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Economics of the Pharmaceutical Industry

Patricia M. Danzon*

The pharmaceutical industry is important because it is a major source of medical innovation. The U.S. research-based industry invests about 17 percent of sales in R and D, and R and D drives performance of individual firms and industry structure. It is also a heavily regulated industry. Drugs are evaluated for safety, efficacy, and manufacturing quality as a condition of market access, and promotional messages must adhere to approved product characteristics. Drug prices also are regulated in most countries with national health insurance systems. My research on the pharmaceutical industry has examined issues related to R and D performance and industry structure, and the effects of regulation on prices, availability, and utilization of

drugs, and on productivity.

R and D, Firm, and Industry Structure

Regulation of market access and promotion derives from uncertainty about drug safety and efficacy. These product characteristics can only be determined from accumulated experience over large numbers of patients in carefully designed trials or observational studies. The design, monitoring, and evaluation of these studies are public goods that in theory can be efficiently produced by an expert regulatory agency.¹ The 1962 Amendments to the FDA Act extended the powers of the FDA to review safety, efficacy, manufacturing quality, and promotion. Subsequent studies concluded that the safety and efficacy requirements added to the intrinsically high cost of R and D, led to launch delay of new drugs and favored large over small firms.

However, more recently the biotechnology revolution has transformed the nature of drug discovery and the structure

of the industry. Increasingly, new drugs originate in small firms, which often out-license their products to more experienced firms for later-stage drug development, regulatory review, and commercialization. In any year the biotechnology industry may comprise a couple of thousand firms, but the identity of these firms changes, as new start-ups are formed and established firms grow, merge, or are acquired by other established companies. Although larger firms have grown in market share, because of mergers, their performance has lagged that of smaller firms, on whom the large firms increasingly rely for new products.

In a series of papers, I and my co-authors have examined the effects on R and D productivity of firm experience and alliance relationships; the nature of the market for alliances between small and large firms; and the effects of mergers and acquisitions. In a study of the determinants of drug success in clinical trials,² we find that returns to a firm's overall experience (number of drugs developed across all therapeutic categories) are small for the relatively simply phase 1 trials, but

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significantly positive (with diminishing returns) for the larger and more complex phase 2 and phase 3 trials that focus on efficacy and remote risks. We find some evidence that focused experience is more valuable than broad experience ("diseconomies of scope across therapeutic classes"). Products developed in an alliance have a higher probability of success in the more complex late stage trials, particularly if the licensee is a large firm. Thus although larger firms enjoy economies of scale in experience for the complex trials, smaller firms can tap into this expertise through licensing agreements.

Product development deals thus define the sharing of responsibilities and rewards between large and small firms. The small firm typically gets cash and/or equity up front, plus contingent milestone and royalties payments, and may choose to participate in late-stage development and co-marketing, in order to gain experience. In return, the large firm obtains rights to develop and market the new product, retaining the majority of product revenues, with specifics depending on the stage of the deal. The efficiency of the market for deals is important because it allocates rents between the smaller and originator firm, as opposed to the larger developer/marketer, and hence influences incentives. It also provides interesting evidence on how participants use contractual structure to control possible distortions attributable to symmetric information and agency.

Our analysis examines the determinants of deal prices, with the caveat that the reported financial values are the simple sum of up front cash, equity, and contingent milestone payments, ignoring the latter's uncertainty and lags; other contractual terms are not reported.³ We find that inexperienced firms received substantially discounted payments on their first deal, although this discount was not consistent with the post-deal performance of these drugs. However, we find that these first deals are associated with substantially higher valuations from venture capital and public equity markets. This evidence suggests that a deal with an experienced pharmaceutical company validates a start-up company's products, sending a positive

signal to prospective investors, and making the deal discount a worthwhile investment for the small firms.

In addition to product licensing, mergers and acquisitions (M&A) are common in the pharma-biotech industry. Large horizontal mergers were particularly frequent in the late 1980s and 1990s, while pharmaceutical acquisitions of biotech companies have become more common recently. Several of the largest firms are the result of successive large horizontal mergers, and this has contributed significantly to industry concentration. Such mergers are often rationalized on grounds of economies of scale and scope in R and D, marketing, and administration. In our analysis of M&A in the pharma-biotech industry, we tested various alternative hypotheses to explain both large and smaller mergers, and then examined the effects of mergers using propensity scores to control for merger endogeneity.⁴ For larger firms, we find that mergers are a response to patent expirations and gaps in a company's product pipeline, which lead to excess capacity of the fixed marketing resources. For smaller firms, mergers are primarily an exit strategy in response to financial trouble, as indicated by a low Tobin's q, few marketed products, and low cash-sales ratios. Controlling for a firm's *ex ante* propensity to merge significantly affects the estimates of merger effects. Firms with relatively high propensity scores experienced slower growth in sales, employees, and R and D, regardless of whether they actually merged; this is consistent with mergers being a response to distress. For large firms, a merger did not significantly affect subsequent performance on average, whereas small firms that merged had slower R and D growth than similar firms that did not merge; this suggests that post-merger integration may divert cash from R and D. This conclusion, that merger is often a response to distress but is usually not an effective solution, is consistent with the subsequent slow-down in M&A in this industry, with the exception of selective, strategic acquisitions, as large firms acquire smaller firms with specifically well-matched capabilities or products. Thus, although the "survivor" evidence—with increased market share

of the top ten firms over time—might suggest that large firms have advantages, recent stock market performance tells a very different story.

Price Regulation—Rationale and Effects

The high rate of entry to the pharmaceutical-biotechnology industry indicates that it is structurally competitive. To the extent that market power exists, it derives from patents that are legal grants of monopoly power to enable originator firms to recoup their R and D costs. Although patents bar generically equivalent products for the life of the patent, they do not prevent entry of similar products that may be therapeutic competitors. Thus, neither natural monopoly nor patents provide a rationale for regulating pharmaceutical prices.

The rationale for drug price regulation derives from pervasive insurance or third party payment, which makes patients insensitive to prices, hence creating incentives for suppliers to charge higher prices than would occur without insurance. Patient co-payments are a weak antidote, if insurance is to retain its value as financial protection. For example, assuming linear demand, if patients have insurance with a 50 percent co-insurance rate, then firms would charge drug prices twice as high as if patients were uninsured. To counteract this supplier moral hazard that applies to all insured health services, including drugs, both private and public insurers limit the prices that they will pay for all insured health services. Private sector pharmacy benefit managers (PBMs) in the United States negotiate price discounts as a condition of preferred formulary status. Public payers in other countries limit either the price the firm may charge or the amount the public payer will reimburse, or both. The fact that a firm may launch an approved drug without price approval if it is unreimbursed confirms that price regulation of drugs is best viewed as a response to insurance. Drug price regulation differs across countries and is multidimensional in its structure and effects, making generalization hazardous. For example, some countries include

a limit on aggregate annual drug spending, with a reduction in prices to offset any overshooting of target volume. Depending on the specifics of a drug price regulatory scheme, it may affect drug prices, availability, utilization, R and D level and location, and factor productivity.⁵

Reference Pricing

An increasingly popular approach to regulation is therapeutic reference pricing (RP). We studied the effects of RP as used in Germany, the Netherlands, and New Zealand.⁶ Under RP, drugs are grouped based on indication, mechanism of action, and effects. The payer sets a maximum reimbursement (the RP) for all drugs in a group, based on the median, minimum, or other low supply price for the group. If a firm charges a price above the RP, the patient pays the excess. Therapeutic referencing is broader than generic referencing, which groups all off-patent products with the same active ingredient. Many countries, and most payers in the United States, use generic referencing. As implemented in the United States, generic RP is a powerful stimulus to generic price competition, because pharmacists are authorized and given incentives to substitute generically equivalent products and to select the cheapest.

Although a stated purpose of therapeutic RP is to stimulate price competition, the theory and evidence suggest that—at least as implemented in these countries—it is ineffective. Unless physicians or patients have incentives to choose cheaper drugs, the RP tends to become a floor as well as a ceiling price. Germany's RP system was largely ineffectual until 2004, because of both weak incentives and the exclusion of new on-patent products until 2004. In the Netherlands, firms discounted extensively to pharmacists on products that the pharmacists could substitute (generics and parallel imports), but there was little impact on list prices and hence little savings to payers. In New Zealand, low prices reflect the government's use of its monopsony power to negotiate price cuts as a condition of reimbursement, rather than market competition under RP. In sum, RP alone was

ineffectual in the three countries we studied, and all three countries adopted other controls.

However, if the United States were to adopt therapeutic RP, with therapeutic groups defined to include both on-patent and off-patent products, negative effects on prices of on-patent drugs would likely be significant, because generic prices are lower in the United States than in other countries. Effects on global R and D would also be much larger, because of the large U.S. share of global sales. Thus it would be a serious mistake to extrapolate from the effects of RP in other countries to its likely effects in the United States.

External Spillovers

One country's system of price regulation can affect not only its domestic prices and availability, but also prices and availability of drugs in other countries. Such external spillovers can occur because of price regulation with external referencing (country A caps its price at the median or lowest price for the same products in a specified set of other countries) or because of parallel trade (also called drug importation). External referencing and parallel trade undermine a pharmaceutical firm's ability to price-discriminate across countries, based on elasticities that are country-specific. Rather, the optimal pricing strategy may be to charge a single price or a narrow pricing band, and to delay or not launch in countries that do not accept the single price. Non-launch is most likely in small countries with low prices, because the foregone revenue of non-launch is small, compared to the revenue loss if a low price contaminates a potentially higher price in a larger market. Findings from our analysis of launch delay for new drugs in 25 markets in the 1990s are consistent with this theory. We find that only 55 percent of the potential launches occurred. Countries with the most launches and shortest delays were the United States, Germany, and the United Kingdom—the three countries with unregulated prices (at that time). New Zealand and Portugal—small countries with low prices—had the fewest launches, except for Japan, which was an outlier

with very few launches because of onerous approval requirements, not low prices. In general, launch hazards are positively related to expected price and expected volume, after controlling for income per capita. Controlling for expected price and volume, launch hazards have been significantly lower for EU countries that are significant parallel exporters.⁷

This evidence on adverse spillovers is highly relevant for proposals in the United States to legalize drug importation and/or limit prices to some average or minimum of foreign prices. Since the United States is the largest pharmaceutical market and has relatively high prices, such policies would make it costly for firms to launch drugs in other countries at prices below U.S. prices. If other countries were unwilling to pay U.S. price levels, they would likely experience delays or non-launch of new drugs; alternatively, they might pay the U.S. prices but restrict utilization in order to control health spending to target levels. Such an outcome would almost certainly reduce overall social welfare, assuming that the socially optimal global pricing strategy for drugs is Ramsey pricing to pay for the joint costs of R and D, with prices inversely related to per capita income as a proxy for elasticity.⁸ There is some evidence suggesting that price spillovers from the United States to Mexico already exist. We find that prices for both drugs and biologics in Mexico were far out of line with per capita income, and utilization was correspondingly low.^{9,10}

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Exchange-Rate Models

Charles Engel*

Recent research that my co-authors and I have undertaken, as well as related research by other NBER researchers, suggests that theoretical models of foreign exchange rates are "not as bad as you think." Since the 1970s, models have emphasized the role of exchange rates as asset prices. The new work, looking at present-value models of exchange rates, highlights the role of expectations in determining exchange rate movements. In this article, I briefly summarize some of the work that I have been involved with, along with a few related papers by other researchers. I also report on some research that has drawn the implications of this new work on exchange rates for open-economy macroeconomic policy.

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Should Exchange Rate Models Out-predict the Random Walk Model?

For many years, the standard criterion for judging exchange rate models has been, do they beat the random-walk model for forecasting changes in exchange rates? This criterion was popularized by the seminal work of Meese and Rogoff.¹ They found that the empirical exchange rate models of the 1970s that seemed to fit very well in-sample tended to have a very poor out-of-sample fit. The mean-squared error of the model's prediction of the exchange rate (using realized values of the explanatory variables) tended to be lower than the mean-squared error of the naïve model that predicts no change in the exchange rate. While Meese and Rogoff's exercise was not strictly speaking "forecasting" (because it used realized explanatory variables to "predict" the exchange rate),

subsequent work has evaluated exchange rate models by the criterion of whether they produce forecasts with a lower mean-squared error than the simple random walk forecast of no change. Mark's (1995) paper was important in reviving interest in empirical exchange rate models.² He found that the models were helpful in predicting exchange rates at long horizons. Subsequent work has cast doubt on whether exchange rates can be forecast at long horizons, so there is a weak consensus that the models are not very helpful in forecasting. (It is worth noting that there is a contingent that believes that non-linear models have forecasting power. When exchange rates are far out of line with the fundamentals, the models are useful in predicting that the exchange rate will return to its fundamental level.)

West and I³ question the standard criterion for judging exchange rate models. Many exchange rate models can be writ-