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Abstract

Developing new products and processes is increasingly a focal point of competition and often requires the development and successful implementation of novel process technologies. The process development and production of a new discovery (new biological entity) are significantly more complex than for the production of small molecule drugs or new chemical entities. Conventional new product development models in the literature on firm level innovation do not capture the evidence we present on development projects for pharmaceuticals. This paper shows why a new perspective is required to understand the management of product and process development for biopharmaceuticals and proposes an explanatory model for this purpose.

1 Introduction

Biotechnology is one of the fastest growing sectors in the global economy, especially as regards applications in the pharmaceutical sector, and has important implications for innovation theory and practice. While the analytical distinction between product and process innovations has proved very useful in engineering-based industries, in life science based activity the distinction is less clear cut. In this paper, we show the difficulties of trying to assign novel development in biopharmaceuticals either to the product innovation category or to the process innovation category, with reference to the transition between discovery and market launch.[1] We find that product and process innovation categories are fuzzy sets in biopharmaceutical innovation; a fuzzy set is one whose members belong to it *to some degree* (Zadeh 1965). It has become clear that in the biopharmaceutical sector, process development is an integral part of product development and that process innovation plays a key role in the transition of product from bench to market (Feldman & Ronzio, 2001; Pisano, 1997). But implications of these findings have not been fully assimilated in innovation theory and bio-manufacturing investment practice.

This article is organized in five parts. The first part provides an overview of biopharmaceutical development and the second examines relevant theoretical perspectives. In the third part, case study material is presented on the development process in new biopharmaceuticals. The fourth part examines the case material in the light of theoretical approaches. A new perspective for the understanding of biopharmaceutical development is proposed in the fifth part.

[1] This transition is referred to as 'licensure' for biologics and 'approval' for drugs (Vargo, 1998)

2 Overview of Biopharmaceutical Development

Biotechnology, is 'the application of scientific and engineering principles to the processing of materials by biological agents to provide goods and services" (OECD[2]). As an enabling technology, biotechnology can trace its origin to fundamental disciplines including biology, genetics, engineering, chemistry and computer science (OECD). Historically, biotechnology been involved in the production of wines, beers and cheese and has been viewed as an art as well as a science (Smith, 1996).

The advances in genetic engineering[3] and hybridoma technology made it commercially feasible to develop proteins with therapeutic applications in large quantities (Walsh, 1998). Biomedical research undertaken in 1950s revealed that a host of molecules produced naturally in the body have therapeutic applications (Walsh, 1998). They can now be produced in large quantities through the application of biotechnology principles. It is often assumed that innovative activity is concentrated at the drug discovery stage of the development process and can be readily separated from the volume production of the newly discovered drug. This assumption is congruent with findings from research on product and process innovation which are largely based on engineering industries rather than life science industries.

3 Theoretical Perspectives

Product development aims to improve the properties and performance of the finished product whereas process development is shaped by internal production objectives such as cost reduction and yields improvements (Lager, 2002; Pisano,1997). Thus product innovation is seen to shift the demand for the product whereas process innovation reduces costs and shifts the supply curve (Pisano, 1997). These issues can be approached from two perspectives. Industrial economics examines differences in patterns of innovation across countries and industrial sectors, the evolution of particular technology over time, and intra-sector differences in the propensity of firms to innovate. Research can also focus on the organisation, examining e.g. how specific products are developed (Brown & Eisenhardt, 1995).

[2] Biotechnology: International Trends and Perspectives, OECD, 1982

[3] Recombinant DNA technologies genetic engineering procedures used to join together DNA segments from different origins in an environment outside a cell or organism. This technique is perfected by Cohen and Boyer and used as a basis for much of the scientific progress that biotechnology has made in cloning cells and drug production

3.1 Industry Level – Life Cycle Model

Understanding the dynamics of process and product development in industry development and competition has been shaped by the work of Abernathy and Utterback (1978). Their model addressed product innovation, process innovation and the competitive environment both at the level of the organizational and in relation to the life cycle of the industry itself. They showed that during the emergence period, the rate of product innovation exceeds the rate of process innovation. When a dominant design emerges, companies focus on process improvement to optimize the cost and quality of the product (Figure 1a). The model was further developed by Utterback (1994) to incorporate innovation in process industries (Figure 1b). A brief review of this influential model will provide a basis for comparison with our findings.

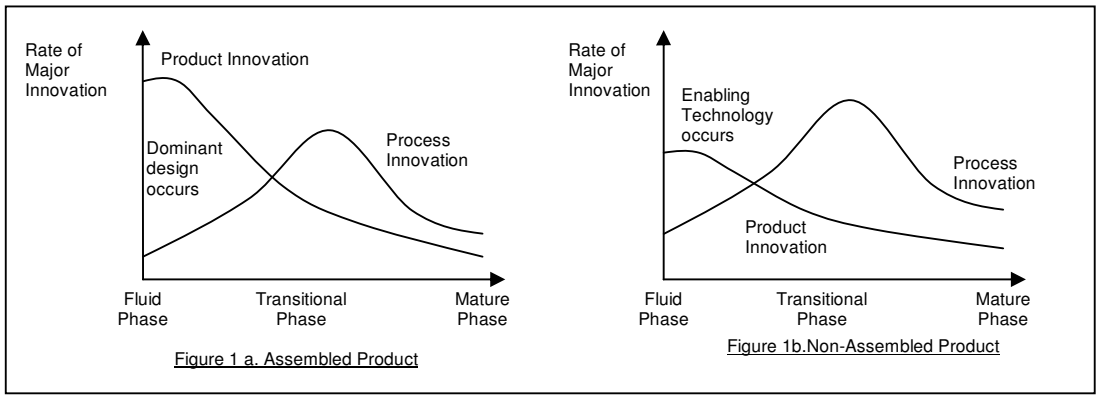

Figure 1: Patterns of Innovation (Utterback, 1994)

The emergence of a dominant design affects the characteristics of innovation of an industry and firms within it. In assembled products, a dominant design is a synthesis based on earlier technological innovations which emerges after a period of experimentation in both the production and functionality of the product. Once a dominant design emerges, other companies follow the new standard and seek economies of production (Utterback, 1994). In industries that produce output other than assembled products, an enabling technology is seen to emerge after a period of variation and experimentation in the production process. This allows the focus of technological effort to shift to process improvement rather than process innovation and design (ibid).

Thus the life cycle model presents an analytical distinction between product and process innovation at the industry level. In the case of assembled products, basic product concepts are formed in the early phase of the industry and once the dominant design emerges, opportunities for radical product innovation recede. Firms in the industry tend to produce similar products and

the competitive basis rests on process innovation to lower the cost of production. Outside assembled product industries, process innovation takes a different form, often resulting in a converging and continuous production process, through the elimination of production steps[4]. Utterback (1994) used the plate glass industry to illustrate this point.

3.2 Firm Level development Models

To move from industry to firm level, there is a large and growing body of literature on the management of new product development. The subject of process development for assembly-based industry is often included as part of the overall product development of process. However, researchers have been addressing the role of process development, especially in process industries (Pisano, 1997; Lager, 2002).

3.2.1 Conventional New Product Development Models

A comprehensive typology by Saren (1984) is relevant to our analysis. He categorized new product development models into five types (1) departmental-stage models (2) activity-stage models (3) decision-stage models (4) conversion process models (5) response models.

In *departmental-stage* models, product development process is based on 'pass-the-parcel' approach, with one functional group handing on to the next on completion of a task. Functions are specialized and segmented (Takeuchi and Nonaka, 1986). The departments or functions are held responsible for the various tasks carried out (Saren, 1984). The development project moves sequentially from phase to phase. One example of this model is the Phased Review Process developed by NASA in the 1960 (Cooper, 1994). It is now widely accepted that this form of project management is deficient in several aspects. First, overall control over the process is fragmented when sequences of tasks are isolated between departments. Second, this method is time consuming. Third, there is no clear ownership of new product by any department. Finally, there is no market feedback on the development process (Hard and Baker, 1994).

[4] "*This phenomenon (process innovation) in nonassembled product lines appears to be linked not to product change but major equipment innovations, often those that combine in one step operations previously done in two or three separate steps.*" Page xxii

Activity-stage models are an improvement on the concept of departmental-based models in that development stages are characterized by certain activities which are supported by relevant departments. Typically there is cross functional expertise involved in each stage. But in practice the development process is prolonged by the passing of tasks from one department to the next.

Decision-based models incorporate evaluation points between each stage of the process. This approach identifies feedback loops overlooked in previous models.[5] Many leading firms have accordingly developed a systematic stage-gate process: a road-map from idea to launch consisting of discrete stages, each stage preceded by a Go/ Kill decision point. These firms include DuPont, 3M, HP and Procter & Gamble (Cooper, 1994).

Conversion process models take a holistic view of new product development as a process by which input is converted into output, to avoid fragmented project management (Hart & Baker, 1994). Which conversion tasks are undertaken depends on the nature of the innovation (Cooper, 1982; Schon, 1967). The conversion process is influenced by human, organization and resource-related factors. This approach comes closest to depicting the evidence we have observed.

3.2.2 Firm level Process Development

At firm level, the extensive literature on new product development models is not matched by similar studies in process based industries, which are rare. Lager (2000) introduces two such models. The first involves four steps (1) Laboratory testing (2) Pilot plant testing (3) Trials in a demonstration plant (4) Production plant tests (See Figure 3). He emphasizes the complex and sometimes chaotic nature of process development in process based industries.

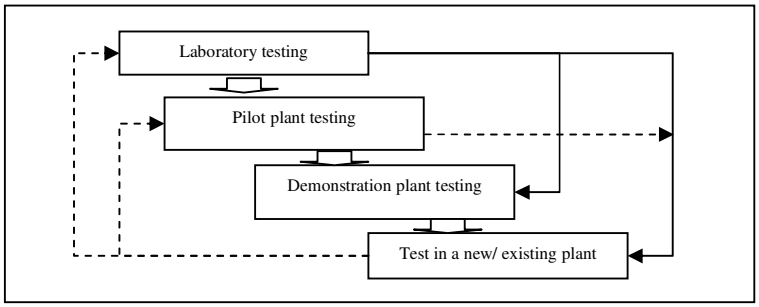

Figure 3: A traditional model for process development (Lager, 2002)

[5] A related approach is the response model which addresses reactions to such changes as new product ideas, or R&D project proposals in terms of acceptance or rejection (Hart and Baker, 1994).

The model depicted in Figure 3 applies to plant operations and does not deal with development projects. Another model, based on Utterback's work, is provided by Lager to deal with the management of product or process development projects and comprises three development phase (See Figure 4). This model does not show how process development might interact with product development.

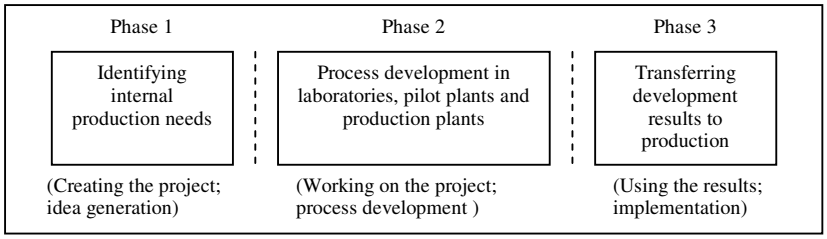

Figure 4: A conceptual model for the 'process development process' (Lager, 2000)

3.2.3 Firm level distinction between Product and Process Innovation

The innovation literature we have been examining does not address the interaction of product and process development. For example, the models of new product development do not show how product and process innovation can be synchonised. However, fast diffusing practices such as simultaneous engineering, cross-functional project teams, and design for manufacturability (Clark & Fujimoto, 1990, Ulrich & Eppinger, 2000) point to the importance of coordinating and integrating both process and product innovation.

Pisano (1997) offered a different perspective on the relations between product and process innovation from that provided in the literature based on engineering industries. He pointed out that the biopharmaceuticals industry is a process enabling industry, where both product and process technologies evolve rapidly and must be synchronized. The reasons for this emerge from the nature of biopharmaceutical production processes.

3.3 Biopharmaceutical Development and Production

3.3.1 Discovery

Biopharmaceutical development starts with the identification of an agent with a desired biological profile. At this stage a number of approaches are adopted. These approaches range

from random screening of a wide range of biological materials to knowledge based drug identification. Once a potential new drug is identified, it is then subjected to a range of tests, namely in-vitro and in animals in order to characterize it in terms of its safety and effectiveness in treating a disease (Walsh, 1998).

3.3.2 Clinical Development

Clinical development is done to gain approval for general medical use and to demonstrate the quality, safety and efficacy of any product (Walsh, 1998). The overall clinical development of biopharmaceuticals up to market entry generally follows a standardized process consisting of six stages (Bergeron et. al., 2001). These stages are discovery, pre-clinical, the three clinical phases (I, II, III) and finally the approval stage (ibid).

Trial Phase	Evaluation undertaken (and usual number of patients)	Average duration (year)
Phase 1	Safety testing in healthy human volunteers (20-80)	1
Phase 2	Efficacy and safety testing in small number of patients (100-300)	2
Phase 3	Large-scale efficacy and safety testing in substantial number of patients (1000-3000)	3
Phase 4	Post marketing safety surveillance undertaken for some drugs which are administered over particularly long period of time (number of patients vary)	Several years

Table 1: The clinical trial process (Walsh, 1998)

Preclinical studies involve mainly pharmacological and toxicological assessment of the potential drug in animals. Phase 1 trials involve measuring the tolerability and pharmacokinetics of the drug in healthy humans. Phase 2 trials are carried out on a limited number of patients with the specific conditions. The aim of this study is to identify the most appropriate dose, and to make an early assessment of whether the drug is effective for the proposed indication. Phase 3 trials provide evidence of the safety and efficacy of a drug by studies in a large cohort of patients. Data from Phase 3 trials is important and typically forms the basis of the application to the regulators for approval to market the product. The final phase is post marketing surveillance, which is sometimes referred to as Phase 4 trials. This phase is conducted for some drugs especially those administered for a long period of time (Walsh, 1998).

3.3.3 Process Development and Production

The bulk of biopharmaceuticals are produced through genetic engineering. A recombinant "production system" is created, consisting of a genetically modified host cell (Smith, 1996). These "production systems" involve either microbial fermentation or processes involving mammalian cell culture. The principles behind the large scale production processes of drug substances are derived from traditional fermentation technology which uses microorganisms for the production of required substances (Smith, 1996). Fermentation involves a multitude of complex enzyme-catalysed reactions within specific microorganisms and hence is critically dependent on the process conditions and environment. The process technologies of at this stage of production (upstream) are essentially based on growing large numbers of cells under controlled conditions. These organisms must be cultivated in an optimum condition to form the desired products.

Extraction and purification of desired proteins from the fermentation broth represents a large part of the overall production process of biopharmaceuticals (Smith, 1996). During the extraction and purification stage (downstream), production processes are primarily concerned with initial separation of the bioreactor broth and subsequent concentration and purification of the desired product (Walsh, 1998). The role of these processes is crucial in determining the final characteristics of the product such as purity and stability (Walsh, 1998).

3.3.4 Biopharmaceutical Development Challenges and Goals

Preclinical trials, clinical trials and product launch require the production of sufficient quantity and quality of product. The material used for pre-clinical and clinical trials should be produced using the same process by which it is intended to undertake final-scale commercial manufacture (Walsh, 1998). As such, extensive early development work is essential and the process developed be scalable and yields be improved. Any significant deviation from the production protocol used to generate the trial material could invalidate the clinical trial results, because changes in the production process could potentially change the final product characteristics.

4 A Case Study – Development of a Novel Biopharmaceutical

We now turn to evidence on product and process innovation from a biopharmaceutical case study.

Product X is a virus vaccine which is able to protect the host without risk of infection through multiple-cycle replication because it lacks a gene. The breakthrough in the discovery of Product X promised attractive clinical applications. There was no pre-defined drug production process. As such, Company X had to develop a new, economically viable production process to make available supplies of the product for necessary development work as well as supplies of a marketable drug at a later stage[6].

In the course of the development project, three key processes (Process A, B and C) were developed. Process A was developed during the initial stage of the development project and used to produce materials for the first part of Clinical Trial 1. Process A is based on cell growth technology, on the surface of roller bottles and a simple harvesting method. This method of production is not complex but yields Product X only at a low concentration. Subsequently, data from Clinical Trial 1 called for a higher concentration. Therefore, Company X had to modify Process A or develop a new process to meet the requirement. Process B was developed to yield a higher concentration of Product X. Process B was used for the supply of Product X for the later part of Clinical Trial 1 and for Clinical Trial 2. Although, Process B is also based on roller bottle cell growth technology, modifications were made to the downstream process. The new Process B yields Product X at a higher concentration. Process A and Process B were based on roller bottle method of production. This method of production is simple, requires low upfront investment and is suitable for development work. However, upon consideration of the potential market demand for Product X, it was decided that the roller bottle method of production was not the preferred option for a larger scale production in the long-term for the following reasons. First, roller bottle production is labour intensive. Second, it produces low yields. Third, it is not scalable (a liter of fermentation broth of microcarriers in liquid suspension is equivalent to approximately 100 roller bottles). Process C was developed to meet the demands of a larger scale production. The company intended to use Process C for the supply of materials for Clinical Trial 3 and subsequently for the market when the product is launched. Process C is based on

[6] Product B failed during clinical trial 2. However, the process development and manufacturing team developed the third process for the anticipation of Clinical Trial 3 and for subsequent in-market supplies.

cell growth on the surface of microcarriers in liquid suspension. This method of production delivers higher yields per ml of fermentation broth and is more scalable. The case summary is presented in Table 2.

	Phase 1	Phase 2	Phase 3
Development Goals	Development for the supply of early stage clinical trials	Development of a process that would yield higher concentration of product	Development of a process for large scale production of materials for late stage clinical trial and for commercial application
Clinical Trials	Early part of clinical 1	Later part of clinical 1 and clinical 2	Clinical 3
Process Design	Cell growth on surface of roller bottles	Improved cell growth condition on surface of roller bottles	Cell growth on surface of microcarriers
	Scraping cells of the roller bottles and using centrifugal sucrose gradient for separation, harvesting cells using syringe	Membrane filtration, and simple formulation methods	Diafiltration and concentration method, freeze drying
Product Specification and Yield	Low virus titre[7] limited by process	Higher virus titre limited by process	Virus titre not limited by process
Resources	In-house development	Partnership with large pharma	Partnership with large pharme
	Process development FTE[8]: ~12 Project FTE: ~20	Process development FTE: ~15 Project FTE: ~25	Process development FTE: ~30 Project FTE: ~50
Business Plan/ drivers	Cost is not a major consideration	Cost/ price of output becoming important	Cost/ price of output very important
	Development time crucial	Development time still important	Distribution and marketing issues become relevant

Table 2: Case summary

[7] Virus titre is a measure of the concentration or activity of the vaccine
[8] FTE: Full Time Equivalent of an employee

5 Discussion

In this case, product and process development cannot be viewed as discrete activities. New chemical entities can be characterized by their chemical identity, but biological molecules are far more complex, context-specific and difficult to specify. As a response to these difficulties, the process used to produce a particular batch of product is actually used for product definition and its specification is used for licensure application and regulatory purposes in the biopharmaceutical industry (Lubiniecki and Vargo, 1994).

The distinction between product and process development is analytically useful and has helped to advance innovation theory when applied to engineering based industries. But perspectives in the literature derived primarily from engineering-based industrie can be misleading when transferred to the biopharmaceutical industry, underpinned by the life sciences. The key concept of 'enabling technology' - as analogous to dominant design in product-based industries - is useful for explaining innovation in process-based engineering industries, but is not sufficient to explain production processes drawing on the life sciences. There are important enabling biotechnologies, including the use of recombinant DNA and hybridomas, but these are generic technologies with a multitude of specialized applications. When attempts are first made to turn a molecular discovery into a drug, new processes must be developed and relatively little is known about their properties and dynamics. This is illustrated by the case study evidence.

We observe a multi-phased development path. During the development of Product X, distinct objectives were set at the beginning of each phase. From one phase to another, development resources in terms of people, skills and equipment changed considerably. There was a repeated need for innovations in process that were quite radical in terms of discontinuity from previous practice. These innovations were not only drivers of the economics and yields of the process but also altered the product characteristics. Conventional new product development models like those summarized in Table 3, which tend to characterise development stage as sequential steps from concept development through to ramp up, are misleading when applied in this context.

New Product Development Stages	Wheelwright and Clark (1992)	Cooper (1994)	Allen (1993)	Schilling and Hill (1998)	Gerwin (1993)
Conceptual	Concept Development	Preliminary investigation	Product concept definition	Opportunity identification/ Concept Development	Investigation of new technology
Planning	Product Planning	Build business Case	Program definition	Product Design	Initiate new product program
Implementation	Product/ Process Engineering	Development	Program implementation	Process Design	Formal product concept & prototype
Industrialisation	Pilot Production/ Ramp-up	Test and validate	Industrialisation	Commercial Production	Testing, pre-production and ramp-up

Table 3: Stages in New Product Development Processes (Source: Wheelwright and Clark (1992), Cooper (1994), Allen (1993), Schilling and Hill (1998), Gerwin (1993))

Key questions on the managerial aspects of biopharmaceutical development remain unaddressed. For example: What are development steps and stages? How should performance be measured? These raise further questions about best practice in managing biopharmaceutical development projects. A new approach is needed to understand the management of development projects in this life science based industry. It is characterized by discontinuous innovations very different from those in engineering industries such as automobile and plate glass production.

6 A New Perspective

6.1 The Development Cycle

Biopharmaceutical development usually involves novel techniques which were previously untried. There is considerable uncertainty in the process technologies, shown in the discontinuity of process development efforts in the development project. The iterative mode of the process development activity is conveyed by the concept of 'development cycles'. The development cycle involves agreeing and formulating objectives for the process design, taking into account the aims of the development, the resources available and the clinical milestone to be met at the particular phase. A development cycle represents a distinct decision making phase in the overall product development project driven by some "primary objective".

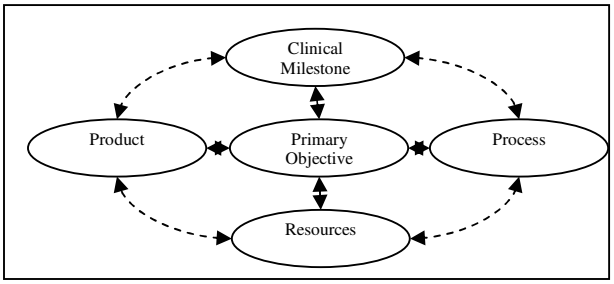

Figure 5: A Development Cycle

6.2 The Development Path

Because most pharmaceutical development consists of new and untried techniques, the development process is iterative. In contrast with development paths of other products described in the current literatures, the primary objective is continually revised as more is learned about very new technologies and markets. Conceptually the overall development project of biopharmaceutical can be represented by Figure 6. On completion of the development work, the product and process may look entirely different from those the team started with. For example, the molecular structure is altered unpredictably by the scaling up process. In the case of Product X, by the end of the development project, the production process had been transformed as compared with that used initially. The product was also different in terms of the concentration and activity of the vaccine (virus titre).

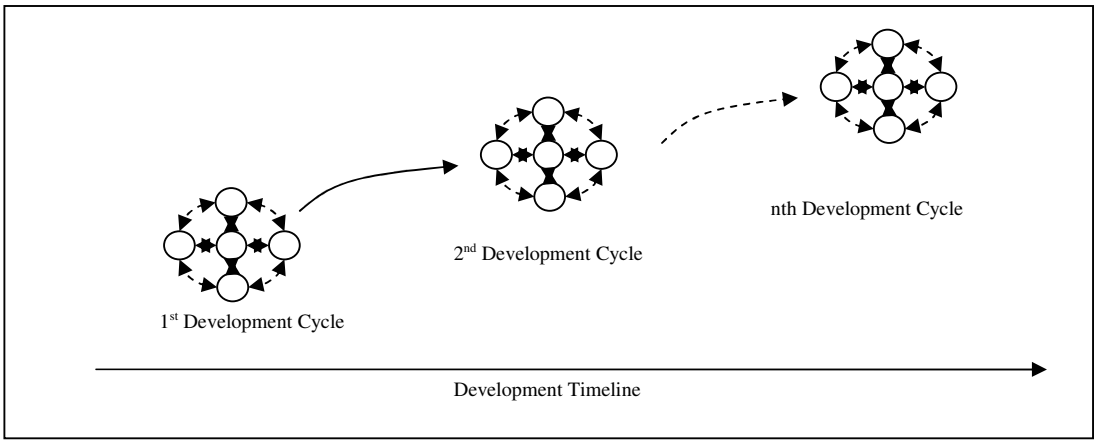

Figure 6: A multi-phase development path

6.3 Summary and Further Work

We have explored the difficulties of trying to assign novel development in biopharmaceuticals either to the product innovation category or to the process innovation category, with reference to the transition between discovery and market launch.[9] In the innovation literature, product and process innovation are addressed at an industry level where they are viewed as different in characteristic and roles. We argue that this view can be misleading when applied to the biopharmaceutical industry. At the firm level, we observed that the development path of biopharmaceutical is multi-phased and interlinked in ways that conventional new product development models do not allow for. A different approach is needed for the management of biopharmaceutical development and strategy.

We offer a development model showing how product and process innovation develop in conjunction with each other. This raises issues of development; how do these activities interact with each other and evolve along a development path? The implication of these activities for the design of business models requires further investigation. The difference in development paths for novel products will be contrasted with products with expiring patents (bio-generics). The context in which bio-generics are developed is different from that of novel biologics. For example, the regulatory milestones and requirements to obtain licensure are not identical to those of from novel biologics. In addition, business models and competitive strategies of bio-generics firms tend to be different from businesses competing on the basis of novel discovery, development and production of new biological entities. We conclude by raising some salient issues for business models of biopharmaceuticals companies.

7 Implication for Business Models

In place of a dichotomy between product and process innovation in the biopharmaceutical industry, we would emphasise a distinction between two other aspects of innovation, namely technological innovation and innovation in business models. Business models are an important dimension of innovation, offering new ways to organize the creation, delivery and capture of value. For example, licensing models and marketing models in the semi-conductors and PC sectors have proved important sources of innovation. There are many types of business model in the biopharmaceutical industry, reflecting differing strategic perspectives and realities. The main

[9] This transition is referred to as 'licensure' for biologics and 'approval' for drugs (Vargo, 1998)

variants include (1) Specialised discovery based business models (2) Discovery and development models (3) Hybrid models (4) Fully integrated drug production models (Garnsey 2003 p.114) The idea that new ventures should use the principle of comparative advantage to specialize in drug discover (product innovation) while established companies specialize in producing and scaling up the drug (introducing suitable process innovations), has been widely accepted as best practice. The distinction is congruent with influential theoretical perspectives that posit a sharp distinction between product and process innovation and view product development as made up of distinct and sequential stages. However there are implications for strategy in our findings in that biopharmaceutical activity, product and process development activities are interlinked. During the development of at least some biologics, product and process innovation advance in iteration. In the case investigated, the process constitutes the product. Industry regulations indicate that the nature of the drug required for efficacy can only be known through detailed process development. Our observations support evidence presented by Feldman and Ronzio (2001) who found that US biotech entrepreneurs preferred to own and control their manufacturing facilities if funding permitted, because they saw disadvantages in separating advances in product innovation from advances in processes. Production experience in biopharmaceuticals provides a source of knowledge that supports effective product-process innovation. How sound are business models based on a false dichotomy between product and process innovation? Dividing bio-processing activities from R&D in separate businesses may inhibit the development of the kind of scientifically grounded but practical expertise required for knowledge-intensive bio-processing. This issue points to a further agenda for research.

8 References

Abernathy, W.J and Utterback, J.M (1978). “Patterns of Industrial Innovation.” Technology Review 80(7):2-9.

Allen, D. (1993). Developing Successful New Products. London, Financial Times.

Bergeron, M. Y., L. Kryzanowski, et al. (2001). "Estimation of capital requirements for the therapeutics sub-segment of the Canadian biotechnology industry." International Journal of Biotechnology **3**(3/4): 362-37.

Brown, S. L. and K. M. Eisenhardt (1995). "Product Development: Past research, present findings, and future directions." Academy of Management Review 20(2): 343 - 359.

Clark, K. B. and T. Fujimoto (1990). "The Power of Product Integrity." Harvard Business Review Nov-Dec: 107-118.

Cooper, R. G. (1982). "New Product Success in Industrial Firms." Industrial Marketing Management 11: 215-223.

Cooper, R. G. (1994). "Perspective: Third-Generation New Product Processes." Journal of Product Innovation Management: 3-14.

Cooper, R. G. (2000). "Product Innovation Strategy." Research-Technology Management.

Garnsey, E. (2003). "Developmental conditions of UK biopharmaceutical ventures." Innovation: management, policy and practice 5: 99-119.

Gehani, R. R. (1992). "Concurrent Product Development for Fast Track Corporation." Long Range Planning 25(6): 40-48.

Gerwin, D. (1993). "Integrating Manufacturing into the Strategic Phase of New Product development." California Management Review Summer: 123-136.

Gerwin, D. and N. J. Barrowman (2002). "An Evaluation of Research on Integrated Product Development." Management Science 48(7): 938-953.

Hard, S. J. and M. J. Baker (1994). "The Multiple Convergence Processing Model of New Product development." International Marketing Review 11(1): 77-92.

Lager, T. (2000). "A new conceptual model for the development of process technology in process industry." International Journal of Innovation Management 4(3): 319-346.

Lager, T. (2002). "Product and process development intensity in process industry: A conceprual and empirical analysis of the allocation of company resources for the development of process technology." International Journal of Innovation Management 6(2): 105-130.

Lager, T. (2002). "A structural analysis of process development in process industry." R&D Management 32(1): 87-95.

Lubiniecki, A. S. and S. A. Vargo (1994). Regulatory Practice for Biopharmaceutical Production. New York, Wiley-Liss.

OECD (1982). Biotechnology: International Trends and Perspectives.

Pisano, G. (1997). "The Development Factory." Harvard University Press.

Saren, M. (1984). "A classification of Review Models of the Intra-firm Innovation Process." R&D Management 14(1): 11-24.

Saywell, T. (2003). Ambition in A Test Tube. Far Eastern Economic Review: 32-36.

Schilling, M. A. and C. W. L. Hill (1998). "Managing the new product development process: Strategic imperatives." Academy of Management Executive 12(3): 67-81.

Schon, D. (1967). "Champions for Radical New Inventions." Harvard Business Review(March-April): 77-86.

Smith, J. E. (1996). Biotechnology. Cambridge, Cambridge University Press.

Strauss, A. and J. Corbin (1998). Basics of Qualitative Research, Sage Publication.

Struck, M. (1994). "Biopharmaceutical R&D Success Rates and Development Times." Bio/ Technology 12: 674:677.

Takeuchi, H. and I. Nonaka (1986). "The new new product development game." Harvard Business Review Jan-Feb: 137-146.

Ulrich, K. and S. D. Eppinger (2000). Product design and development. Boston, London, Irwin McGraw-Hill.

Utterback, J. M. (1994). Mastering the Dynamics of Innovation, Harvard Business School Press.
von Hippel, E. (1994). "'Sticky Information' and the Locus of Problem Solving: Implications for Innovation." Management Science 40(4): 429-440.

Walsh, G. (1998). Biopharmaceutical: Biochemistry and Biotechnology, John Wiley.

Wheelwright, S. C. and K. B. Clark (1992). "Competing Through Development Capability in a Manufacturing-Based Organization." Business Horizon: 29-43.

Wheelwright, S. C. and J. W. E. Sasser (1989). "The New Product Development Map." Harvard Business Review May-June: 112-120.

Yin, R. K. (1994). Case study research: design and methods, Thousand Oaks: Sage Publications.

Zadeh, L. A. (1965). "Fuzzy Sets." Information and Control 8: 51-52.