Decisions of Pharmaceutical Firms for New Product Development

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ABSTRACT

This paper examines the new product development decisions of firms in the pharmaceutical industry over the period 1985-96. Firms choose from a variety of development alternatives. The traditional and predominant development process in this industry has been integrated or in-house development. More recently, however, firms have undertaken non-integrated routes for new drug development. These less integrated methods include: (1) Development via a merger or acquisition, (2) Development through a joint venture or strategic alliance, and (3) Development with a patent license. Strategic alliances and joint ventures in particular have attracted increased attention in the trade press. This paper describes an economic model that incorporates the most important considerations influencing an innovator's choice among these alternatives, and derives estimable equations for this development decision.

We are able to consider the impact of several firm and drug characteristics correlated with uncertainty, asymmetric information, appropriability, and potential synergies upon new product development decisions. We find that a firm's patent stock, number of previous approved drugs and the complexity of the disease that a new product targets significantly affect the decision process. Additionally, contrary to what has been portrayed in the popular press, after controlling for firm and drug characteristics, we do not observe a significant industry shift towards non-integrated development of ***marketed drug products*** through the end of 1996. These findings are robust to a variety of model specifications.

I. Introduction

On March 29, 1991, Chiron Corporation received a product license approval (PLA) from the Food and Drug Administration (FDA) to market its Hepatitis B vaccine, which achieved over $200 million in revenues in the year immediately following its introduction. The significance of this new product introduction was not that it derived from a biotech firm, but that industry giant Merck, well-known for its own innovative prowess, had guided the product through the costly clinical trials, in partnership with Chiron. Shortly after this successful venture, Merck allied itself with Repligen, Inc., in an even more costly effort ($20m in R&D, in addition to complete clinical trial financing and marketing) to market the first human immuno-deficiency virus (HIV) vaccine. In addition to its partnership with Repligen, to hedge its efforts, Merck also licensed a complementary vaccine technology, Bacillus Calmette Guerin (BCG) from MedImmune, Inc. Such a strategy on the part of an industry leader who has been perceived as rather self-reliant in the area of R&D is particularly noteworthy, given Merck's own historical success in new product introduction.[1] More recently (October 1996), a relatively small biotech firm, Onyx Pharmaceuticals, in a joint venture with German giant Bayer, initiated Phase II trials of a mutant adenovirus that had been genetically engineered to kill cancer tumors resistant to chemotherapy. The common characteristic of these major advances in drug therapy is their multi-firm nature.[2]

[1] Over the period 1964-94, for instance, Merck received approval for 52 new molecular entities, according to drug approval data from the FDA, second only to Wyeth-Ayerst Labs, who received approval for 64 such products. Merck led the way, however, with 33 priority-ranked products vs. 24 for Wyeth-Ayerst. Priority-ranked products are those products that the FDA has ranked as providing a significant therapeutic advance over previously approved remedies.

[2] This contrasts with the following characterization of the pharmaceutical industry made ten years ago by Thomas (1988: 173): "The most striking feature of corporate structures in the modern pharmaceutical industry is the extensive vertical integration between innovation, manufacture, and marketing of new drugs."

During this same five-year period (1991-96), however, we have had the introduction of numerous products through in-house development routes. In particular, in 1994, venlafaxine hydrochloride, a successful antidepressant, was brought to market by American Home Products from its wholly owned subsidiary, Wyeth-Ayerst labs. Merck and Pfizer have brought several successful products to market during the 1991-94 period, from completely in-house sources.[3] Despite the growing number of products being developed via alliances, the majority of products still arrive at the marketplace primarily from in-house development.

Mergers and acquisitions have also been undertaken for the purpose of bringing specific new drug products to market. Three relatively recent examples of this strategy are: (1) The Hoechst $7.12 billion cash acquisition of Marion Merrell Dow in 1995, (2) The UpJohn and Pharmacia merger, a $6.32 billion stock swap deal announced in August of 1995, and (3) The Roche acquisition of Syntex for $5.3 billion, which was completed in October 1994. In these transactions, Hoechst, UpJohn, and Roche explicitly moved to address weak pipelines of new drug products. Since these transactions, the resulting companies have received FDA approval for nine new products.[4] In addition to these examples of acquisition-focused development strategy, there are firms such as Merck and the biotechnology giant, Genentech, which have pursued a diversified development strategy by proceeding with both in-house and external new drug development. This shift in Genentech's development strategy was

[3] Merck brought to market Zocor, while Pfizer brought to market Zithromax and Norvasc.
[4] Hoechst Marion Rousell obtained approval for Allegra and Amaryl. Pharmacia and UpJohn received approval for five new products, while Roche-Syntex received two new drug approvals.

prompted by a negative experience with Eli Lilly.[5] Genentech chose to develop its last ten products through a combination of in-house means, joint ventures, and patent licenses, where five products were developed via the in-house route, and five products were developed through non-integrated means. These examples demonstrate the diversity of development of new drug products.

Given the variety of methods by which pharmaceutical firms can bring new products to market, it is interesting to ask what economic considerations drive these important development decisions. This decision process involves numerous considerations. We focus our analysis on measurable variables that are correlated with the factors suggested by current economic theory as the most relevant for the development of new products. The variables in our analysis derive first, from firm characteristics such as firm size, patent stock, previous approved drugs, publicly traded status, and reliance on drug sales. Secondly, the analysis draws upon drug characteristics such as the disease category, year of patent approval, and whether the drug requires biotechnology or originated from a foreign patent. We then examine the question of how firms organize new product development by considering the relationship between firm and product characteristics and the firm development decision.

This question is particularly interesting in light of recent trends observed by the trade press that innovating firms in the pharmaceutical industry have increasingly turned to multi-firm strategies to get their new drug products to market.[6] Given this observed

[5] Eli Lilly was charged with using Genentech's technology acquired through a restricted patent license for the development of other drug products to compete directly with Genentech. Rather than undergo judicial proceedings, Eli Lilly settled with Genentech out of court.

[6] Sugawara (1992:C1) observes that "A decade ago, in the early days of biotechnology, some enthusiasts predicted that the little companies then emerging around the new technology would soon grow into major operations that would challenge the huge pharmaceutical companies by making many of their chemical

trend, we can then ask, is this trend due to ***organizational adaptation*** by firms in the industry to changing ***economic conditions*** and ***technological focus***, and does this portend a new optimal strategy for R&D and new product development?

Due to the complexity of these questions and the availability of data, we choose to focus on one specific industry, the pharmaceutical industry. Since new biological drug products are in direct competition with conventional drug products, we define the pharmaceutical industry to include human therapeutic products produced by biotech firms as well.[7] Of the various new drug products introduced to the market, we focus our attention on new molecular entities (NMEs), the most innovative of the newly marketed products.[8] We then analyze the process by which these new products ultimately obtain FDA approval in the form of a new drug application (NDA) approval. During the first few decades following the seminal 1964 Drug Act, new drug products were primarily brought to market through integrated means.[9] Over the past decade or so, this appears to be changing. ***Windhover's Pharmaceutical Strategic Alliances*** (1994), for example, reports that between 1986 and 1994, the total number of strategic alliances involving prescription drugs rose from 125 to over 400. In 1995, 170 strategic alliances involved biotech companies alone. The recent merger and acquisition wave in the industry is well

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drugs obsolete. But as a series of alliances between established pharmaceutical companies and financially strapped biotech companies suggests, things have not turned out that way."

[7] We do not include biotech products produced for agriculture, plasma substitutes, or veterinary uses because those products are irrelevant for our analysis of new drug development for the human therapeutic market.

[8] The FDA differentiates new molecular entities (NMEs) from "me-too" drugs to determine their allocation of resources for application processing. NMEs receive greater emphasis, because of their potential contributions to the current state of drug therapy. Note that we also include new biological entities (NBEs) in our analysis as well.

[9] See Temin (1980) for a detailed description of how FDA regulations biased new drug development towards large integrated firms.

documented, with about 700 transactions between 1990 and the end of 1996.[10,11] We examine a dataset comprised of over 300 new drug products (to include those products derived from biotechnology) introduced into the U.S. pharmaceutical market from 1985-96, which consists of 318 new drug approvals (NDAs) and 45 product license approvals (PLAs). These data are used to describe the trends in the industry toward multifirm strategies and identify the most significant determinants of these trends.[12] Our analysis addresses several questions regarding this increasing tendency toward non-integrated development. In particular, after controlling for firm and drug characteristics do we still see non-integrated R&D strategies manifesting themselves in newly marketed drug products?

Our findings indicate that several recent trends in the industry that have affected the relative benefits and costs of each of these development routes have not moved the industry toward non-integrated development as evidenced by ***successfully introduced products***.[13] This is surprising given the significant synergies that appear to exist between more specialized research intensive firms and the larger established firms experienced at negotiating the lengthy and costly FDA approval process. It is not such a surprising result when one considers that this transition in the organization of R&D is

[10] The source for these transactions are the ***Investor's Dealer's Digest*** (***1990-95***) and the ***Merger Yearbook (1990-95)***. The vast majority of these transactions, however, have occurred for reasons other than product development, although in many instances it is difficult to distinguish this category from fully integrated development after transactions are consummated.
[11] See Ravenscraft and Long (1997) for a recent analysis of some of these mergers.
[12] We define the pharmaceutical industry as those firms engaged in the production or research for the production of conventional pharmaceutical products and therapeutic biotechnology products. Restricting biotechnology products to the class of therapeutic products is important, since the broader category includes plant and diagnostic products as well.
[13] We discuss in greater detail the impact of focusing our analysis on FDA approved products in Section IV, our data section.

most likely a difficult and lengthy process. These results remain after controlling for firm characteristics and drug characteristics in a variety of specifications.

One trend that one might expect to move the industry towards less integrated development is the general acceptance of the validity of biotechnology products. As a technology shock reducing the minimum efficient scale for firms, the increasing efficacy of biotechnology has made research-focused biotechnology firms viable.[14, 15] These research-focused firms might then turn to larger drug companies for assistance in development to continue their specialization. Another relevant industry trend that has coincided with this one has been the increased price competition due to regulatory changes and the rise of managed health care. The proliferation of generic drugs and the increased exclusivity for new products due to the 1984 Drug Amendments have increased the returns to efficient research. This increase in returns may in some cases have encouraged the specialization that has continued to encourage the entry of smaller research-focused firms into the biotechnology industry.

Another regulatory change occurred in 1984 to spur the formation of joint ventures. Joint ventures were specifically encouraged by the National Cooperative Research Act of 1984, which was passed to encourage joint research and development ventures.[16] Additionally, new technology in the field of drug discovery such as genomic technology and combinatorial chemistry has continued to favor less scale-intensive and more specialized research over the traditional research methods of established firms. Despite

[14] Williamson (1979: 254) reasons that "To the extent that uncertainty decreases as an industry matures, which is the usual case, the benefits that accrue to integration presumably decline."
[15] On the penetration of biotech therapeutic products into the pharmaceutical industry see Bienz-Tadmor et al. (1992), who document that, "Overall, biotechnology drugs succeed clinically at a considerably higher rate and within less time than do conventional drugs."

these trends, the failed acquisitions of biotech companies by pharmaceutical firms, high profile biotechnology-derived drug product failures to combat sepsis, and other factors which have continued to make technology transfer difficult in this industry, appear to have significantly slowed the adoption of the non-integrated R&D strategy until very recently.[17]

The major findings resulting from our analysis are: (1) The size of the discovering firm (as measured by revenues, market capitalization, or access to capital markets) is strongly correlated with a propensity towards integrated development, (2) A firm's previous patenting expertise (which we use to proxy for asymmetric information) is correlated with a propensity towards non-integrated development, (3) A firm's previous drug development experience is positively correlated with a propensity towards integrated development, and (4) New drugs in difficult disease categories (such as cancer, cardiovascular, and central nervous system [not depression]) tend to be developed in-house.

Before proceeding with a description of the basic model employed in our analysis, we provide a survey of the relevant literature in Section II. Following our description of the drug development process in Section III and a justification for the variables that we consider we describe the data with summary statistics in Section IV. In Section V, we discuss our estimation procedures and results. Section VI considers several plausible

[16] Specifically, Public Law 98-462 was passed on October 11, 1984, shortly after the 1984 Drug Amendments to "promote research and development, encourage innovation, stimulate trade, and make necessary and appropriate modifications in the operation of antitrust laws."

[17] Longman (1994) describes the well-known failed biotech acquisitions in 1985 by industry giants Eli Lilly (who acquired Hybritech for $375 million) and Bristol-Meyers (who acquired Genetic Systems Corp. for $250 million), due to the departure of essential scientists and managers following these acquisitions. In the words of many observers, these acquisitions were utter failures, because the embodiment of the target firms' value "walked out the door."

interpretations of our results. Section VII concludes by identifying the implications of our results for future drug development and discusses future related research.

II. Survey of the Literature

We conduct this survey in two parts. The first part considers the most relevant theoretical literature, and the second reviews the most relevant empirical literature. The question of R&D outsourcing for new product development in the pharmaceutical industry addressed in this paper derives from the central question about the optimal firm organization for research and development. Schumpeter (1942), who asserted that large firms were the "most powerful engines of progress," was on of the first economists to address this question. His assertion was based on the following four assumptions: (1) Capital market imperfections yield an advantage to large firms in obtaining financing for risky R&D projects, (2) There exist scale economies in the technology of R&D, (3) The returns from R&D are higher when the innovating firm has a greater sales volume over which to spread the fixed cost of R&D, and (4) R&D is more productive in large firms because of synergies between R&D and other non-manufacturing activities.[18] Two decades later, Arrow (1962) provided additional support for this view. In that seminal paper, Arrow refers to research as a "risky process" against which there is "bound to be some discrimination." In particular, "The only way, within the private enterprise system, to minimize this problem [of discrimination against worthy risky projects] is the conduct of research by large corporations with many projects going on, each small in scale compared with the net revenue of the corporation." Arrow's perspective at that time is consistent with the R&D we observed in the pharmaceutical industry over the period

[18] See Cohen and Levin (1989:1067) for a review of the extensive literature examining the relationship between firm size and innovation.

1964-84. During this period, the industry's largest fully integrated pharmaceutical firms introduced the vast majority of new drug products.[19] We can appropriately refer to this period as the era of ***integrated new product development.***

This prescription for the organization of R&D, however, appears to be inconsistent with more recent R&D in the industry. Arrow (1983) discusses the relationship between communication channels and the "capital-allocation mechanism" within firms conducting R&D. In this more recent analysis, Arrow modifies his earlier stance on the organization of R&D. Arrow decomposes R&D into a two-stage process requiring first research expenditures to determine the feasibility of a project and secondly, development expenditures to complete the project. He argues that the efficiency of communication about "novel ventures" will be superior in small firms because of their proximity to the technical aspects of the ventures. Researchers in such firms are simply closer to the resource allocation decision. Additionally, small-firm researchers are not influenced by incentives that may adversely affect resource allocation decisions in larger, more bureaucratic firms.[20] Large firms, however, still retain an advantage in financing that suggests that "large firms will be superior if [development] costs are large." Development costs in the United States pharmaceutical market are significant indeed, usually comprising up to two-thirds of the total cost to bring a new drug to market.[21]

[19] Between 1964-83 there were 92 firms responsible for the 383 new molecular entities approved by the FDA, whereas between 1984-94, there were 87 firms responsible for the 294 new molecular entities approved by the FDA.

[20] For instance, consider that in large pharmaceutical firms, research scientists gain in stature when their proposed projects are developed beyond the initial stages regardless of whether or not it yields a marketable product. This manifestation of the standard agency problem suggests particularly high agency costs due to the inherent risky nature of new drug research. Specifically, research activities are particularly difficult to monitor and their risky nature makes the efficient risk-sharing incentive tradeoff acute.

[21] DiMasi, et al. (1991:121) estimates that pre-NDA development costs exceeded $20 million (1987 dollars) on average.

These arguments generally support the current strategy in the pharmaceutical industry that we refer to as the ***specialization strategy***.[22]

Another classical perspective on the location of R&D among firms comes from the transaction cost economics literature. Beginning with Coase (1937) who stated that "transactions will be organized in the firm when the cost of doing this is lower than the cost of using the market," and continuing with Williamson (1975,1985), this theoretical approach focuses upon the costs and benefits of integrated versus non-integrated transactions. The primary assumptions underlying the modern version of this theory are that firm managers behave opportunistically and with bounded rationality. Because of this type of behavior, firm organizations which "economize on bounded rationality" and "safeguard transactions against the hazards of opportunism will be favored and will tend to displace inferior modes in these respects."[23] In this theory, transactions are represented in three crucial dimensions: (1) The frequency with which they occur, (2) The degree and type of uncertainty (in particular, that derived from systematic or nondiversifiable risk)[24] to which they are subject, and (3) The condition of asset specificity (the degree to which an asset can be redeployed to alternative uses and by alternative users without sacrifice of productive value). Internal organization rather than discrete market contracting best governs transactions characterized by high frequency, a high degree of uncertainty, and requiring investment in transaction-specific assets.

[22] We refer to this as the "current strategy" because of the frequent reference made to the significance of outsourcing in the pharmaceutical industry. The Pharmaceutical Manufacturers Research Association (1997) estimates that a full 20% of all industry R&D expenditures in 1996 was outsourced (that is $6 billion of $30 billion).

[23] See Williamson (1989) for a recent and concise, but detailed exposition of transactions costs economics. For a more comprehensive discussion, see Williamson (1985).

[24] See Helfat and Teece (1987) for empirical support of the assertion that internal organization (vertical integration) reduces a firm's exposure to systematic risk. They analyze U.S. firms involved in vertical

The initial transaction cost approach, however, does not explain why vertical integration, which reduces transaction costs, will not always be the preferred firm organization. Nor does this approach give an operational definition of integration.

Following the increased attention to transaction costs and the recommendation by Arrow (1985), several researchers have extended the standard production cost minimization approach to incorporate transactions costs as an additional component of firm costs.[25] This approach is presented in Silver (1984), Riordan and Williamson (1985), and Williamson (1989). Silver focuses upon the importance of information impactedness as the driving force behind the vertical integration decision.[26] He cites numerous historical examples to support his emphasis on the reduction in information transmission costs as the appropriate justification for integration.[27] Silver also points out that the costs of vertical integration derive from increasing production costs resulting from "diseconomies of scope." Riordan and Williamson (1985) and Williamson (1989) include governance costs and asset specificity explicitly in a modified profit maximization model. Given the additional choice variable of asset specificity, firms choose the level of asset specificity to minimize the sum of production and governance costs given output. Therefore, since asset specificity has "greater cost reducing impact, internal organization is progressively favored (Riordan and Williamson, 1985: 373)."

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mergers between 1948 and 1979 inclusive, as reported by the Federal Trade Commission, and find a significant reduction in the asset betas following vertical merger transactions.

[25] Arrow (1985: 303) suggests that, "new theories of economic organization take on greater 'analytic usefulness when these are founded on more directly neoclassical lines."

[26] Williamson (1975: 14) defines this as "partly an information asymmetry condition: one of the agents to a contract has deeper knowledge than does the other . . .. But more than asymmetry is implied . . .. It is also costly for the party with less information to achieve information parity."

[27] British sugar companies with operations in Guyana during the nineteenth century for instance integrated forward after demand uncertainty had been resolved (Silver, 1984:72).

Similarly, when the negative bureaucratic effects of internal organization are low, internal procurement will be favored.

Grossman and Hart (1986), hereafter G&H, extend the transaction cost theory. They formalize the theory with an incomplete contracts framework. They consider a two-firm model in which the managers of each firm engage in a two-period relationship governed by a contract that maximizes the sum of the total net benefits of the two firms. Their model "emphasizes the distortions, due to contractual incompleteness, that can prevent a party from getting the ex post return required to compensate her for her ex ante investment." They find that the primary distinction between non-integration and integration is that under non-integration, ex post surplus is divided more evenly, so that each "firm will invest to a moderate extent." This is optimal for cases in which investment into the relationship by both parties is important for the realization of gains from the relationship. On the other hand, integration is preferred when the ex ante investment of one of the firms "is much more important" than the other firm's investment.[28] They operationalize the concept of integration by defining it "in terms of ownership of assets" and demonstrate that residual rights can be allocated through asset ownership to generate optimal firm performance. In contrast to the earlier transactions-costs literature, G&H emphasize that "integration can impose costs as well as benefits."[29]

The theoretical literature on the organization of innovation has followed this more general work addressing the question of when transactions should be completed within

[28] See the discussion in Grossman and Hart (1986: 708).
[29] Building upon the analysis of G&H, Hart and Moore (1990) provide a detailed analysis of "how employees' incentives change as integration occurs . . . as asset ownership

a firm versus through the market. Aghion and Tirole (1994), Holmstrom (1989), and Teece (1992, 1996) emphasize different aspects of the R&D transaction. Aghion and Tirole provide a detailed model of the organization of R&D activity using an incomplete contract framework extending the analysis of G&H and Hart and Moore to the organization of R&D. Their model defines two agents, the research unit and the customer, who negotiate a contract governing the property rights (in the sense of G&H) on any forthcoming innovation, a sharing rule on the verifiable revenue (license fee) obtained by the research unit, and any verifiable amount of customer investment. The two pertinent assumptions underlying the Aghion and Tirole model extension of G&H are: (1) "The research unit has no initial cash endowment, and its income cannot be negative," and (2) "The exact nature of the innovation is ill-defined ex ante," so that the two parties cannot contract for delivery of a specific innovation. They conclude that:

> Whether C [the customer for research output] or RU [the research unit which conducts the research] should own the innovation hinges on two basic considerations: (a) the marginal efficiency of RU's effort compared with the marginal efficiency of C's investment; (b) the ex ante bargaining power of the two parties (who proposes the initial contract), which reflects the extent to which the research unit is the only candidate to perform the research.[30]

With regard to financing, they find that, "Financial constraints . . . bias the organizational form toward the use of creative inputs and away from capital expenditures." This suggests that outsourcing will be undertaken more frequently by firms experiencing lackluster research performance and with difficulties accessing capital markets.

Holmstrom (1989) provides a theoretical foundation for the argument that "Larger firms are at a comparative disadvantage in conducting highly innovative research . . .."

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becomes more or less concentrated." Intuitively, their model predicts integration for complementary assets and non-integration for economically independent assets.

[30] See page 1190.

He employs agency theory to show that “innovation activities may mix poorly with relatively routine activities in an organization.” The firm characteristics and managerial style that make for a particularly effective drug manufacturer and distributor do not necessarily carry over to the task of incorporating the latest research technologies. Holmstrom argues that the two primary motivations for integration according to the Williamsonian incomplete contracts approach are: (1) “Incentives for investment in relationship specific assets,” and (2) “Improved coordination of decision making.” Neither of these two is particularly relevant for innovative activities where relationship-specific investment is “limited to small groups,” and large firms frequently make an effort to keep different projects segregated. Additionally, when human capital is a key asset for the realization of firm output, as it is for R&D, “incentives for effort may be significantly diluted by removing title to transferable assets from those whose efforts are central to production” as is done under integration. This is the well-known problem of low-powered incentives.

Teece (1992) approaches the question of the organization of R&D from an organizational theory perspective. He emphasizes the potential synergies that may be realized through non-integrated R&D strategies and concludes that, “Alliance structures can facilitate innovation, and are increasingly necessary as the sources of innovation and the capacities necessary to effectuate commercialization become increasingly dispersed.” Teece (1996) contends that whether a firm integrates or not is likely to depend critically on four sets of factors: (1) technology transferability, (2) intellectual property protection, (3) contractibility, and (4) accessibility of complementary competences. Teece further argues that providing adequate incentives for development,

manufacturing, and innovative activities is more costly "within one organization than through separate organizations." This conclusion supports the current industry mantra that to maintain viable new product pipelines established pharmaceutical firms are better served by turning to smaller firms strictly specializing in research.

In sum, there is a diverse and extensive body of theoretical literature analyzing the organization of firm activities, and more recently, the organization of firm R&D activity. We have reviewed the papers we feel are the most relevant for our analysis. We have grouped these approaches by their methodology and the aspects of firm and firm R&D activity, which they emphasize in Table 1.

Before moving to the related empirical work in this area, it is important to briefly mention the conventional wisdom of industry participants given the apparently contradictory theoretical predictions. A recent article in the ***Nature Biotechnology*** magazine proclaims that significant cooperation in drug R&D is needed to maintain pharmaceutical industry growth.[31] Standard arguments supporting this view include: (1) Rapid technological change has forced established firms to play catch-up through alliances (outright acquisitions are not as effective due to incentive effects), (2) New product development has become so expensive and risky that even the largest firms have been looking to share risk, and (3) Increased competition has forced firms to seek more rapid innovation through partnering.

A good place to begin with in the modern empirical literature is Mowery (1983) who investigated "the role of independent research organizations and the relationship between in-house and contract research during the early years of industrial research in

[31] More precisely, "pharmaceutical and biotechnology firms and other research institutions need to collaborate to an unprecedented degree in order for the drug industry to maintain a 10% growth rate."

American manufacturing." He finds support from the early part of the century, 1900-1940, for the proposition that firms without in-house research facilities were at a competitive disadvantage in R&D competition, despite the significant presence of capable independent contract research organizations. For this reason, he finds that independent research laboratories functioned as ***complements*** rather than ***substitutes*** for in-house research. This is relevant for the pharmaceutical industry of the 1990s where a majority of drug firms conducted in-house research in biotechnology in addition to outsourcing this research.[32] Mowery qualifies his findings by noting that the development of industrial research within the manufacturing firm of the early 1900s resulted from the "shortcomings of market institutions as mechanisms for the conduct of research and development." This suggests that the magnitude of transaction costs in the earlier part of this century (because of the lack of legal instruments to facilitate the outsourcing of research) constrained market transactions. Given Mowery's findings, however, it is interesting to note that the outsourcing of R&D dates back well before the advent of the current emphasis on outsourcing.

Pisano (1990, 1991, 1993, and 1997), Arora and Gambardella (1990), Balakrishnan and Kosa (1993), and Gambardella (1995) have conducted industry specific research. Pisano focuses on the biotechnology industry, analyzing integration and collaboration within the industry to develop and commercialize new drug products. In his 1990 paper, he considers 78 (mostly incomplete) biotechnology R&D projects arguing that although collaborative arrangements for development are common in the industry, prohibitive transactions costs have encouraged larger new biotechnology firms (NBFs) to integrate

[32] The Pharmaceutical Research and Manufacturing Association (1997) estimates that in 1997, pharmaceutical companies will spend close to $1 billion on biotechnology research in-house. This

forward. Pisano (1991) concludes, “small-numbers bargaining problems motivate firms to internalize R&D.” More recently, Pisano (1997) provides a thorough analysis of 23 biotechnology firms, which emphasizes the role of “process innovation” in the new drug development process, and how this encourages integration over specialization. Pisano’s aggregated analysis provides support for the integration strategy of new drug development.

Arora and Gambardella (1990) provide and test a model of the presence of synergies between the different types of firm collaborations, finding that “research agreements with universities, minority participations in NBFs, and acquisitions of NBFs are positively correlated even after controlling for firm characteristics.” This finding is consistent with the proposition that large firms have not monopolized innovation in pharmaceuticals. Therefore, we can expect substantial new innovation to occur within the “network of inter-organizational relations” among pharmaceutical and biotech firms. Gambardella (1995) provides a thorough overview of the impact of technological advances affecting the industry within the context of relevant economic and institutional factors. Gambardella, unlike Pisano predicts market growth “based on an extensive division of labor” between “flexibly organized, research-intensive suppliers, with comparative advantages in producing ideas, and very big firms with comparative advantages in large-scale development and commercialization.” The current analysis is a first step in testing the contradictory predictions of the Pisano (integrated) and Gambardella (specialization) models of new drug development. In contrast to this earlier work, we take a closer look at the economic forces which are driving the industry toward one mode of research organization or the other, or a combination of the two. Additionally, we

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compares to an estimated total of $7.7 billion for biotechnology firms.

consider a comprehensive dataset of approved drug products rather than early stage research projects to determine the prevalence of development strategies through the product approval stage.

III. Drug Development

Figure 2 provides a useful schematic of drug discovery and development which is essential for understanding our analysis of new product development decisions within this industry. The first step in bringing a new drug product to market is discovery, which includes the research phase and pre-clinical trials up to the point where a discovering firm submits an investigational new drug (IND) application. This is the portion of R&D that is increasingly being accomplished by biotech firms because of their newer and apparently more productive research technology. The development period begins with the filing of an investigational new drug (IND) application that allows for the testing of the experimental drug product on human subjects. Upon approval of the IND, the FDA allows Phase I trials for drug safety on small groups of human subjects.[33] This is followed by Phase II clinical trials for efficacy on a limited number of carefully selected human subjects, and Phase III clinical trials for safety and efficacy on a larger sample of human subjects. As shown in the figure, this process has on average taken from 10 to 13 years in the past. For our more recent sample, the mean time to FDA approval has fallen slightly but still remains quite lengthy at over 9 years.[34]

Discovering firms ultimately choose to develop products in one of four ways: (1) With their own development resources (in-house), (2) Through a merger or acquisition which

[33] "Before any drug can be tested on humans, the drug's sponsor must submit an investigational new drug application to FDA that summarizes the preclinical work, lays out a plan for how the drug will be tested on humans, and provides assurances that appropriate measures will be taken to protect them." See GAO (1996a: p. 2).

becomes an in-house development, (3) With a patent license, or (4) Through a joint venture or strategic alliance (see Figure 1).[35] For a drug product to be classified as an in-house development, the same firm that received the NDA approval for the product, must also have discovered the new drug by obtaining the original patents that ultimately led to its NDA approval. If at any point between the patent grant and the NDA approval the product or a portion of the product changes hands, then we have a non-integrated development. The category of mergers and acquisitions is problematic within this scheme. For those instances in which a firm owning a patent that leads to a new drug product is acquired or merges with another company prior to FDA approval for the new drug product, we have new product development via a merger or acquisition. Given that such transactions include a change in property rights regarding the new drug product, one might be inclined to consider these new product developments within the non-integrated category. Since such transactions, however, bring the new product development within in one firm (or in-house) we have chosen to include them within the integrated category in our bivariate analysis. We complete our empirical analysis with and without this group of new product developments.

We posit that firms in this industry are intertemporal profit maximizers who determine their optimal development decision as a function of firm and product characteristics. We can model the decision process using a variety of econometric techniques. If we employ a sequential model such as a nested logit model, we assume that a firm first focuses on

[34] See GAO (1996a, 1996b, and 1996c) for discussions of the reduction in approval times for NDAs.
[35] The distinction between strategic alliances and joint ventures is as follows: joint ventures result from the creation of a new corporate entity separate from either of the two partners, but employing resources, staff, and management from both of the partnering firms, whereas, strategic alliances are short-term, goal-oriented partnerships in which a bilateral exchange of knowledge takes place. See Tucci (1996) for additional clarification of this distinction.

the choice of internal versus external development and then chooses the most appropriate multifirm method given an external development choice. Alternatively, we can assume that the firm treats the different methods of development as varying degrees of integration. Under this decision model, the firm makes a single choice based on its preferred level of integration, given the relative benefits and costs of each method of development. In this case, we estimate the decision with an ordered probit estimation. We do not suggest that either model is a more accurate representation of the decision making process. Examples in the trade press of both decision making processes are abundant. The primary purpose of putting forth these two representations of the development decision process is to provide us with flexibility during our subsequent econometric estimation so that we may better capture the likely correlations between a firm's preference for one choice or another.

As with many economic decisions, we cannot hope to capture the full complexity of the decision process undertaken by firms for new product development. We can, however, attempt to document some of the more important elements involved in this process in accordance with previous theoretical and empirical analyses, and our own inquiry into this process within the U.S. drug industry. We posit that several firm characteristics and several new drug characteristics that we can observe should be correlated with the new drug development decision as we have defined it here. In particular, we include the following firm characteristics in the year of the patent grant in our analysis of firm development decisions: 1) firm size, 2) patent stock, 3) the number of previously approved drugs, 4) the number of years since the firm's first drug approval, 5) whether the firm is publicly traded, and 6) the firm's R&D expenditures and

dependence on drug sales if it is publicly traded. We also include data on the following drug characteristics: 1) whether or not the drug was developed using biotechnology, 2) the therapeutic class for which the drug was approved (we use this data to categorize products into a difficult disease category), 3) the year of application for the patent from which the drug was derived, 4) whether or not the patent was originally assigned to a foreign inventor, and 5) the number of other approved drugs within the same therapeutic category. See Appendix A for a detailed discussion of the construction of each of these variables. We now turn to a brief discussion of why each of these variables should be included in our analysis and how they might effect the new product development decision.

Firm size is a variable that we normally include in economic analyses which consider firm decisions. Within our analysis, there are several reasons why firm size might be important for the development decision. First, since the development process is a very long and costly process, greater access to capital due to larger firm size may allow larger firms to choose in-house development more frequently than smaller firms. Second, larger firms with multiple ongoing projects may be more capable of sustaining losses from any one development project. This greater ability for undertaking a risk burden should make them more likely to undertake in-house development. We therefore include the firm size variable in our analysis expecting that it will be positively correlated with the level of integration of new product development decisions.

Patent stock represents a firm's accumulated technological expertise as embodied by legally protected intellectual capital. This stock also represents publicly available information about a firm's technical expertise. The primary reason to include this

variable in the analysis is that it represents information about a company's expertise that potential development partner firms can analyze which may facilitate non-integrated development options. A second reason is that a higher patent stock may represent a firm's ability to appropriate gains from new product development. Firms that have a number of patents that technically approximate their most important patents can more effectively prevent competitors from encroaching upon their intellectual property assets. The first reason for including this variable in our analysis noted here suggests that a greater patent stock might be associated with less integrated development. Our second reason goes in the opposite direction implying that a greater patent stock might be correlated with more integrated development. The most likely affect of this variable upon the development decision is an empirical question that we answer in the following sections.

The number of ***previously approved drugs*** for a firm that is in the position to make a development decision as a result of a new discovery is important because it represents that firm's accumulated expertise in drug development. Similarly, the number of ***years since a firm's first drug approval*** represents also represents a firm's cumulative drug development experience. A firm with a larger number of previously approved products and a greater number of years since its first drug approval is a firm that has greater experience in negotiating the lengthy and complex clinical trials required by the FDA. This greater experience should encourage a firm to opt for integrated development over non-integrated development. Both of these variables should therefore be positively correlated with the level of integration in the drug development decision.

We also include a variable that indicates whether or not a firm is ***publicly traded*** in our analysis for two reasons. First, a firm that is publicly traded will have access to equity markets not available to firms that are not. Second, firms that are publicly traded must divulge more information about their operations than firms that are not, which may facilitate non-integrated development. Our first reason here for including this variable suggests that publicly traded firms should be more likely to engage in in-house development than their privately held counterparts. The second reason suggests the reverse relationship. Given the central importance of capital funding for new product development in this industry, however, we anticipate that this variable should be positively correlated with integrated development.

Two final firm characteristics that we include in our analysis which are available for our publicly traded firms are: 1) the level of firm R&D expenditures and 2) the dependence of a firm upon drug sales. The first variable here represents the size of a firm's overall R&D program and is most likely positively correlated with a firm's in-house development capabilities. Greater R&D expenditures should therefore be positively correlated with integrated development. Similarly, the more dependent a firm is upon drug sales (as measured by the proportion of drug sales to overall sales), the more likely that firm should opt for more integrated development.[36]

In addition to this set of firm characteristics, we are also able to include five drug characteristics in our analysis of the firm development decision. The first characteristic we include is an indicator for drugs derived from ***biotechnology***. Such products are more likely to reach approval through non-integrated development when biotechnology has

been sufficiently accepted among providers of capital to allow for effective multifirm new drug development.[37] Since this requirement was most likely not met for significant portions during the earlier part of our sample (1985-90 and again in 1994), it is likely that this effect is time-dependent. During the early history of the evolution of the biotechnology industry, funding for biotechnology-derived drug products was difficult to obtain, requiring firms with such products to develop them in-house. As biotechnology became more widely acknowledged as a viable source of new therapeutics, funding became easier, thereby facilitating non-integrated development. By contrast, the early biotechnology firms that evolved into integrated discovery-development firms themselves became more capable of in-house development. This trend would suggest that over time, biotechnology-derived products might become more associated with in-house development. Taken in combination with the greater capital market acceptance of biotechnology, however, we cannot a priori predict the relationship between the level of integration in the development process and whether or not the new product derives from biotechnology. The countervailing trends we have noted here will offset to a degree. Given the continued proliferation of alliances among biotechnology firms over the recent past, however, we might predict that the impetus for non-integrated development due to the greater acceptance of biotechnology would yield the greater effect. This would result in a negative correlation between the level of integration and a ***biotechnology-year*** interactive term.

[36] Pisano (1990: 168, 171) makes a similar argument for the same variable, which he labels, FOCUS. He finds for his particular dataset that "Companies more dependent on pharmaceutical sales seemed to be more likely to internalize biotechnology R&D projects."
[37] Venture capitalists and investors in the NASDAQ exchange qualify as the relevant providers of capital.

The second drug characteristic variable we include in our analysis is ***a therapeutic indicator***, which identifies products being developed for diseases categorized as particularly difficult by the Center for Disease Control (CDC). We hypothesize that such products would be more likely developed in-house due to the difficulties inherent when attempting to contract over development responsibilities for such drug products. This view is consistent with the transaction cost economics perspective that the more complex a product is, the more costly it is to transfer here across firms. Our difficult disease indicator should therefore be positively correlated with in-house development.

The next two drug characteristics that we include in our analysis come from the underlying patents of the approved drugs in our sample. These are the ***application year*** of the patent and an indicator, ***foreign patent***, which identifies those drug products that emanated from a patent assigned to an entity outside of the United States. The application year variable here allows us to explicitly consider the trend towards non-integrated development (at least for the sample of approved drug products that we consider here) that has been emphasized in much of the trade press. If there has in fact been a trend towards non-integrated development, we should observe a statistically significant negative coefficient on our application year, indicating a negative correlation between time and the level of integrated development among new drug developers. For those drug products originating overseas, we should expect a higher degree of non-integrated development given the relative rigor of the FDA approval process in the U.S. Foreign firms attempting to develop new drug products in the U.S. have often sought American partners to facilitate negotiation of the different regulatory hurdles in this

country. We, therefore, expect a negative coefficient on our foreign patent indicator variable.

The final drug characteristic we include in our analysis is a count of the number of ***drugs previously approved*** within the same therapeutic category as the drug in our sample. The larger the number of previously approved drugs within the same category, the less uncertainty there should be about the viability of developing the product. A higher number of previously approved drugs within the same therapeutic class, however, may make it more difficult to obtain approval for a drug that can effectively differentiate itself from its competitors. These two effects should move the discovering firm in slightly different directions with regard to the development decision. Reduced uncertainty should facilitate non-integrated development. Reduced expected value, however, may hinder non-integrated development. If we consider that the costs of conducting non-integrated development include transactional costs in addition to the normal costs of development, than a lower reduced expected value for the drug product under development should discourage non-integrated development. The relationship between this variable and the development decision is then ultimately an empirical question. We now turn to our data and results.

IV. The Data

The construction of our dataset begins with all of the approved new drug applications (NDAs) and product license applications (PLAs) beginning in 1985 to the end of 1996, obtained from the Food and Drug Administration (FDA).[38] We restrict our data to the

[38] The ***Approved Drug Products with Therapeutic Equivalence Evaluations*** (commonly referred to as the "Orange Book") published by the U.S. Department of Health and Human Services published lists new drug products with pertinent patent numbers after September 24, 1984, the effective date of the 1984 Drug Act.

new molecular entities (NMEs) because these products represent distinct innovations from previous treatments.[39] Since the FDA must approve all new drugs sold in the U.S., this dataset includes the universe of all new drugs marketed in the U.S. during this time period.[40] Our dataset contains 318 new conventional drug products and 45 new biological products marketed in the US during this time period.[41] A number of conventional drugs from our original dataset of over 400 products, however, did not constitute sufficiently different technology from previous products in their area such that they did not have corresponding patent information (i.e., did not require a new discovery). Since our focus is on the process by which firms take novel discoveries to market in the form of new products, we focused on those products with new patents qualifying for patent term extension consideration, leaving us with our sample of 363 total products.

President Reagan signed the 1984 Drug Price Competition and Patent Term Restoration Act (1984 Amendments) on September 24, 1984. This act requires that firms applying for new drug approvals include relevant patent information to receive consideration for patent term extension. It also includes drug products (vaccines, therapeutics, and diagnostics) with approval under Section 505 of the Act administered by the Center for Biologics Evaluation and Research (CBER). These two laws have allowed us to construct our unique dataset, which traces marketed drug products back

[39] The FDA defines NMEs as "an active moiety that has not previously been approved (either as the parent compound or as a salt, ester, or derivative of the parent compound) in the United States for use in a drug product either as a single ingredient or as part of a combination."
[40] Note that new generic drugs are not included in the analysis, since they do not require approval based on the lengthy clinical trials portrayed in Figure 2.
[41] Note that we only include biological products that are designated for human therapeutic use only, to include several valuable vaccines, and the first biotech product brought to market by Genentech in 1982, Humulin (human insulin). We exclude biological products for human diagnostic purposes, veterinary use, or agricultural use.

to their originating discoveries or patents. In conjunction with a detailed patent dataset from the U.S. Patent and Trademark Office (USPTO), we have been able to attach all of the relevant patent information for each patent leading to a new drug product, either conventional or biologic. Given this mapping of discoveries to marketed drug products, we identified the methods employed by the discovering firms (which may or may not have been the same firm as the developing firm) to eventually get their discoveries to market. In this identification process we used a combination of FDC Reports ("Pink" and "Blue" sheets), ***Windhover's Pharmaceutical Strategic Alliances*** (various volumes), and other publicly available sources such as newspapers, business and trade magazines.[42] In general, the majority of successful development occurs in-house.

An important qualifier regarding our data is that we are focused on ***successful new product development***. We are therefore conditioning our analysis on those products that reach the NDA approval stage, a minority of all products that undergo some development. A critique of this dataset construction is that by selecting our sample in such a manner we capture only a fraction of all new attempted drug developments. Figure 3 represents a hypothetical depiction of our sample selection. Our analysis, therefore, applies to the most successful drug discovery programs of the entire universe of drug discovery programs.

Of the 363 drug products that we examine, 211 are developed in-house.[43] Table 2 shows the development decisions for the new drug products in our dataset. Several features of this data are striking. First, over 58% of new drug products over our period of

[42] The publicly available sources were searched through the on-line services: Dow Jones News Retrieval Serviceã and Lexis-Nexisã .

[43] The data describing these products, and identifying the developing firm was derived from a dataset provided by the FDA under a Freedom of Information Act request.

analysis 1985-96 have been brought to market with in-house development. Second, the tendency towards integrated development is surprisingly strong for the biotech products in our dataset with 62% of those products being developed in-house. Finally, when we group our observations into the initial six-year period versus the latter six-year period, the widely reported trend towards non-integrated development does not appear very strongly. This publicized trend, however, due to its recent nature, may only characterize the most recent new product development decisions and have yet to be reflected in actual new product approvals. With our sample of approved new pharmaceutical and biotechnology human therapeutic products, we observe relatively little movement towards non-integrated development as the proportion of in-house development remains above 60% through the 1996 approval year. To determine why the expected move towards non-integrated development has not appeared, we continue with appropriate econometric analyses as prescribed by our discussion of the factors expected to influence the new drug development decision.

We present the relevant variables for our econometric analysis in Table 3 along with a brief explanation of how they might affect the development decision consistent with our previous discussion. Table 4 provides summary statistics on the variables used in our estimation and Figure 4 presents a schematic summary of our dataset construction consistent with our previous description.

V. Estimation

We estimate four variants of discrete choice econometric models of the development decision. The estimation is ordered from the more restrictive models to the least restrictive. First, we estimate an ordered probit model, which characterizes the

development decision as an ordinal choice among increasing levels of integration. Second, we combine our development alternatives into two possibilities, integrated versus non-integrated development and estimate a probit model. Third, we model the development decision as a nested logit model. Last, we estimate a multinomial logit model, which characterizes the decision as a choice among four unranked alternatives.

For the ordered probit model, we rank the four possible development decisions as shown in Figure 1. In this framework, in-house development represents the highest level of integration (coded numerically as 4), merger or acquisition is the next most integrated level (coded as 3), then joint ventures or alliances (codes as 2) and finally, patent licenses which represent the lowest level of integration (coded numerically as 1). Under these assumptions we estimate the following ordered probit model:

$$\Pr(d = i) = \Pr(\gamma_{i-1} < \beta_1 X_{1j} + \beta_2 X_{2j} + ... + \beta_k X_{kj} + \varepsilon_j \leq \gamma_i)$$

where ***i=1,2,3, or 4,*** $\varepsilon_j \sim N(0,1)$ and the γ's represent the relevant cut points. The basic model includes all of the relevant firm and product characteristics with a time trend represented by the ***appyr*** variable, and an interactive term, ***bioyr***, between the biotechnology indicator, ***bio***, and the patent application year (***appyr***). We present the results from this regression in the first column of Table 5.[44] Table 5A reports the marginal effects of each of the independent variables, computed at the sample means except for the 0-1 indicator variables, in which case, the marginal coefficient represents the increased probability of moving to the next level caused by a change from 0 to 1 in the indicator. Numerically, this is: $\partial \Pr ob[cell\_i] / \partial x_j$, the marginal increase in the probability of observing a decision in cell i due to a marginal increase in variable j.

[44] The ordered logit specification was estimated as well with no significant differences.

The results are interesting as much for the variables that are not significant as for the variables that do enter significantly. First, let us consider the firm characteristic variables. The variable measuring firm size enters significantly with the expected positive sign. Larger firms have the capability to conduct the costly development process in-house and are therefore more likely to opt for integrated development. Our patent count variable, measuring expertise in discovery, enters significantly with a negative sign, suggesting that there may be some specialization among the firms making new drug product discoveries. In other words, firms that are particularly good at new drug discovery as evidenced by high patent stocks, are not always the same firms that market the resulting new drug product. A significant share of these firms proficient in drug discovery has chosen to undertake non-integrated development. The drug count variable, measuring previous drug development experience is significant and positive, suggesting that firms that have already gone through the FDA approval process are more likely to pursue development on their own, rather than seek a partner. The indicator for publicly traded firms enters with a strong positive coefficient as predicted. Those firms with access to equity markets, conditional on firm size and past success, are much more likely to undertake in-house development over non-integrated development.

The therapeutic indicator, showing those products developed for cancer, cardiovascular, and central nervous system diseases is significantly positive, suggesting that discovering firms that have discovered new products in these areas are more likely to want to keep their new discovery in-house. This result could also reflect the higher transactional costs associated with new products that attempt to address particularly

complex disease categories. The biotech and foreign indicators enter with the expected negative sign, but are both insignificant. The trend variables, ***appyr*** and ***bioyr,*** are both close to zero, which is somewhat surprising in light of the tremendous trade press on alliances within the industry. This result suggests that the movement towards non-integrated development emphasized in the trade press is not yet apparent for successful new drug products. In sum, the primary drug characteristic important for the development decision appears to be the complexity of the disease category that the drug attempts to address. Other characteristics such as whether or not the drug emanated from biotechnology and how recently it was discovered were not as significant as anticipated.

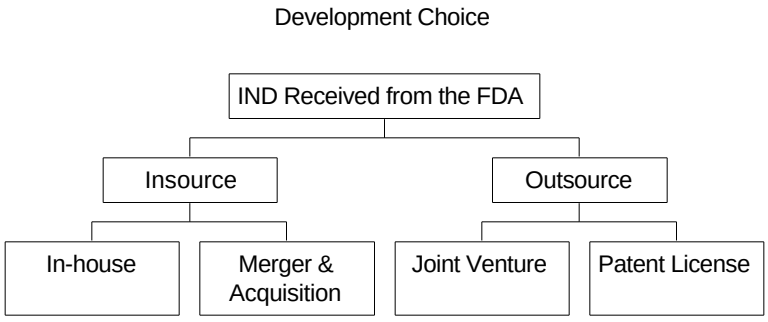
Our conclusions from the trend results, however, must be tempered by the possibility that this trend may take longer to show up in approved products than originally anticipated. A review of current products in the pipeline suggests that the addition of more recent data up through December 1997 may show a slightly greater proportion of new drug products brought to market via non-integrated methods.[45] Still, a majority of new therapeutic drug products emanate from in-house sources.[46] Despite these very recent trends, twelve years after the 1984 Drug Act and the 1984 Joint Venture Act, integrated R&D continues to be a prominent R&D strategy of firms in the industry.

To avoid the small cell problem we group the observations from the in-house and mergers and acquisitions categories into a combined integrated category, and the joint ventures, strategic alliances, and patent licenses into a combined non-integrated

[45] A good example of this recent trend towards non-integrated development is the recently approved treatment for cancerous tumors, Rituxan. This product was co-developed by Idec Pharmaceuticals and Genentech, Inc.

category. We present the results of a probit regression for a sample in Table 6. The dependent variable for these regressions is a 1-0 dummy variable that assumes a value of one for outsourced or non-integrated development and zero otherwise. We present the coefficient estimates as marginal probabilities evaluated at the mean values of the independent variables.[47] These results are consistent with our previous specifications. The coefficients for firm size, firm drug count, and public indicator are the most significant firm characteristics, and our firm patent count variable is significant at the 5% level. The trend coefficients are insignificant, and the therapeutic indicator for difficult products enters significantly with a negative sign, suggesting that complex new drug products are more likely to reach the market via in-house development.

An alternative model of the development decision characterizes the choice as a staged decision. At the first stage, the firm decides whether or not to outsource development, and in the second stage, decides among options within the chosen branch. We implement this using a nested logit framework. We consider the following tree structure:



[46] The biggest blockbuster drug of the year (1996), Evista, which has been shown to prevent osteoporosis in women, was discovered and developed in-house by Eli Lilly.
[47] The coefficient estimates for our binary independent variables (***biotech, foreign, public***, and ***ccca***) represent the effect of going from zero to one.

We model the choice as a function of the attributes of the choices, the attributes of the individual firm making the choice, and the interaction of individual firm attributes with the choice attributes.[48] Let $\Pi_{ij} = F_{ij} + \varepsilon_{ij}$, where F is a vector of attributes relevant for the firm's profit maximizing development decision, and ε_{ij} is a residual that captures the effects of unmeasured variables. This residual is assumed to be independently and identically distributed with the extreme-value distribution. The probability that a firm will choose the (i,j)th alternative can be represented by the following equation:

$P_{ij} = e^{F_{ij}} \Big/ \sum_{m=1}^{2} \sum_{n=1}^{2} e^{F_{mn}}$ where i = 1,2 (insource versus outsource choice) and j = 1,2 within each nest. If we suppose that $F_{ij} = \beta' X_{ij}$, where X_{ij} is the vector of observed attributes that vary with firm and drug we can write the likelihood of our (i,j)th alternative as

$P_{ij} = P_{j|} * P_i = e^{\beta' X_{ij}} / \sum_{k=1}^{2} e^{\beta' X_{ik}} * \left(\sum_{j=1}^{2} e^{\beta' X_{ij}} / \sum_{n=1}^{2} e^{\beta' X_n} \right)$. We employ full information maximum likelihood to obtain estimates for the log-likelihood, which is:

$\ln L = \sum_{i=1}^{4} \ln[\Pr ob(choice|branch) * \Pr ob(branch)]_i$, where branch = insource or outsource and choice is one of our four development choices.[49] The inclusive value for the ith branch = $I_i = \ln \sum_{j=1}^{2} e^{\beta' X_{ji}}$. This represents an estimate by our model of the probability that a particular development decision is included in one nest (say outsource) versus the other nests at that level. For a model to be feasible, the inclusive values must fall between 0 and 1, which provides a specification test during our estimation.

[48] See Maddala (1983) pp. 68-73 for a more formal presentation of the nested logit model.
[49] See Greene (1997: 923) for an explanation of why this method is preferred to the sequential estimation method.

Table 7 provides the results for our nested logit estimation. In this table we report the inclusive value for the in-house versus outsource nests, and the elasticity for the four attributes (ln [size], patent count, drug count, therapeutic indicator [***ccca***]) which we found to be significant in the earlier models. Our inclusive value for the insource versus outsource nest is .74, which is not statistically different from a value of one, suggesting that our nested logit model of the development decision does not provide a significant improvement over our non-nested estimations. This coefficient is related to the correlation in the error terms between development branches. A value close to one reflects the inability of our model to clearly distinguish between the decision to insource versus outsource. Since our value is not significantly different from one, we can assert that the nested framework is not the most appropriate framework for our analysis and fail to reject the independence of irrelevant alternatives assumption that is consistent with the multinomial logit estimation.

Our elasticity results, however, are generally consistent with our ordered probit regression, although we observe lower levels of significance here, and incorrect signs for some of the variables for our “internal” options, joint ventures and mergers and acquisitions. As previously noted, the merger and acquisition observations, although seemingly compatible with in-house development, prove problematic during our estimation. The basic results that we are left with, however, are encouraging in that they further support the relevance of several of our covariates for the pharmaceutical or biotechnology firm’s development decision.

Given the difficulty, theoretically and empirically, of ranking the merger and acquisition choice, we re-estimate both the ordered probit and multinomial logit

regressions on a subsample excluding the merger and acquisition category. These results do not change our coefficients appreciably from those presented in Tables 5, 5A, and 5B.

The final estimation that we conduct requires the least amount of restrictions on the covariates. Here we relax the assumption that development options can be ordinally ranked, and employ a multinomial regression model. We specify this as:

$$P(d=1) = \frac{e^{x\beta^{(1)}}}{e^{x\beta^{(1)}} + e^{x\beta^{(2)}} + e^{x\beta^{(3)}} + e^{x\beta^{(4)}}};\ P(d=2) = \frac{e^{x\beta^{(1)}}}{e^{x\beta^{(1)}} + e^{x\beta^{(2)}} + e^{x\beta^{(3)}} + e^{x\beta^{(4)}}};$$

$$P(d=3) = \frac{e^{x\beta^{(1)}}}{e^{x\beta^{(1)}} + e^{x\beta^{(2)}} + e^{x\beta^{(3)}} + e^{x\beta^{(4)}}}$$, where each of the numbered $\beta's$ corresponds to its respective decision group. We estimate the coefficients relative to the case of in-house development where ***d = 4***. Our multinomial logit regression results are presented in the second through fourth columns of Table 5. These results suggest that our previous ordering may not be robust. In contrast to the ordered probit results, in which the firm size coefficient exerts a significant and positive effect on the development choice, the firm size coefficients across the alternatives in the multinomial logit model do not monotonically increase from our least integrated option to our most integrated option. Firm size effects increase between the patent license option and the joint venture option, but fall as we move to the merger and acquisition option. In general, our other significant variables in the ordered probit regression such as patent stock, previous drugs approved and the therapeutic indicator increase or decrease across alternatives in a manner consistent with the order estimation. Constraining the development options to follow our hypothesized ordinal relationship to varying levels of integration, however, does not appear to significantly improve the fit of our model. The

cut point estimates in our ordered probit are consistent with the hypothesized ranking but are imprecise.[50]

The firm size and drug count variables are both significant, suggesting that firms with greater internal resources are more likely to develop their discoveries in-house. If a discovering firm has already invested in substantial development resources, as many of the larger pharmaceutical firms have done, it has no need to look externally to appropriate the returns from its discovery. Computing the marginal probabilities at the mean of our explanatory variables for the log (size) and patent stock variables for our first ordered probit specification, however, does not suggest particularly strong effects by these variables. For log (size), d (prob. of in-house development) / d (log [size]) = .05 at the mean value of our log (size) variable which is 5.5 or $244.7 million. This means that for an increase of 10% in annual revenues (a relatively frequent occurrence for pharmaceutical and biotechnology firms over the past decade) integrated development is only 0.5% more likely. For our patent stock variable, d (prob. in-house development)/d (ln [1 + patent stock]) = -.023 at our mean patent stock value of 6.15 or 468 patents. A discovering firm that increases its patent stock by 23 patents, (which is 5% of our mean value for patent stock) is .115% less likely to choose in-house development over other possible choices. A one-half standard deviation increase in a firm's patent stock decreases the probability of in-house development by 6%. These results are consistent with several interpretations. One possibility is that firms specializing in discovery (those with a significant number of discoveries) consider non-integrated development as a

[50] This result may reflect the fact that our dataset is populated with relatively few observations within the inner categories (joint venture and strategic alliance developments and merger and acquisition developments). Both of these categories will surely add more observations, as more recent data becomes available.

means of continuing to specialize in discovery. Another interpretation is that firms with a track record of discoveries are more capable of finding partners to assist them with development due to the elimination of asymmetric information inherent in the partnering process. A larger patent stock allows for potential partners to more effectively determine the expected value of investing in the development of a discovery by that firm.

Additional examination of our marginal effect tables yields the following additional results. Our most significant variable, drugs previously developed, with a coefficient three times its standard error, actually has a relatively small marginal effect on the probability of development choice. We find marginal effects of less than 1% across all possibilities in either specification, at least when computed at the mean level of previous drugs approved for our sample, 11. The distribution for this variable is particularly skewed, however, with over 40% of our sample with at most one previously approved drug product. Given this skewed distribution, a more appropriate measure of the impact of this variable on the development decision is to consider the marginal effect when going from zero to one, or given a one-half standard deviation increase in the number of previously approved drugs. To compute the marginal effect when moving from zero to one, we compute d[probability of in-house]/d[drug count] when the independent variables assume their mean value, and the drug count variable = 0. The marginal effect increases slightly to -0.009 from -0.008 for our multinomial logit and ordered probit model patent license option. The marginal effect due to a one-half standard deviation increase in the number of previous approved drugs is to induce a 12% higher probability for in-house development.

Our next most significant variable, the therapeutic indicator for difficult diseases has a very strong marginal effect in both the ordered probit and multinomial logit estimations. Drug products which fall into this category are about 10% more likely to be developed in-house versus non-integrated methods. This is a significant and interesting result suggesting that the drugs being developed for the most difficult diseases are more often than not being developed in-house. One possible interpretation of this result is that firms with previous development experience are more capable of undertaking more complex projects because they can more easily afford to withstand negative revenue shocks as compared to firms with fewer or no successful previous products. A more precise interpretation of this result would require a more thorough examination of the development of these specific products, which constitute 19% of our products.

Finally, note the consistency of the marginal effect results across our variables for the patent license and in-house options in Table 5A. In contrast to these marginal effects are the much smaller marginal effects found for the joint venture and merger and acquisition options. Given that the number of observations in those two categories is significantly smaller than for patent licenses and in-house developments, this outcome is not surprising.

Our econometric estimation then suggests that for a variety of estimations several of our hypothesized factors are consistently correlated with firm development decisions. In particular, firm development capability as evidenced by firm size, access to equity markets, and most importantly the number of previously approved drugs, are very important for predicting integrated new drug development.[51] In addition to these firm

[51] Interestingly, this contrasts with the finding in Pisano (1990) that firm size is irrelevant for the R&D-sourcing decision for a sample of biotechnology projects.

characteristics which predict integrated development, our patent stock variable tends to be associated with less integrated development throughout our analysis, suggesting a significant level of specialization in the discovery process even in our sample of approved drug products from 1985-96. The drug characteristic most important for determining the level of integration in the development process is surprisingly not our indicator for biotechnology or foreign origin, but our difficult diseases indicator. The trend towards non-integrated development fails to appear in any of our estimations.

VI. Interpretation of Results

Given the complexity of the phenomenon that we attempt to model here, it is difficult to link our empirical results directly with any of the various economic theories that attempt to explain the organization of R&D. We can, however, offer several plausible interpretations. Table 8 summarizes our empirical results across the various specifications we employed in our estimation. Four variables are consistently statistically significant throughout our analysis***: lnsize, patcnt, drgcnt, and ccca***. Four other variables are consistently insignificant throughout our analysis: ***bio, appyr, bioyr***, and ***foreign***. One other variable, ***public***, is only significant for our probit regression. Several other variables for which we had partial data, previous alliances, and reliance on drug sales were not included in the results presented here due to their incomplete coverage or in the case of time since first drug (***firstyr***), high collinearity with ***drgcnt***.

In general, our results are consistent with several descriptive conclusions. First, scale as evidenced by firm size is important for the drug development process. Second, firm drug development experience as evidenced by previous drugs approved is also very important for the drug development process. Third, specialization in discovery as

evidenced by the correlation of patent stocks and non-integrated development does characterize new drug development in the US over the past decade. Fourth, complex drug products are less likely to be developed through outsourced development. Additionally, despite significant potential synergies that could be realized through development outsourcing, biotechnology-derived and/or foreign discoveries have gotten to market through in-house development almost as often as through outsourced development. A viable interpretation of this result is that the transaction costs characterizing outsourced development have not been sufficiently reduced to entice firms to realize the potential synergies from interfirm efforts in new drug development. A more detailed explanation of this result requires additional analysis. The trend towards non-integrated development, which has been highlighted by the trade press, then appears to have progressed in a rather deliberate fashion.

In terms of how these conclusions relate to the economic factors emphasized in the previous literature on the organization of firm activities we refer to Table 3. Firm size is most likely related with all four of the factors we list in the first column of the table. As such, our consistently significant positive coefficient for firm size is difficult to interpret precisely. One interpretation consistent with the conventional wisdom regarding new drug development is that even though biotechnology may have reduced the economies of scale for drug discovery, it has not reduced the economies of scale for drug development.

The number of previous drugs approved for a firm is a variable that may be associated with asymmetry of information and appropriability. From the empirical results, the association between the number of previously approved drugs and the

propensity for integrated development is robust. As indicated in Table 3, the higher the number of previously approved drugs the lower should be the level of asymmetric information between that discovering firm and potential development partners. This would suggest a tendency towards non-integrated development. We observe, however, a strong tendency in the other direction. This suggests that the appropriability effect, which encourages in-house development, appears to be more significant. Alternatively, this result may indicate previous in-house choices and/or success.

The third firm characteristic that enters significantly throughout the analysis is patent count. This variable is arguable correlated with two of the four economic factors listed in Table 3, asymmetry of information and appropriability. Unlike with previous drugs approved, however, this variable is plausibly more closely correlated with reducing asymmetric information between discovering firms and possible development partners. In particular, increased patent stock may be correlated with greater appropriability on the part of a firm, and with less asymmetric information. The appropriability effect here encourages integrated development that would result in a positive patent stock coefficient. The asymmetric information reduction effect is more important, however, resulting in a significant negative relationship between patent count and integrated development. This result is also consistent with specialization in discovery.

The drug characteristic that is significant in our analysis is the indicator for difficult diseases, which is associated with uncertainty. This characteristic is also possibly associated with asymmetric information. The development process for more complex new products is most likely characterized by greater uncertainty and a higher degree of asymmetric information between discoverers and developers. In this case, both effects

appear to move development in the same direction, towards integrated development. This interpretation is consistent with our results, which show a strong positive correlation between the complexity of the disease target for new drug products and the level of integration in the development of those products.

Now we turn our attention to an interpretation of the insignificant correlations in our analysis. The biotech and foreign patent indicators that we expected to be negatively correlated with integrated development are not significant in any of our specifications. Biotechnology-derived new drug products comprise a small portion of the sample; and of the products that have actually made it to market, the focus of the analysis, nearly as many have been developed in-house as through outsourced development. This may be due to the difficulty in effectively transferring new biotech drug products for development during the infancy of the biotechnology industry, which is what is reflected in the dataset. A similar interpretation is appropriate for new products derived from foreign patents. The well-known difficulties inherent in coordinating cross-border interfirm new product development may have prevented many firms from choosing non-integrated development, despite the potential synergies from such development. The costs of such transactions may have outweighed the benefits in my instances. Both of these effects may arguably dissipate in the near future, as the biotechnology industry evolves into maturity, and as cross-national ties among drug and biotechnology firms increase. They appear to exert significant influence, however, for this sample of approved new drugs.

One final interpretation is in order regarding the insignificant results on the time trend variable, ***appyr***, and the interaction of the time trend variable with the biotechnology indicator, ***bioyr***. We had anticipated that as biotechnology became more widely

accepted that non-integrated development would become more feasible, because of the decreasing economies of scale for discovery and increasing returns to specialization in discovery. These effects were not reflected in the analysis for two possible reasons. First, the significant increase in alliances and non-integrated development in this industry is a relatively recent phenomenon, arising primarily in the 1990s. As such, this trend has not had time to be reflected in approved drug products (which normally take six or more years even today) through the end of 1996 (the extent of our sample). Second, industry observers may have underestimated the difficulties in overcoming the high transactions costs involved in effectively carrying out non-integrated development for new drug products. It appears to have taken pharmaceutical and biotechnology firms several years to develop effective interfirm governance structures to make non-integrated new drug development to work.

VII. Conclusion

The results from our analysis by conditioning on successfully marketed drug products contradicts the general perception that pharmaceutical firms have quickly adopted non-integrated R&D strategies to maintain their innovative capacity in the face of significant change in the industry. The generally perceived trend in new drug development towards non-integrated modes, which appear to provide greater value for consumers at relatively faster times to market, has not manifested itself to the degree portrayed in the trade press in newly marketed drug products, at least through the end of 1996. This result suggests that the integrated method of new product development has been more successful and resilient than generally believed, given that the industry has been considered an international success by most measures. Political pressure on

the FDA to speed approval has no doubt aided the trend towards faster time to market, and the advent of new technologies within the industry such as combinatorial chemistry and genomics has contributed to the move towards less integrated development arrangements. The experience of the pharmaceutical firms themselves, however, appears to have offset these forces to a degree. These conclusions are consistent with two observations made several decades ago by Williamson (1971: 122) regarding vertical integration in general. He observes that, “the extensive variety of circumstances in which internalization is attractive tends not to be fully appreciated” and “a broader a priori case for vertical integration of production exists than is commonly acknowledged.”

Through a variety of estimation techniques, several factors are consistently correlated with firm development decisions: size of the firm, patenting expertise, previous drug development experiences, and the therapeutic category of the firm. Their effects are consistent with our a priori hypotheses, but not easily interpretable within the framework drawn from existing theoretical research in the area. Econometrically, we do not find that the ordered probit and nested logit models provide significant improvements in estimation over the basic multinomial logit model. Although some rank ordering and differentiation between insourced and outsourced development appears consistent with the data, it is not strongly supported by the analysis.

Figure 1. Sequential Decision Model vs. Single-Choice Model

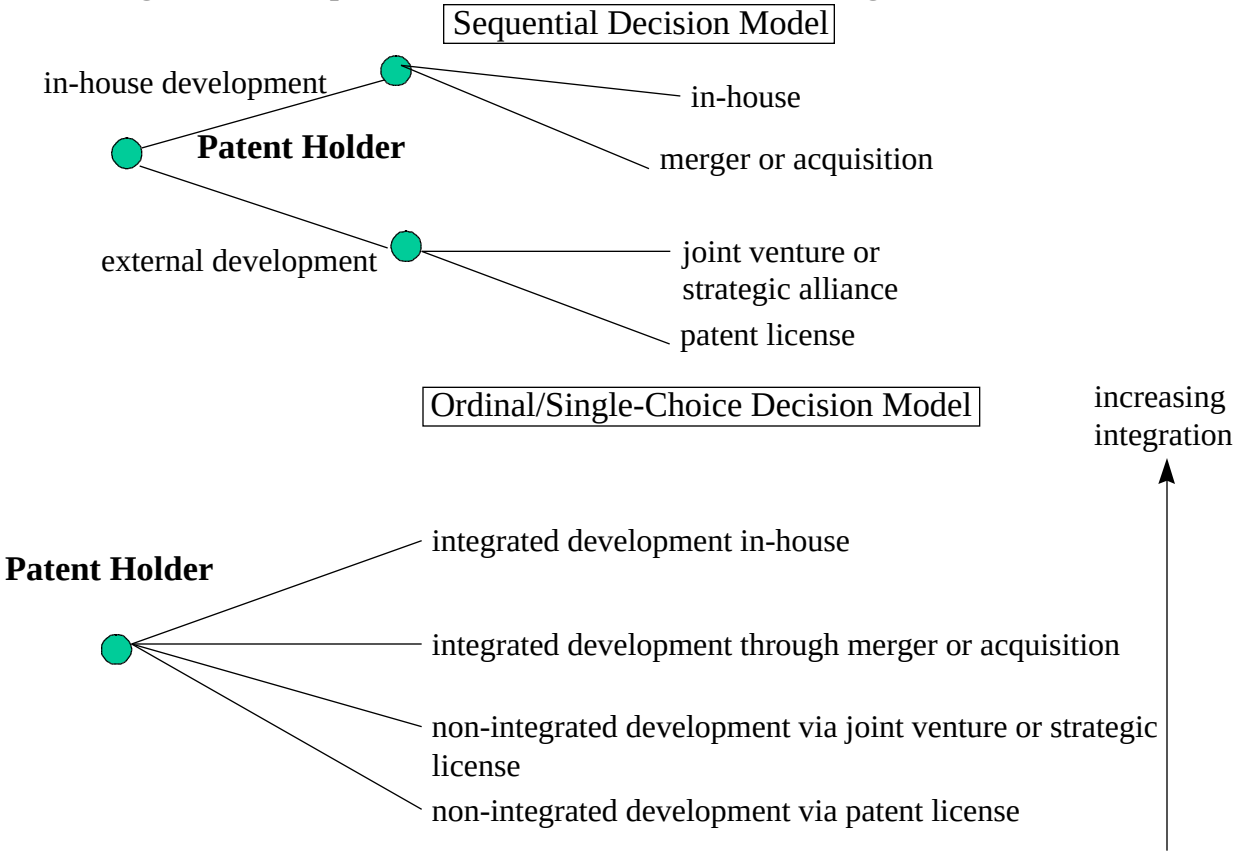


Figure 2. The New Drug Development Process

	Pre-Clinical Testing, R&D	**Clinical R&D**	**NDA Review**	**Post-Marketing Surveillance**
Timing	1-3 years	3-6 years	2 months - 7 years	As long as the drug is on the market
Description	Identify new moleculuar entity via animal and chemical testing	Phase I, II, & III clinical trials (safety, efficacy, and then safety & efficacy combined)		Continued Inspections
End Result	Patent & Investigational New Drug (IND) = FDA approval for testing in humans	Results in NDA Submission	NDA Approval	

Drug Discovery Phase | Drug Development Phase