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The impacts of the rise of Paragraph IV challenges on startup alliance formation and firm value in the pharmaceutical industry

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ABSTRACT

Court decisions in 1998 encouraged generic producers to pursue Paragraph IV patent challenges. A follow-up decision in 2000 marked the first successful challenge involving a blockbuster and brought further attention to this pathway for generic entry. We consider the impacts of these decisions on R&D-based startups, and we focus on the propensity to form alliances as a primary channel of impact. We find substantial negative impacts on alliance formation and firm value, and only the first event's impacts are restricted to small molecules. The results suggest that policy analyses in settings with R&D-based startups should consider impacts on alliance formation.

1. Introduction

Solow (1957) established that innovation is the primary source of long-run economic growth. The contribution of innovation to welfare is perhaps most important in the area of health, and Murphy and Topel (2003, 2006) estimate that enormous welfare gains could result from even incremental improvements in the rate of discovery of medical innovations. Given this, it is important to conduct thorough assessments of policies that impact the generation and diffusion of medical innovations.

This paper focuses on intellectual property rights (IPR) policies in the pharmaceutical industry – a key source of medical innovations. Nordhaus (1969) describes how optimal policies must strike a balance between innovation and diffusion: weakening IPR reduces innovation, while strengthening IPR reduces the diffusion of existing products and processes. Judicial decisions in 1998 and 2000 (described in detail in the next section) affected the balance between innovation and diffusion by encouraging generic producers to pursue "Paragraph IV" patent challenges against innovators. We analyze the impacts of these policy changes on R&D-based startups, and we focus on the propensity to form alliances as a primary channel of impact.

The role of alliances in policy analysis is understudied, and a more typical approach would focus on other channels of impact, such as the rate of startup formation or the direct impacts on the flow of discovery research projects or candidates in development (as opposed to indirect impacts due to fewer alliances). These channels are likely to be less important in our context. R&D-based startups in the pharmaceutical industry are typically founded to commercialize academic findings, and given the difficulties associated with forecasting profitability at early stages of R&D, founding decisions likely depend more on the state of academic research than economic factors. Zucker, Darby, and Brewer's (1998) results are consistent with this view: the availability of star scientists is positively associated with the number of startups formed each year, whereas the availability of venture capital and measures of the state of the economy are not. Given this, policy changes that impact profitability likely impact startup formation and the choice of projects to pursue less than in other contexts. Further, Danzon et al. (2005) results suggest that younger firms are less likely to aban-

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don candidates in the face of bad economic prospects than older firms. Less experienced firms might not recognize weaknesses, or they might worry more about damaging the firm's image with potential investors than the ultimate impacts on profits. Highly specialized human capital might also make firms reluctant to abandon projects.

While startups might underemphasize prospects for profitability in their decision making, Nicholson, Danzon, and McCullough's (2005) results suggest that potential allies are uniquely positioned to assess these prospects. Potential allies have clear incentives to act on their information by forming alliances involving good projects and avoiding others, so policy changes that reduce profitability likely impact alliance formation. Policy changes might also impact contract terms (see Lerner and Merges, 1998 and Higgins, 2007 on the allocation of contractual rights in alliances), but we limit our scope to formation. For marginal alliances (where both parties are close to indifferent between pursuing the alliance and pursuing other opportunities) it will often not be possible to revise terms to satisfy both parties in the face of a decline in expected profits. Thus, we expect to see an impact of profit-reducing policies on alliance formation, and our empirical results suggest that such an impact occurs.

There was no generic pathway for "large" (primarily biological) molecules during the period we examine (1995–2007), so our tests allow for different impacts on traditional "small" molecules and large ones. However, as Paragraph IV challenges lead to more generics, the resulting lower market shares and prices reduce the prospective returns of all types of subsequent R&D in the affected classes, not just R&D involving small molecules, so we expect to see eventual impacts on large-molecule alliance formation. There are also factors other than the policy changes we consider that could cause the size-specific propensities for alliance formation to evolve in different ways over time. For example, the high prices received by some large molecules in rheumatoid arthritis and oncology during the period we examine likely made large-molecule alliances relatively more attractive in these areas. However, the critical issue for our analysis is whether large vs. small molecule opportunities in these or other areas shifted substantially in 1998 or 2000 (which seems unlikely). Beyond these considerations, firms likely anticipated that a generic pathway for large molecules would eventually emerge. Given that it takes an average of 12 years to go from initiating research to introducing a new approved drug (DiMasi et al., 2003; DiMasi and Grabowski, 2007), firms evaluating large-molecule projects late in our period might expect to face essentially the same IPR regime as small molecules by the time a marketable product would be available.

Our findings suggest there were impacts on small molecules initially and more widespread impacts later on. The 1998 event results in substantial long-term reductions in small-molecule alliance formation, while the 2000 event has a negative impact on all molecules. Limited evidence also suggests that the events increased alliance terminations, and terminations involving small molecules were affected more. The events reduced firm value, and the impacts on young firms are comparable to those on large established firms. Portfolios in which firms lack previous alliances for their molecules in R&D suffer more, and for the 1998 event, firms with a greater fraction of small molecules in their R&D pipelines experience greater negative effects. On the whole, our results suggest that the reduction in expected patent protection reduced the incentives of strategic partners to form R&D alliances with young firms, and the value of the impacted firms fell. We conclude that a thorough assessment of the policy change inherent in the judicial decisions must consider impacts on R&D-based startups.

2. IPR policy changes and Paragraph IV patent challenges

The time a drug spends in human clinical trials has been rising for decades (DiMasi et al., 2003). Firms typically apply for one or more patents involving their molecules prior to beginning phase 1, so much of the patent life of a new molecule is used up during the development period. The resulting reduction in expected profits reduces the incentive to undertake R&D. The Drug Price Competition and Patent Term Restoration Act of 1984 (commonly referred to as the Hatch-Waxman Act) addressed this problem by extending the patent life of innovator drugs. Policy makers recognized the basic Nordhaus tradeoff described above, so they also included the abbreviated new drug application (ANDA) approval process, which allows generic drugs to be approved without going through clinical trials. Prior to the Hatch-Waxman Act, generic firms would typically have to wait until the innovator's patent expired to even begin clinical trials on their generic copies (assuming, as was typical, that rights would not be licensed by the patent-holder). After the amendment, generics were only required to satisfy the lesser requirement of bioequivalency, and their efforts were permitted to begin well prior to patent expiration, so generic drugs could be marketed as soon as patents expired.

For our study, the Hatch-Waxman Act's requirements regarding IPR are of particular concern. Our summary draws from three main sources: www.paragraphfour.com (accessed December 2008), FDA (1998), and FTC (2002). Under the Hatch-Waxman Act, innovators are required to list their drug-specific patents in the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book). When a generic firm files an ANDA, it makes one of four possible claims. The first is that there are no patents listed in the Orange Book. The second is that the listed patents have expired. The third is that the FDA should grant approval effective after the date the last patent expires. The fourth, which is the Paragraph IV filing, is that either the generic product does not infringe on the listed patents or that those patents are not enforceable. We focus on Paragraph IV filings.

If a generic firm is the first to file its ANDA with a Paragraph IV certification and is successful, it is granted a 180-day period of market exclusivity that begins either from the date of the first commercial marketing of the generic or from the court decision declaring the patents invalid or not infringed, whichever comes sooner (once the innovator is notified of the generic firm's Paragraph IV filing it has 45 days to file a patent infringement action against the generic firm). During the 180-day exclusivity period, no competing generic firms can produce the drug. Of course, even with the FDA's grant of exclusivity, generic firms still face risks if they enter prior to success in the patent dispute, and penalties for infringement can result in payments to the patent-holder of up to three times actual damages. Because of this, generic firms typically wait to market their drug until either a court has decided in their favor or it becomes clear the innovator will not file for infringement.

The 180-day exclusivity period provides a strong incentive to be first to file, because avoiding other generic competition results in exceptional profits. Grabowski and Vernon (1992, 1996) find that the average branded price immediately prior to patent expiration is six times the generic price after generics have diffused, and Grabowski and Kyle (2007) show that on average, 4–7 generic firms begin producing generic versions of the off-patent product in the year following patent expiration. Such dramatic price reductions and rapid entry quickly deplete above-normal profits. In contrast, under generic exclusivity, all the generic firm must do is slightly undercut the price of the branded competitor in order to obtain a large market share, and it can enjoy a high markup and high profits for a 6-month period. The generic firm's market share would also benefit from state-level drug substitution laws that encourage or