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Development and Commercialization Strategies for New Technologies: Essays on Biotech Innovation

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Abstract

This dissertation presents two empirical investigations on central aspects of technological innovation. These are the formation and performance of pre-market alliances between firms with complementary capabilities, and the extent to which market size fuels innovation. The biotech industry provides the empirical context. This industry has grown to become the source of the most radical therapeutic breakthroughs, thus achieving enormous economic and societal importance. Owing to its rich data availability and well-structured development process, it constitutes an unmatched arena for quantitative research on technological innovation.

Category: Innovation, Entrepreneurship, Markets for technology, Pharmaceutical Industry
Keywords: Licensing, New technologies, Drug innovation, Biotechnology, Dynamic contracting, Innovation, Markets for technology

Development and Commercialization Strategies for New Technologies:
Essays on Biotech Innovation

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Essay 1: "Development and Commercialization Strategies for New Technologies: An Empirical Study of Pre-Market Licensing for Drug Innovation"

To an increasing extent, the innovation of new technology products has become a multi-firm effort: commercializing firms are not necessarily those that produce the key technological innovations. Upstream innovators and downstream commercializers meet in a market for intermediate technological inputs –a market for technology (Arora et al., 2001)– where trade operates through licensing contracts. Focusing on the drug innovation industry, in this paper I investigate the empirical determinants of upstream innovators' development and commercialization strategies when faced with the possibility of entering this market.

The emergence of biotechnology in the second half of the 1970's generated a drastic change in the process of drug innovation, eliminating large entry barriers to the production of drug candidates (Pisano, 2006). Since then, a fringe of small and highly specialized biotech firms has emerged to produce many of the most innovative candidates. Due to the large risks, high development and distribution costs, a common strategy for these firms is to partner with downstream big pharma commercializers, who contribute their important complimentary assets (risk diversification capabilities, funding for development, established sales force) in exchange for a share of market revenues. This study of biotech firms' development and commercialization focuses the important decision of whether to license the compound, and if so, at which stage of development to do it. I develop an empirical framework to rationalize substantial variation in observed propensities and time-to-license decisions, based on the importance of complimentary assets, the evolution of licensing contracts throughout stages, and the existence of imperfections of technology transfer.

Studying biotech firms' decisions in this context encounters two important challenges. The first is based on the fact that the licensing decision poses a dynamic trade-off. At each stage, a drug candidate's development may have to be terminated if testing results suggest it is not safe or efficacious enough. In addition, licensing contracts become more attractive for biotech firms the more advanced the development stage is. Thus, in deciding whether to license, a biotech manager

weighs the risk of observing adverse testing results that lead to development termination against the benefits of a more attractive later stage licensing contract and the option to in-house commercialization. I model this trade-off explicitly, assuming that biotech decisions can be cast as those of a rational dynamic optimizing agent. Licensing contracts depend on the stage of development a compound is at, its market potential, and other idiosyncrasies of the negotiation process. Consequently, by choosing to keep the compound on in-house development for one further stage, a biotech firm exposes itself to two types of uncertainty, one stemming from the compound's testing outcome and the other from the negotiation of contracts.

The second challenge spurs from the imperfect nature of the technology transfer process. The novelty and complexity of underlying technologies, and the imperfect contractibility of post-licensing biotech success-promoting actions create the potential for adverse selection and moral hazard problems. The relevance of these frictions is consistent with the observed design of contracts, which deliver most compensation in form of contingent payments. Contracts have three parts –upfront fees (paid at time the deal is struck), milestone payments (paid as the compound enters new development stages), and royalties (paid as a share of market revenues)– and it is estimated that contingent payments (milestones and royalties) make up for as much as 80% of potential compensation (Ernst and Young, 2012). The employed dataset offers further reinforcement for the existence of these imperfections, as it allows us to observe a success gap: at each stage of development, in-house (i.e., not yet licensed) compounds are significantly more likely to generate successful development outcomes than licensed ones.

To account for the strategic implications of imperfections in technology transfer, we model contracts' three-part structure and allow for both adverse selection and moral hazard. A compound's probability of advancing past a given development stage is assumed to shift with technological and regulatory observables, but also with its quality and the level of effort exerted by the biotech firm. Quality is observed by the biotech firm but not by potential big-pharma in-licensors, who only observe its distribution in the population. Development effort is chosen by the biotech firm on a period-by-period basis and its provision cannot be contracted upon. Contracts incentivize the licensing of high quality compounds and the exertion of effort with milestone payments and royalties. The microeconomic structure imposed by the model plays a functional role, as it allows us to augment from data the two key variables –compounds' qualities and biotech firms' effort– that are otherwise unobservable.

Making imperfections in technology transfer explicit in the model allows us to establish a connection between firms' strategies and the productivity of drug innovation, as the anatomy of the

adverse selection and moral hazard problem may impact the number of candidates that reach the market and their average cost. Establishing their relative significance is important, since different conclusions inform managerial and public policy in different ways. Empirically, we are able to identify adverse selection because firms holding higher quality compound face lower risk to wait until further stages to license, therefore, conditional variation in time-to-license reveals the distribution of privately observed compound qualities. Furthermore, naturally occurring development attrition modifies compounds' market potential, introducing identifying variation that allows me to pin down firms' provision of effort. Evidence of reduced form models supports our identification rationale and suggests that adverse selection is the more important problem of the two.

Results of the structural model reveal a sharp divide in compounds' intrinsic probability of achieving successful outcomes, as given by the effects of privately observed qualities. About a quarter of compounds entered into the testing process have low quality, which implies a significant disadvantage: at each stage, their intrinsic probability of achieving successful outcomes is about 0.13 lower than that of high quality counterparts. This induces strong licensing dynamics that make of adverse selection the success gap's primary cause. Biotech firms license low quality compounds early in the process and hold on to high quality ones for longer, retaining the option for in-house commercialization or a more attractive late-stage licensing contract. Big pharma firms' in-licensed pipelines get rapidly crowded with low quality compounds, which cause them to underperform. While biotech firms' effort increases success probabilities in as much as 0.03, its provision does not meaningfully drop after licensing, suggesting that moral hazard is a less important determinant of the gap. These results are consistent with the findings of Pisano (1997), but stand in contrast with those Danzon et al. (2005) and Arora et al. (2009), who find no evidence of adverse selection. Differences in results may be explained because, as opposed to these studies (and others in the literature, Guedj, 2005; Allain et al., 2011), we make explicit dynamics and contract design.

Estimates of development and distribution costs show that the former are generally higher, but have a disproportionally large effect on the probability of licensing. Empirically, we proxy for development costs with the number of patients enrolled in each phase of clinical trials, and for distribution costs, with the number of active physicians in the specialties that prescribe each drug. This result follows because distribution costs are contingent upon (the relatively unlikely event of) receiving FDA marketing approval, while development costs are sunk as the compound advances through testing stages. Biotech firms holding low quality compounds are relatively less sensitive to either type of cost, as their licensing decisions are primarily driven by the need to avoid the

relatively larger attrition risks. In contrast, firms holding high quality compounds are more likely to develop the compound through the more expensive late-stage trials or commercialize it in-house, making their licensing decisions more sensible to the magnitude of costs. From these insights, I conclude that currently used valuation practices and big pharma in-licensing strategies may benefit from incorporating behavioral determinants of biotech firms' licensing decisions in their assessments of compounds' probabilities to reach the market.

My results point to the importance of complementary assets as determinants for the propensity to partner with established firms, which has been highlighted in literature of commercialization strategies in markets for technology (Teece, 1986; Rothaermel, 2001; Arora et al., 2001; Arora and Ceccagnoli, 2006) and markets for ideas (Gans et al., 2002; Gans and Stern, 2003; Luo, 2011). As opposed to existing empirical studies, the structural framework herein providea sharp estimates of their causal effects on behavior of innovators. These findings also inform the marketing literature in that this has so far focused on the interaction of R&D and marketing capabilities within a single firm (Griffin and Hauser, 1992, 1996; Moorman and Slotegraaf, 1999; Dutta et al., 1999), as opposed to the increasingly relevant scenario of multi-firm based innovation (Chesbrough, 2003). Besides the focus and timing of innovation efforts (Cohen et al., 1996; Sorescu et al., 2003; Chandy et al., 2006), in this context, I emphasize, the extent to which a consumer-oriented firm will generate successful innovation outcomes depends on its marketing capabilities, the ability to identify external potential and set the correct contractual incentives.

Examining the effects of contract design, it is observed that royalty rates are the most relevant part of contracts, in the sense that they have the highest impact on the propensity and time-to-license. Indeed, we estimate that a 1% increase in royalty rates increases in 3.15% the probability of reaching the market having been licensed, while for upfront fees and milestone payments, this impact is much lower, respectively at 0.08% and 0.35%. Marginal increases in royalty rates increase the probability of licensing at all development stages, but particularly towards the end of the process, suggesting that they have the potential to incentivize firms who would have otherwise commercialized their compound in-house to partner with big pharma, and to do it as the compound nears the market.

These results highlight the connection of my research with a literature that rationalizes contract design for technology transmission, or more broadly, the licensing of intellectual property (Kamien and Tauman, 1986; Gallini and Wright, 1990; Macho-Stadler et al., 1996; Bousquet et al., 1998; Choi, 2001; Jensen and Thursby, 2001; Crama et al., 2008; Dechenaux et al., 2009; Harris et al., 2012). This literature has mostly focused on two part contracts (upfront

fees and royalties) and encountered difficulties explaining the simultaneous use of milestone payments and royalty rates. While my results do not speak to the determinants of contract design, this paper makes a contribution by illustrating how different sources of identification can be combined to estimate the impact of contract design on licensors' behavior, while recognizing the existence of uncertainty over contracting opportunities and the fact that bargaining power may not reside on only one of the parties.

Essay 2: "Pharmaceutical Profits and the Social Value of Innovation" (with David Dranove and Craig Garthwaite)

The profits of pharmaceutical firms receive a large amount of attention and have caused many in the popular press and policymaking community to propose various policies to limit them (e.g. Rome, 2013). Critics claim that firms selling branded drugs under patent protection set prices at many multiples of marginal costs, excessively exploiting both their monopoly power and the inelastic demand for these often life-saving products. Industry defenders counter that high prices are necessary to offset expensive and uncertain research and development, and that if profits were to fall, incentives for future innovation would suffer. Danzon (2000) provides the quintessential defense of the industry: "[a]ny form of price regulation, including the setting of uniform prices within the United States or cross-nationally, would discourage innovation." Similarly, discussing the re-importation of low-price pharmaceuticals to the United States, Bast (2004) wrote "increasing importation means cutting off the stream of investment that makes this system sustainable. It means fewer new lifesaving drugs."

Many studies bolster the arguments of pharmaceutical industry supporters by documenting a causal relationship between expected profitability, primarily from changes in market size, and new products. Some of these studies find a link between demand and research activity (Ward and Dranove, 1997; Kyle and McGahan, 2012; Blume-Kohut and Sood, 2013; Finkelstein, 2004) while others find that higher expected profits result in a greater number of products actually reaching market (Acemoglu and Linn, 2004; Finkelstein, 2004; Cerda 2007; Dubois et al., 2014).

Industry critics counter that most recently approved new drugs are little more than slightly modified versions of existing products whose development costs far outstrip any benefits (e.g. Spector, 2005; Angell, 2012). Marcia Angell, former editor of the *New England Journal of Medicine*, has been an outspoken critic stating "[i]n fact, the big drug companies now concentrate mainly on … producing *variations of top-selling drugs already on the market* (emphasis added) —called 'me-too'

drugs. There is very little innovative research in the modern pharmaceutical industry, despite its claims to the contrary" (Angell, 2010). According to Angell and other industry critics, restrictions on industry prices and profits will not harm welfare even if they deter new product development, because they will largely affect this "me-too" innovation.

Prior research connecting demand and research investments does little to address the concerns of these industry critics because the studies generally fail to determine whether the marginal products are actually "innovative," i.e. they make positive contributions to social value, or simply represent rent-seeking by private firms. For example, Acemoglu and Linn (2004) found an increase in *new molecular entities* targeting conditions with growing patient populations which they suggest represents new innovation. However, they do not distinguish between new molecular entities that represent genuine welfare-improving therapeutic breakthroughs and those that are simply "variations of top-selling drugs already on the market." As an illustration of this point, consider the first anti-cholesterol statin drug Lovostatin. This product uses a radically different biochemical pathway which makes it far more effective than prior cholesterol reducing drugs. Therefore, it might be considered more innovative, i.e. offer a larger increase in welfare, than the subsequent ten statin drugs to reach the market, all of which were new molecular entities that effectively use the same pathway as Lovostatin. Since each subsequent statin was a new chemical entity, Acemoglu and Linn's classification would broadly consider each to be equally innovative.

We contribute to this debate by examining how biotechnology firms responded to the creation of Medicare Part D (hereafter Part D) – a large expansion of pharmaceutical insurance coverage for elderly Americans. Blume-Kohut and Sood (BKS; 2013) found that Part D increased research investments in the overall pharmaceutical sector. However, much like the previous literature, BKS did not distinguish between the type of firm (i.e. traditional pharmaceutical or biotechnology), the type of pharmaceutical (i.e. small molecule or biologic), or any other measure of the potential welfare contributions of the new products. Without these distinctions, it is possible that most of the research activity identified in BKS provides little social value because it involves the me-too products frequently cited by critics of pharmaceutical firms. We overcome this limitation by classifying research activity using several measures of the novelty of the innovation.

This classification is not merely an exercise in taxonomy. At the broadest level, new pharmaceutical products can improve health and/or decrease prices, both of which provide value to consumers but have far different welfare consequences. If research investments in the pharmaceutical sector are aimed at "me-too" products then they primarily represent business stealing. If the demand in the product category is inelastic, as is the case with many

pharmaceuticals, this business stealing may lower prices without meaningfully increasing welfare. However, if investments result in novel products that improve health, they will increase welfare – though much of the increase may initially be captured by pharmaceutical firms through monopoly prices charged while the product is under patent. Partly as a result of this distinction, Weyl and Tirole (2012) suggested that monopoly rights granted under intellectual property law should, to some extent, be a function of the social value of the product rather than simply its chemical composition.

It is not surprising that previous work has failed to systematically classify individual products based on their contribution to social value. Trusheim, Aitken and Berndt (2010) state, "[i]t is difficult if not impossible to quantify reliably, objectively and unambiguously the extent to which new biopharmaceuticals embody significant innovation and address unmet medical needs." This difficulty stems, at least in part, from the fact that drugs can be novel across two broad attributes, both of which are difficult to fully quantify. First, a product could be a true innovation in molecular development and therefore represent *scientific advancement.* Products in this category are by definition not simply variations of existing treatments. Second, new products could expand treatment applications by targeting conditions that previously had few or no existing options. Products exhibiting such *therapeutic innovation* likely have the most immediate effect on welfare. However, scientific advancements may also contribute to welfare for conditions with existing treatments by offering novel pathways for patients that do not respond to available options. In addition, progress in basic science could facilitate the future development of products that target untreated conditions. New products that are neither meaningful scientific advancements nor an expansion of treatment applications primarily represent business stealing with little welfare improvement.

Of course, each new product represents varying degrees of scientific advancement and therapeutic innovation, which makes classifying them on a product by product basis quite difficult. This is particularly true for products that are relatively early in development process. In our analysis, we take two steps in that direction. First, we concentrate on products developed by biotechnology firms. The firms in our sample distinguish themselves from traditional pharmaceutical firms by primarily using biological technologies and/or targeting conditions that have an unmet medical need (Thompson Reuters, 2014). Biological products (biologics) are, almost by definition, scientific advancements to some degree. They certainly are not "variations of top selling" small molecule drugs already on the market and, by the nature of the science, they are not even simple variations of each other – i.e. one cannot easily create a new biologic through a simple

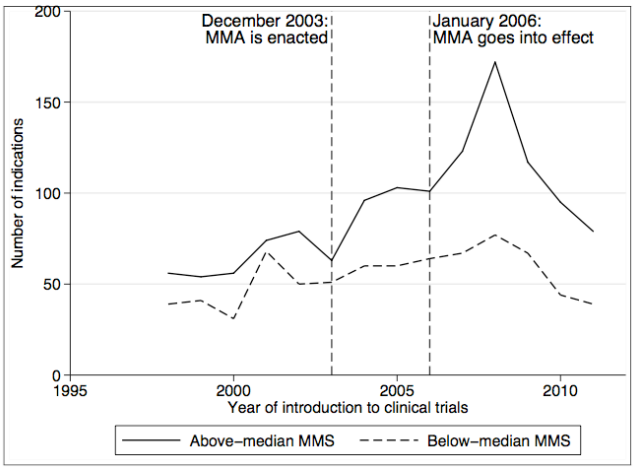
manipulation of an existing one. In addition to biologics, many biotechnology firms also research and produce a limited number of small molecule products targeting unmet medical needs such as hepatitis C (Gilead's Sovaldi) and multiple sclerosis (Biogen Idec's Tecfidera). We are unable to separately identify all small molecule products in our sample, but note that they are in the minority.

By demonstrating a specific link between demand and research in the biotech sector, we can provide initial evidence that profitability drives the development of products that are likely to be scientifically innovative. We also consider whether profitability drives the development of therapeutically innovative products. First we note that as a product category, biologics have historically represented therapeutic innovations. For example, these products are more likely than small molecule products to target orphan diseases which are designated by the FDA as relatively rare diseases that lack existing treatments (Trusheim, Aitken, and Berndt, 2010). However, this historical description may not apply to the new research activity after a marginal demand shock and, as we noted above, some biotech products in our data are small molecules. Therefore, we next distinguish between those biotech products that are "first to treat" a condition (henceforth FTTs) and those that augment the arsenal (henceforth AAs).

Though there will be exceptions, it is likely that FTT drugs provide greater welfare benefits than AAs. For example, contrast Gilead's small molecule product Sovaldi with Sanofi's biologic product Zaltrap. Sovaldi provides the first cure for hepatitis C and represents a large welfare increase, which Gilead is set to capture through very high prices that are unlikely to greatly limit demand. In contrast, Zaltrap treats metastatic colon cancer, which is treated to a similar degree by several existing products such as Avastin, Erbitux, Stivarga, and Vectibix. Perhaps as an indication of its relatively small welfare contribution, Sanofi's revenues from Zaltrap put it far short of blockbuster status.

We acknowledge that the FTT versus AA distinction may fail to capture some important aspects of therapeutic innovation. Therefore, we also consider whether marginal demand shocks encourage socially valuable products as indicated by three designations awarded by the FDA during the development and review process: orphan drug designation, fast track status, and priority review. As mentioned earlier, orphan drugs treat rare conditions lacking existing cures. The FDA grants fast track status to drugs undergoing clinical trials that promise to provide treatment for conditions for which no other drug works as well. Similarly, the FDA grants priority review to promising drugs that have completed clinical trials and await final approval. Together, these three designations are intended to promote the development of welfare improving products.

Figure 1: Number of new indications by Medicare Market Share (MMS)

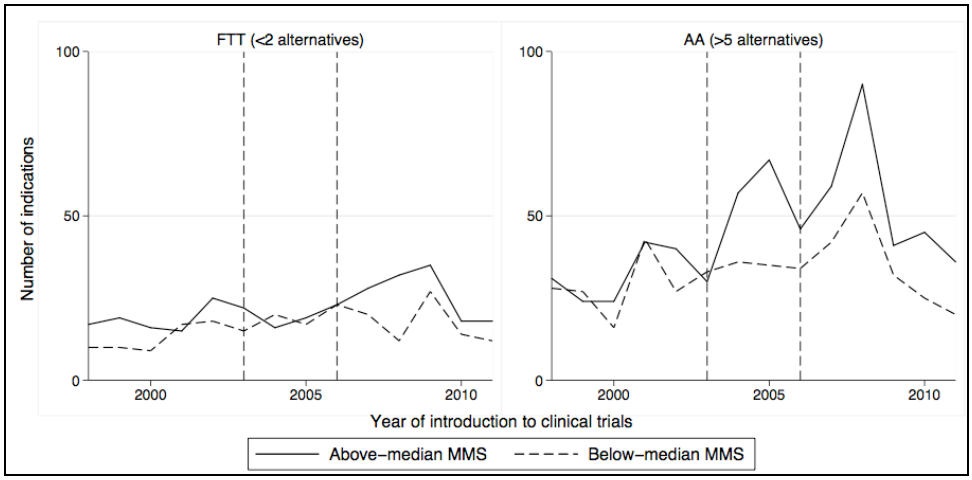


We find that following the passage of Part D there was a relative increase in clinical trial activity for biotech products aimed at diseases that have a higher Medicare market share (MMS), i.e. diseases that are more prevalent among elderly Americans. Figure 1 shows the number of clinical trials by whether a disease has an above or below median MMS. Prior to the passage of Part D, clinical trial activity was very similar in level and trend across these two categories. However, after the passage there is a marked increase in clinical trials for products aimed at drugs with a higher MMS. The number of clinical trials for above-median MMS drugs peaks in 2008 and then declines. A similar decline is seen for below-median MMS drugs suggesting that this was primarily a secular change, perhaps as a result of the broad decline in the macroeconomy. These results are generally similar to the pattern for the more traditional pharmaceutical sector contained in the data used by BKS. However, as discussed earlier, the biologics that represent the major component of the product portfolio for the biotech firms in our sample, are generally more scientifically and therapeutically innovative than small molecule products. Therefore, our results suggest the increase in expected profits did more than simply spur the development of "me-too" products and instead encouraged some degree of scientific advancement.

The extent to which expansions in market size can spur therapeutic innovation is unclear, as pre-existing scientific barriers may outweigh any marginal increases in profitability. Figure 2 previews the results of these analyses. The left panel contains the number of indications entered to clinical trials by above or below median MMS status for diseases with at most one existing treatment (i.e. FTTs). Both categories have a large and similar number of clinical trials each year before Part D – suggesting that this was a relatively active area of research that was not driven by the average age of the patient population. There is no change in this pattern following the passage

of Part D. This suggests that scientific rather than market barriers are the constraint on investments in FTTs.

Figure 2: Number of indications, MMS and number of available therapeutical alternatives.



In contrast, the right panel of figure 2 contains the number of clinical trials by year for diseases with five or more existing treatments (i.e. AAs). Prior to the passage of Part D there was little difference in the level or trends in clinical trial activity based on MMS. Beginning immediately after the insurance expansion there was a marked increase in the number of clinical trials for products aimed at diseases with an above median MMS. Figure 2 suggests that research activity for AAs is far more sensitive to demand shocks than for diseases with FTTs. We find thematically similar results when we look at FDA designations of a product's innovativeness—i.e. there was no increase in innovative products targeting the elderly after the passage of Part D.

Taken together, our results provide a far more nuanced view of innovation in the pharmaceutical sector than is offered by either supporters or critics of the industry. In the biotech sector, a category dominated by firms believed to be creating a greater proportion of scientifically innovative products, we see a clear response in research activity following a demand shock. This demonstrates that, at the broadest level, financial incentives do more than simply reward pure copy-cat firms. However, our results also suggest that, at least over the first decade, marginal changes in demand do not appear to spur new clinical trial activity for diseases that currently have few to no treatment options. It is possible that it takes longer than a decade to generate the science necessary to develop truly innovative products that are ready for clinical trials. However, it is important to note that our indicator of research investments, the first clinical trials for human subjects, is fairly early in the drug development process. At a minimum, our results show that if Part D spurred the new science necessary for FTT drugs, it will take a long time for consumers to realize the benefits.

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