, final, stages of the process R&D cycle, in the active ingredient sub-sector these stages tend to involve staff with a higher level of education.

4.5 Evolution of process R&D

Section 4.2 showed that the number of people involved in process R&D has grown in a substantial number of establishments and that employment in process R&D has grown faster than total employment in the pharmaceutical companies. This section investigates the evolution of the process R&D activities in terms of the actual scope of the activities and the role of the Irish establishments.

The interviews confirmed that the greater role of Irish subsidiaries in process R&D was primarily driven by global changes in the competitive and technological environment since the 1980s (Van Egeraat, 2007*).* As pointed out earlier in the paper, pharmaceutical companies have come under pressure to increase efficiency in R&D and have located process R&D activities near branch plants to facilitate integration of, and communication between, the process R&D function and the manufacturing operations. In most of the Irish subsidiaries the greater role did not develop overnight, however. The interviews showed that, although some, more recently established, operations have been involved in a relatively broad range of process R&D activities from the start of operations, the evolution of the role of most establishments is characterised by incremental upgrading.

Most interviewed plants had a very limited role in process R&D at the time of establishment. Typically, involvement in process R&D originated from a manufacturing support or technical services unit such as can be found in most pharmaceutical plants. Over time these units increased their involvement in a range of process R&D activities, notably continuous improvement, and technology-transfer-related activities such as running of validation batches and optimisation. This typically was a gradual process which typically led to the formation of a separate group within technical services or the establishment of a separate process development unit. “It gets to a state where you give it a name” (Manager Process Technology Unit, formulation plant, firm 8, 2006).

In some cases such upgrading was followed by the establishment of a pilot plant, which would typically have had multiple functions. It would have served as a trouble-shooting facility to facilitate the continuous improvement and optimisation activities, and as a production unit for clinical trials. These developments, in turn, have in some cases led to an earlier and more substantial involvement of local staff in the up-stream stages of the process R&D cycle. Local establishments that have reached this level of involvement and mandate are typically considered as one of the few 'strategic sites' in the global network of the company, with responsibility for new product launches. In a very small number of cases such developments have been followed by the establishment of units involved in activities at an even earlier stage of the process R&D cycle, such as pre-formulation research units, or units with a greater geographical mandate (for example facilities to develop second-generation processes for the global network). Such units are typically part of the global R&D organisation of the company.

Most of the longer-established subsidiaries have experienced an incremental upgrading process over time. This might suggest that, at least initially, the local host country environment and local subsidiary management have played an important part in driving the changing role of the Irish subsidiaries in process R&D by actively working towards upgrading the local factor conditions and competence/capabilities of subsidiary staff. However, interviewees typically gave evidence of comparable upgrading of process R&D activities at several other (strategic) manufacturing establishments in the companies' global production networks. This suggests that the primary driver for the greater involvement of Irish subsidiaries lies in the changing global competitive and technological environment and the related corporate response.

4.6 A case study of the evolution of process R&D activities

This sub-section presents a case study of how the process R&D function has evolved in one pharmaceutical company based in Ireland. The firm in question is a subsidiary of a global UK/US-based pharmaceutical company, formed from a recent merger. In the rationalisation process that followed the merger, the number of manufacturing sites was reduced from 108 to 80. The company now operates 13 active ingredient plants in a range of countries, two of which (those in Ireland and Singapore) are considered "strategic", i.e. responsible for the introduction of new product out of the R&D pipeline and the global supply of key substances to the drug product plants. Each of these two plants is responsible for about one third of the company's active ingredients output. R&D is conducted in over 20 sites worldwide. The number of sites and their locations are partly a legacy of the strong merger and acquisition history of the company. Chemical process R&D is strongly concentrated at two main locations in the UK and the USA. One of these chemical R&D groups (UK) employs about 250 staff. Some decentralisation occurred in the 2000s with the establishment of two new pilot plants at the strategic substance manufacturing sites, firstly in Ireland and later in Singapore.

The Irish subsidiary was established in the mid 1970s as a drug substance manufacturing plant. For a long time the plant was responsible for the production of one of the main blockbuster products of the company. Production was supported by a typical technical support team of eight people. During the 1990s, this group steadily

increased its process-development-related activities. In the early 1990s it began to work on process optimisation. From 1994 on, more and more new products started to be introduced in the plant and the facility was designated as the principal strategic site for drug substance manufacturing in the company's network. To facilitate this, the technical support team increased its involvement in technology transfer and the running of validation batches. By the end of the 1990s, the team had grown to 20 staff.

In the second half of the 1990s, the UK-based chemical development (R&D) division, in partnership with the manufacturing organisation, decided to establish a pilot plant at the Irish manufacturing site. This came on stream in 2001. The pilot plant is used for the manufacture of clinical trial material and for the development of chemical processes. The first of these functions is carried out by locally-based operators from the chemical development organisation. The second function is carried out by teams made up of staff from the synthetic chemistry organisation and the now renamed "technical operations" group. Although the pilot plant is located in Ireland, many of the staff of the chemical development organisation, working on pilot development, are actually based in the UK/USA. Each time they decide to put a new product into the Irish pilot plant, UK/USA-based staff come over to Ireland to conduct work on the process in conjunction with local chemists and engineers seconded from the technical operations group. Due to seamless links with the central development groups, including remote tuning of research equipment, elements of the development work and data analysis in the pilot plants can actually be conducted from the UK/USA. Although it is a team effort, much of the actual development work is in the hands of the UK staff. Typically staff from the local technical operations group take a very active involvement towards the end of Phase III when a technology transfer team is put in place to move the process into the commercial manufacturing plant. The pilot plant was further expanded in 2004 and now employs 25 staff, made up of 12 technical staff and 13 operators.

At the beginning of the 2000s, the technical operations group increased its involvement in process redevelopment of the drug substance (second generation). Redevelopment is again a team effort involving the manufacturing and R&D organisations. However the second-generation project is 'owned' by the technical operations group in the manufacturing organisation. This group also carries out most of the development work. This work required an expansion of the local skills set, notably in the area of physical properties of the drug substance, synthetic chemistry and engineering scale-up. In 2004 a new physical properties laboratory was established to accommodate the 10 additional researchers.

In 2004 the role of the Irish subsidiary was further expanded with the establishment of a pre-formulation facility for drug products, employing a further 10 staff. The activities are as much related to drug product development as they are to active ingredient development (and both types of sites were considered as a location). But due to the specific technology involved, it was deemed to be more appropriate to have this particular part of the formulation development on an active ingredient site.

So, over a period of 15 years, the process R&D activities of the Irish facilities have been significantly enhanced. From a situation where there was no involvement in process R&D at the start of the 1990s, by 2005 the Irish subsidiary had a core

development group of about 40 people (not including about 10 operators in the pilot plant and a further 10 staff for technical support of the commercial plant) involved in various aspects of the process R&D cycle. The qualifications of the staff suggest a high level of value creation - 38 of the 40 staff in the core group have a PhD degree.

Yet, even in this success story, the involvement of the Irish staff mainly concerns the final phases of the process R&D cycle. The early stage active ingredient process research and process development work for new substances is in the hands of staff based at the central active ingredient R&D sites in the UK and USA.

5. Conclusions

For a long time the pharmaceutical industry in Ireland had a strongly truncated character, dominated by foreign branch plants focussing on production with little control or R&D functions. The Irish government has specifically identified process R&D as an opportunity for higher value-added activities in the industry. This was inspired by evidence that multinational pharmaceutical companies are changing the organisation and spatial configuration of their internal process R&D activities. Since the 1980s, confronted with changes in the global competitive and technological environment, pharmaceutical companies have come under pressure to increase the efficiency in process R&D. Part of the answer is sought in a greater co-ordination between the various R&D activities as well as between R&D and other functions, including manufacturing and sales. Anecdotal evidence suggests that, in an effort to facilitate the greater co-ordination with manufacturing operations, companies are increasingly locating process R&D activities at manufacturing branch plants.

The principal objective of this article has been to describe how the evolving nature and spatial configuration of process R&D in the pharmaceutical industry are reflected in the changing nature of process R&D activities of pharmaceutical enterprises operating in Ireland. In doing so the article has opened the “black box” of process R&D in pharmaceutical companies. It was shown that, far from being a uniform undifferentiated function, process R&D in the pharmaceutical industry comprises a wide range of activities that individually involve different tendencies in relation to decentralisation.

The results suggest that the Irish Government has been partially successful in its endeavour to promote process R&D activities in Ireland. Process R&D activities in Ireland have expanded rapidly with process R&D staff numbers growing at a substantially faster rate than overall employment numbers in the industry. In addition, more than half of the surveyed companies reported that they had concrete plans to expand their process R&D activities in Ireland over the following five years. However, the number of people employed in process R&D varies considerably from company to company. In addition, staff involved in process R&D are not necessarily working in dedicated process R&D units but are often part of other functions, notably production, technical support and quality control.

By unpacking the “black box” of process R&D, the study was able to show that, although Irish subsidiary staff, as members of global project teams, have at least some

involvement in most process R&D activities, this involvement only becomes substantial after the proof-of-concept point of the cycle, at the start of the phase III clinical trials. 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.

This focus on the last stages of the process R&D cycle does not necessarily discount the sophistication of the process R&D activities in Ireland - nearly all staff involved in process R&D hold a third-level degree and 30 per cent hold a Ph.D. Yet there are important differences between sub-sectors. Although there are no systematic differences between local active ingredient and drug formulation plants with respect to the level of involvement of staff in the various process R&D activities, active ingredient plants tend to involve staff with a higher level of education.

Most of the longer-established subsidiaries have experienced an incremental upgrading process over time. This might suggest that, at least initially, changes in the local host country environment and the actions of local subsidiary management have played a part in driving the changing role of the Irish subsidiaries in process R&D. However, in fact, the primary driver of this changing role is the changing global competitive and technological environment and the related corporate response.

The corporate response appears to involve a selective decentralisation of process R&D activities. Part of the explanation lies in the requirement for co-ordination between process R&D and product R&D. As discussed above, firms still tend to concentrate their high-level and innovative research at central laboratories in the core global regions for innovation. In this situation, decentralisation of process R&D to the branch plants may facilitate communication with manufacturing, but it will decrease the efficiency of face-to-face communication between staff involved in process R&D and staff involved in product R&D located in the core regions (see also Malecki, 1997).

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. On the other hand serious challenges remain in relation to the up-stream phases of the process R&D cycle. 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.

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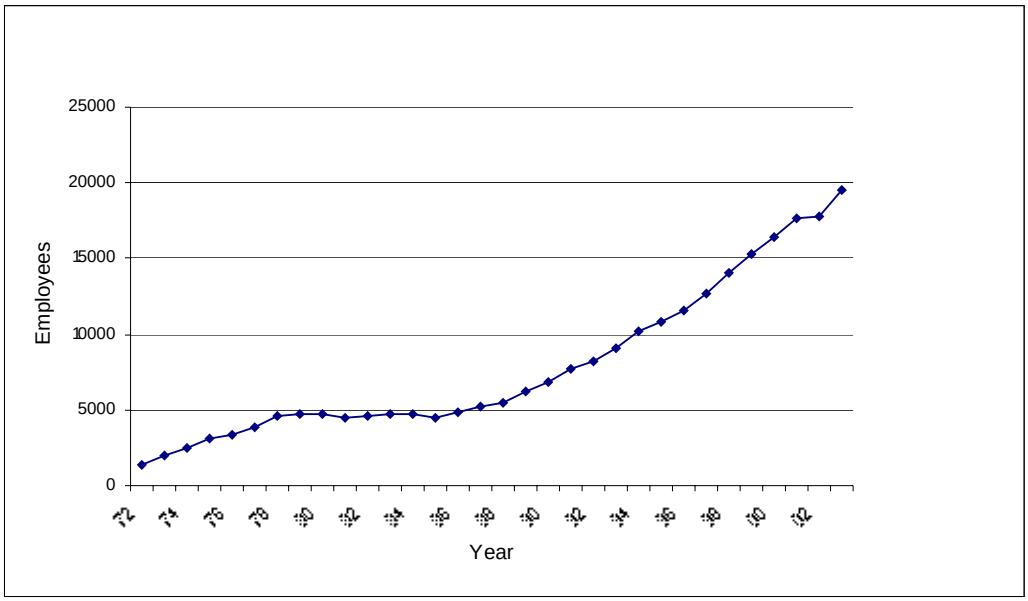
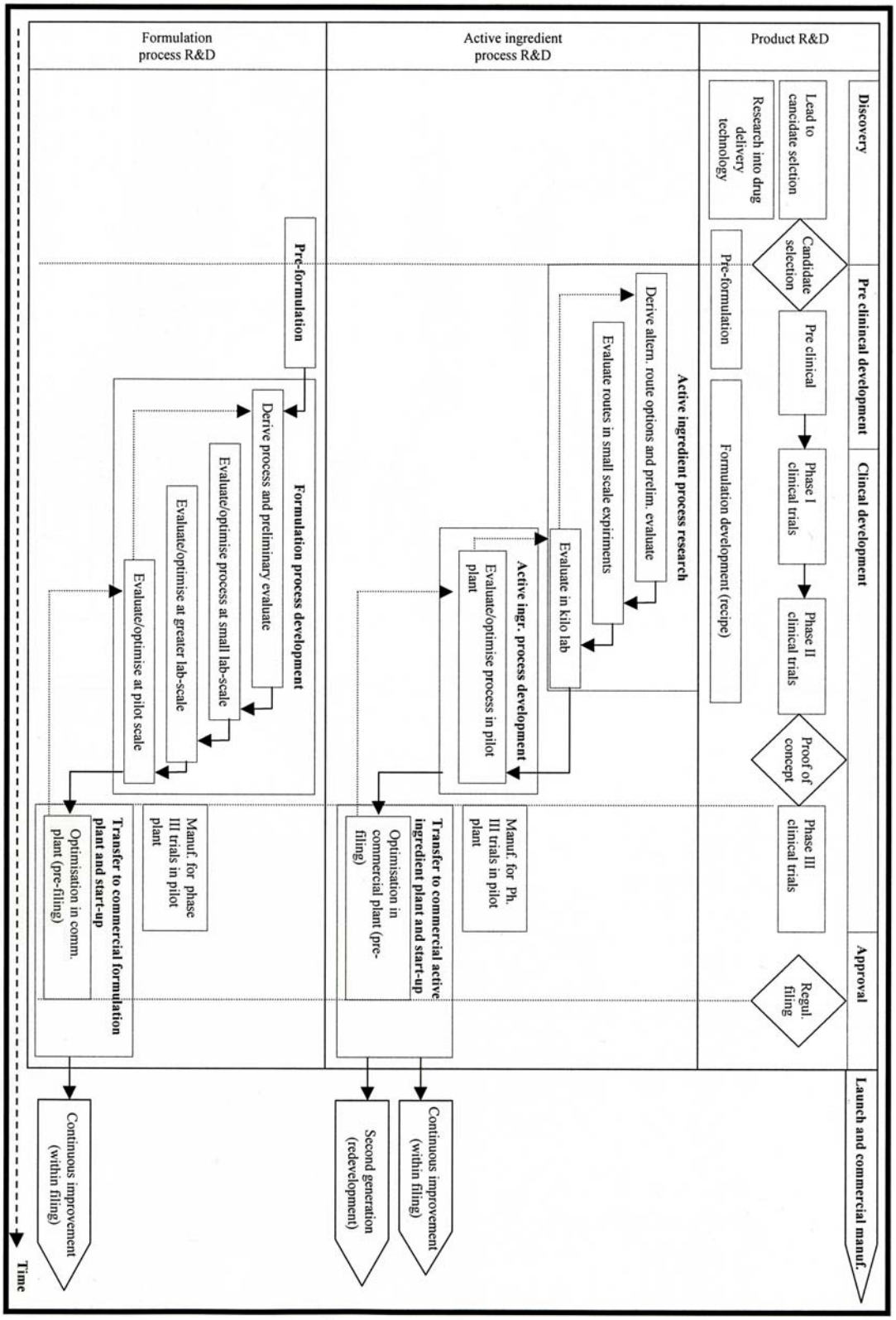
Figure 1: Employment in the Irish pharmaceutical industry 1972-2003



(Source: Van Egeraat, 2006)

Figure 2: Process R&D cycle for chemically synthesised drugs



Source: Van Egeraat, 2007

Figure 3: Number of persons employed in process R&D (percentage of companies in size category)

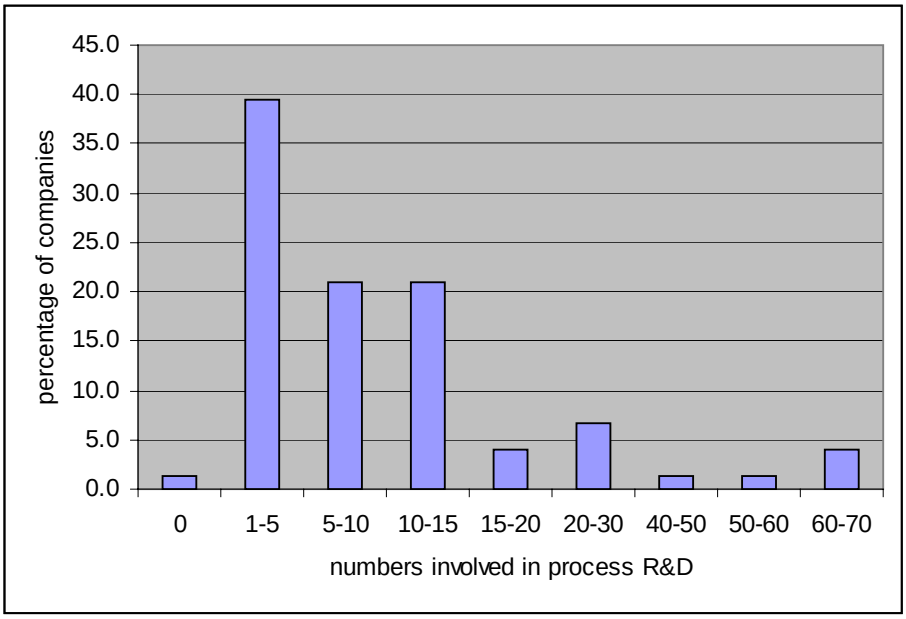


Figure 4: Growth in process development staff 2000–2006 (incumbent companies)

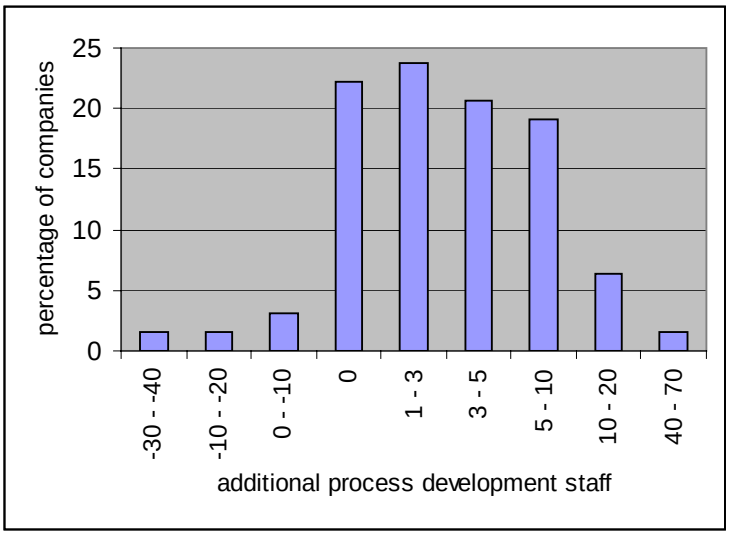
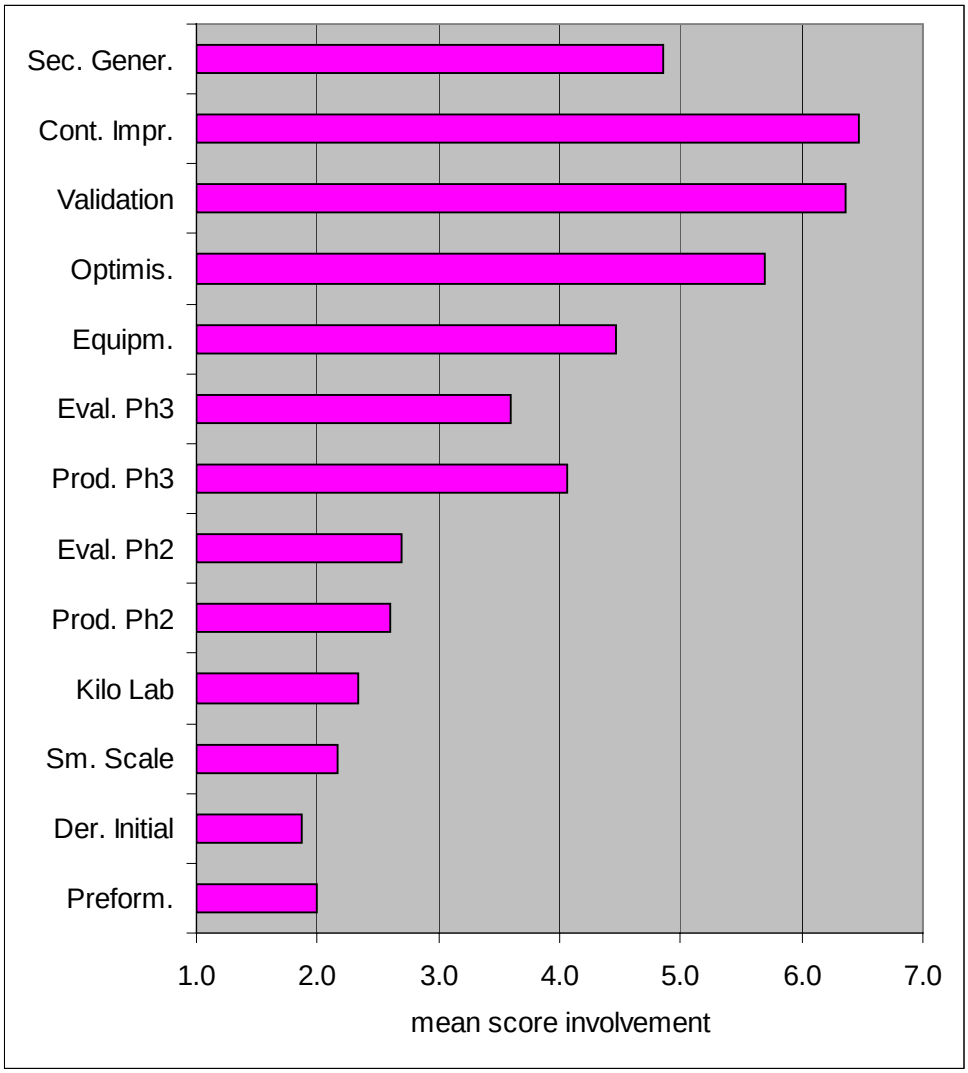
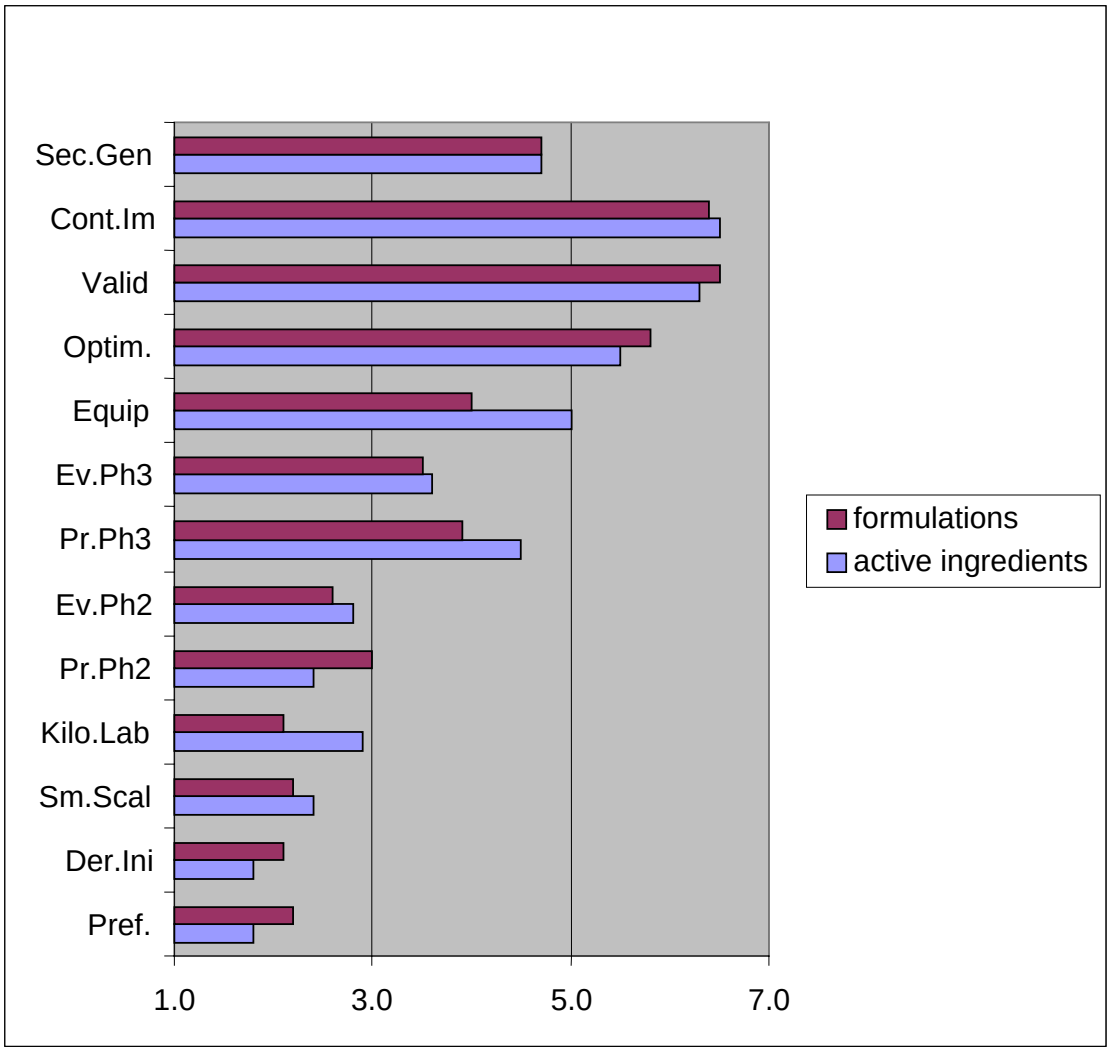


Figure 5: Involvement of Irish subsidiaries in process R&D activities



Notes:
a Average scores on a seven-point Likert scale (1 = no involvement; 7 = sole ownership)
b For full names of categories see text.

Figure 6 Involvement of Irish subsidiaries in process R&D activities by sub-sector



Notes:
a Average scores on a seven-point Likert scale (1 = no involvement; 7 = sole ownership)
b For full names of categories see text.

Figure 7: Ph.Ds in process R&D as a percentage of all staff

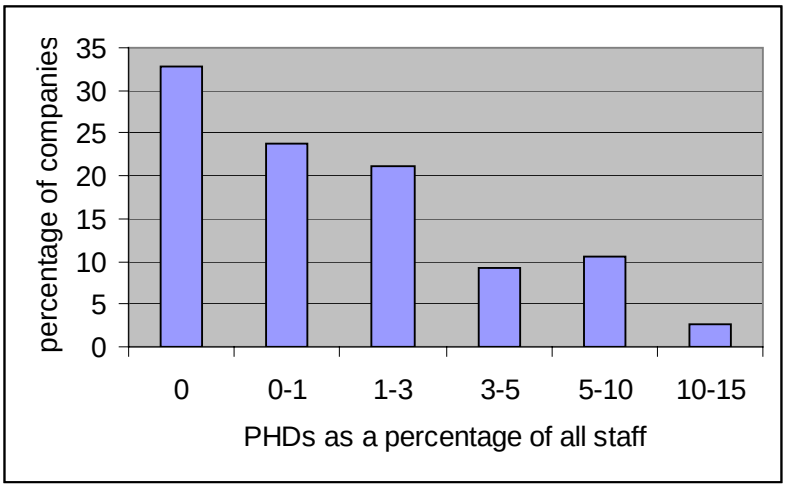
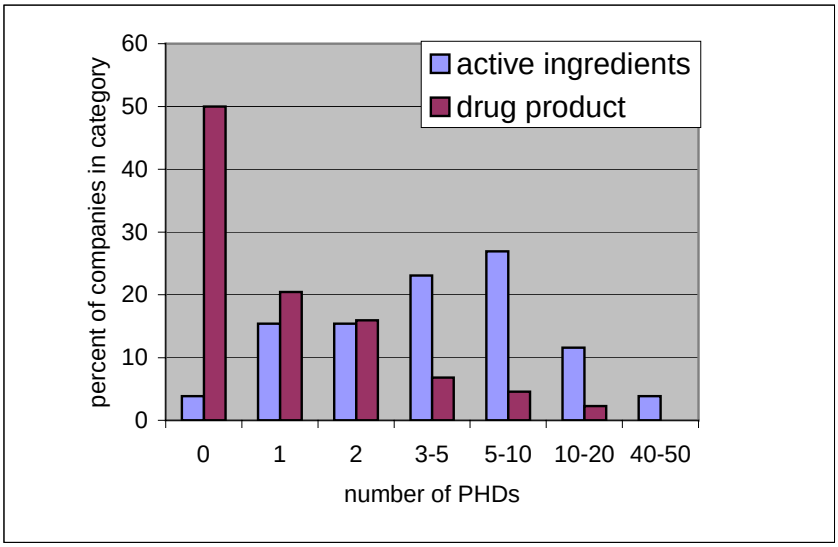


Figure 8: Number of PhDs in process R&D by sub-sector



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

[ii] Much of the literature tends to focus on the R&D cycle for active ingredients (see for example Pisano, 1997).

[iii] At a basic level some companies conduct ongoing research into new drug delivery technologies.

[iv] In addition, the results of the pre-formulation studies feed back into the chemical process research units in the drug substance R&D cycle (see below).

[v] Although, a particular disease or function can be targeted in different ways, using different proteins

[vi] For a more detailed report of definitional and recoding issues see Van Egeraat (2006).

[vii] No distinction will be made between bio-pharmaceutical drug substance plants and chemical drug substance plants during the discussion of the results. The scores for biopharmaceutical process R&D activities are treated as scores for the corresponding stage in the chemical drug substance process R&D

cycle. For example, the category “initial identification of potential cell lines” is related to the category “derive initial route/process options and preliminary evaluation (paper experiments)”.

[viii] The figure for 2000 does not include the employment of one company for which data are not available.