

Empirical Facts and Innovation Markets: Analysis of the Pharmaceutical Industry

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Over the last ten years, the Federal Trade Commission has analyzed the effects of a number of mergers in industries where innovation is an important dimension of competition. It brought an action or required a divestiture in a number of these mergers because of potential anticompetitive effects.¹ Consequently, a debate has ensued over whether the agency's market analysis should be limited to potential competition for actual goods or should also include actual competition for potential goods.

In a recent article, Ilene Knable Gotts and Richard T. Rapp analyzed ten mergers and found that no drugs had yet entered the U.S. market in four of the cases, one drug had entered the U.S. market in two of the cases, and two or more drugs had entered the U.S. market in the four remaining cases.² Gotts and Rapp argue that these results support their view that agency decision making would be improved by limiting enforcement to mergers involving potential competition for actual goods: "Proper enforcement involving future goods can only happen when the good is far enough along in the development process to allow it to be identified as a source of potential competition, along with its close substitutes, in a forecast relevant goods market."³

In contrast, FTC Commissioners Harbour and Thompson argued in the *Genzyme* case that the merger was problematic because it reduced actual competition for potential goods.⁴ As Commissioner Thompson explained in his dissent.

The basic facts of this matter are clear and for the most part uncontested. The *Genzyme/Novazyme* merger constitutes a consummated merger to monopoly in the research and development of a highly specialized drug, and entry of a new market participant is not likely to replace the innovation competition eliminated by the merger. The presumption of anticompetitive effects from this merger to monopoly has not been rebutted and is therefore sufficient to indicate that a Commission challenge is warranted.⁵

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or their clients. All errors
are our own.

¹ See Amgen Inc., FTC Docket No. C-4056 (Sept. 3, 2002) (consent order), available at <http://www.ftc.gov/os/caselist/c4056.htm>; FTC Press Release, FTC Seeks to Block Cytoc Corp.'s Acquisition of Digene Corp. (June 24, 2002), available at http://www.ftc.gov/opa/2002/06/cytc_digene.htm; Glaxo Wellcome plc, FTC Docket No. C-3990 (Jan. 26, 2001) (consent order), available at <http://www.ftc.gov/os/caselist/c3990.htm>; Pfizer Inc., FTC Docket No. C-3957 (July 27, 2000) (consent order), available at <http://www.ftc.gov/os/caselist/c3957.htm>; CIBA-Geigy Ltd., FTC Docket No. C-3725 (Mar. 24, 1997) (consent order), available at <http://www.ftc.gov/os/caselist/c3725.htm>; Baxter Int'l, FTC Docket No. C-3726 (Mar. 24, 1997) (consent order), available at <http://www.ftc.gov/os/caselist/c3726.htm>; Am. Home Prods. Corp., FTC Docket No. C-3557 (Feb. 14, 1995) (consent order); Glaxo plc, FTC Docket No. C-3586 (June 14, 1995) (consent order); Hoechst AG, FTC Docket No. C-3269 (Dec. 5, 1995) (consent order); Upjohn Co., FTC Docket No. C-3638 (Feb. 8, 1996) (consent order).

² Ilene Knable Gotts & Richard T. Rapp, *Antitrust Treatment of Mergers Involving Future Goods*, ANTITRUST, Fall 2004, at 100.

³ *Id.* at 102.

⁴ See David A. Balto & Scott A. Sher, *Refining the Innovation Focus: The FTC's Genzyme Decision*, ANTITRUST, Spring 2004, at 28.

⁵ Dissenting Statement of Commissioner Mozelle W. Thompson, *Genzyme Corporation's Acquisition of Novazyme Pharmaceuticals Inc.*, File No. 021-0026 (Jan. 13, 2004), available at <http://www.ftc.gov/os/2004/01/thompsongenzymestmt.pdf>.

According to Commissioner Harbour, “[t]he creation of innovation monopolies in such an industry eliminates the all important race-to-innovate aspect of innovation competition, [and] diminishes important diversity in research approaches”⁶

This article summarizes the empirical analysis of new drug development in the pharmaceutical industry that we presented in a recent FTC Bureau of Economics Working Paper.⁷ This article does not enter into the innovation market analysis debate, but instead provides empirical facts in the context of arguments that have been made on both sides of the debate.⁸

Stages of the Drug Development Process

The drug development process from initial discovery to FDA approval and release to the market consists of a number of distinct stages. After initial discovery, drugs are analyzed and tested in the laboratory. Pharmaceutical firms and other researchers analyze the likely efficacy of the drug using genetic analysis and “animal models,” among other things. Information from these tests is subsequently provided to the FDA (or another similar regulatory agency) when the drug company applies to begin a series of tests in humans.

Phase I of the human clinical trials involves a small number of healthy patients. These Phase I trials are aimed at proving that the drug is relatively safe. After Phase I, the drug moves into Phase II, where trials are conducted on a few hundred patients with the disease in question. Phase II trials are also focused on safety, but with some additional analysis of the drug’s efficacy. Phase III trials are much larger, with upwards of 3000 patients involved, and are aimed at determining the effectiveness of the drug. While overlap sometimes occurs between these phases of the human clinical trials, drug tests generally progress sequentially from Phase I through to Phase III.

Once the trials are completed, the data is sent to the FDA for analysis. After review, the FDA can approve the drug for a particular disease indication. Once approved, the drug can be marketed for that indication.⁹

Merger Enforcement

Potential Competition for Actual Goods. Gotts and Rapp argue that the agencies should concentrate merger enforcement on those cases where “potential competitors can be considered in goods (or, where applicable, service) markets that are reasonably likely to exist within a foresee-

⁶ Statement of Commissioner Pamela Jones Harbour, Genzyme Corporations’s Acquisition of Novazyme Pharmaceuticals Inc., File No. 021-0026 (Jan. 13, 2004), available at <http://www.ftc.gov/os/2004/01/harbourgenzymestmt.pdf>.

⁷ ABRANTES-METZ ET AL., PHARMACEUTICAL DEVELOPMENT PHASES: A DURATION ANALYSIS (Bureau of Economics, Federal Trade Commission Working Paper No. 274, Oct. 2004), available at <http://www.ftc.gov/be/workpapers/wp274.pdf>.

⁸ Others have used the empirical facts drawn from the authors’ work in analyzing mergers in the pharmaceutical industry. Then Federal Trade Commission Chairman Timothy Muris cited the authors’ work in his defense of the FTC’s decision not to prosecute the *Genzyme* case. Chairman Muris wrote a statement supporting the Commission’s position to close the case, while Commissioner Thompson wrote a dissenting statement, and Commissioner Harbour wrote a statement expressing some concerns about the decision. See FTC Press Release, FTC Closes Its Investigation of Genzyme Corporation’s 2001 Acquisition of Novazyme Pharmaceuticals, Inc. (Jan. 13, 2004), available at <http://www.ftc.gov/opa/2004/01/genzyme.htm>. Gotts and Rapp cite the authors’ work in describing the background for recommending that antitrust enforcement be limited to cases where the identities of sellers can be predicted and their capacities approximated. See Gotts & Rapp, *supra* note 2, at n.25.

⁹ A number of firms also do Phase IV trials, but it is our understanding that these generally are not needed for marketing approval. For a more detailed discussion of the development process, see ABRANTES-METZ ET AL., *supra* note 7.

able time frame.”¹⁰ The question, of course, remains, what is “reasonably likely” and when is “foreseeable?”

In the *Genzyme* case, neither firm had a product that was even as far along the development process as human clinical trials.¹¹ In contrast, in the *Glaxo Wellcome/SmithKline Beecham* merger, the FTC cited concerns in the market for topical antiviral cold sore (herpes) drugs.¹² SmithKline Beecham owned Denavir, which was the only drug approved by the FDA for treating such infections, while Glaxo Wellcome owned Zovirex, which was approved in Europe and a year away from approval in the United States. According to the FTC, “[t]he merger, as proposed, would eliminate the only potential entrant into the market—Glaxo’s Zovirex—as the combined Glaxo SmithKline would likely not bring Zovirex to market to compete against its own product, Denavir.”¹³ The examples of *Genzyme* and *Glaxo Wellcome/SmithKline Beecham* seem to occupy opposite ends of the spectrum. In *Genzyme* the probability of bringing either of the drugs in development to market seemed very small and the time to market very long.¹⁴ Meanwhile, in the *Glaxo Wellcome/SmithKline Beecham* merger, the likelihood of entry was high and the time to market was short.¹⁵

But what is the probability that a drug will ever get to market? How does the probability change as the drug moves through the development process? How does the probability of getting to market vary across drugs? In our work, we present “crude” probabilities that are calculated by simply observing the number of drugs that successfully reach the market divided by the total number of drugs that go into development.¹⁶ We also present simulation results from a type of regression analysis called a duration model. This model enables us to determine how different features of the drug determine the drug’s success rate. For example, the model helps to determine whether the high crude success rate of a cancer drug is due to the drug’s indication or due to some other characteristic like the drug’s route of administration.

Overall, it seems that only about 1 in 4000 drugs proposed in preclinical testing actually ever makes it to market.¹⁷ Once the drug gets to Phase I, the probability of success seems to increase substantially.¹⁸ In our data, we find that about 26 percent of Phase I drugs are launched on the market. For drugs that reach Phase II, the probability that the drug will get to market increases

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¹⁰ Gotts & Rapp, *supra* note 2.

¹¹ Balto & Sher, *supra* note 4.

¹² FTC Press Release, Resolving Competitive Concerns, FTC Agreement Clears \$182 Billion Merger of SmithKline Beecham and Glaxo Wellcome (Dec. 18, 2000), available at <http://www.ftc.gov/opa/2000/12/skb.htm>.

¹³ *Id.*

¹⁴ Based on the FDA’s analysis and the analysis presented in our paper, one in four thousand drugs in preclinical testing make it to market. See DEP’T OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMIN., FDA AND THE DRUG DEVELOPMENT PROCESS: HOW THE AGENCY ENSURES THAT DRUGS ARE SAFE AND EFFECTIVE (FDA Publication No. FS 02-5, Feb. 2002), available at <http://www.fda.gov/opacom/factsheets/justthefacts/17drgdev.html> [hereinafter FDA REPORT]. Other works cited below and our work suggest that it takes between 13.5 and 8.5 years for a drug to go from preclinical testing to market.

¹⁵ Below we discuss evidence on the probability of success and time to market for drugs in the FDA approval process.

¹⁶ To be precise, it is the total number of drugs that go into human clinical trials and for which we observe the drug exit (either successfully to the next phase or as a failure).

¹⁷ This is based on the FDA’s statement that 1 in 1000 drugs make it to human clinical trials and our result that one in four drugs make it from human clinical trials to market. FDA REPORT, *supra* note 14.

¹⁸ This sample includes drugs that first entered human clinical trials between 1989 and 2002 and for which the data base includes information on when the drug began at least one of the phases of the human clinical trials. For a more detailed description of the data used in this analysis and the duration model that we estimate, see ABRANTES-METZ ET AL., *supra* note 7.

somewhat to 33 percent. For drugs that reach Phase III, the probability of success is 57 percent. Unfortunately, we were not able to determine the probability of success for drugs that entered the FDA approval process after completing Phase III trials.

While these averages provide a solid foundation for understanding the probability of entry from the different stages of a drug's development, there is substantial variation in these probabilities across different types of drugs. For instance, in our sample, we find that biological drugs, such as those at issue in *Genzyme*, have a 42 percent probability of getting from Phase I to market and a 70 percent probability of getting from Phase III to market.¹⁹ We find that AIDS drugs have a 50 percent probability of getting from Phase I to market, with a 94 percent probability of getting from Phase III to market. At the other end of the spectrum, we find that drugs for Alzheimer's have only a 16 percent probability of getting from Phase I to market and a 33 percent probability of getting from Phase III to market.

How much of this variation is due to differences between diseases and how much is due to differences in the drug's chemistry or its molecule's size? In our sample, we find that a cancer drug has a 42 percent probability of getting from Phase I to market and a 66 percent probability of getting from Phase III to market. Both of these probabilities are much higher than the average and suggest that cancer drugs have a greater chance of getting to market. Our regression analysis shows, however, that this difference is due to other characteristics of the drug, such as the drug's chemistry or route of administration. The value of the regression analysis is that it is able to separate out how different characteristics of the drug contribute to the drug's success rate. For this reason, we find that all else being equal, drugs indicated for cancer actually possess a decreased probability of getting to market. The regression analysis thus suggests that cancer is a particularly difficult disease for which to find a successful treatment. This fact seems to be masked by the tendency of cancer drugs to have other characteristics more typically associated with higher success rates.

What is a drug's time to market from the different stages of development and how does time to market vary across drugs? Other research suggests that it takes about 13.5 years for a drug to go from discovery to approval.²⁰ Our research presents both the average durations through each phase of the human clinical trials and simulation results from the regression analysis. Once a drug gets to Phase I, we find that it takes an average of 8.5 years to be launched on to the market. For drugs in Phase II, it takes about 6.5 years. It takes an average of 3.75 years for a drug to go from the beginning of Phase III trials to market launch. We do not present any data on the average length of time from the start of regulatory approval (the time following the completion of Phase III trials) to market. Recent work analyzing FDA approval times, however, finds that these times have fallen from an average of 24.2 months in 1991 to 14.2 months in 2002.²¹ This decrease in approval times is also found in our work and appears to stem from the introduction of the Prescription Drug

¹⁹ Biological drugs are drugs based on chemistry that is naturally occurring in the body, such as proteins. The drugs at issue in *Genzyme* and in *Amgen/Immunex* were biologicals.

²⁰ David Dranove & David Meltzer, *Do Important Drugs Reach the Market Sooner?*, 25 RAND J. ECON. 402 (1994); Joseph A. DiMasi et al., *The Price of Innovation: New Estimates of Drug Development Costs*, 22 J. HEALTH ECON. 151 (2003) (estimating that the time from discovery to marketing approval is a little over twelve years).

²¹ For a detailed discussion of the acts and the effect the acts have had on the approval process, see ERNST R. BERNDT ET AL., *ASSESSING THE IMPACTS OF THE PRESCRIPTION DRUG USER FEE ACT (PDUFA) ON THE FDA APPROVAL PROCESS* (National Bureau of Econ. Research Working Paper 10822, Oct. 2004), available at <http://www.nber.org/books/frontiers8/w10822.pdf>.

User Fee Act (PDUFA) in 1992.²² PDUFA enables the FDA to collect user fees associated with drug approval applications, with the understanding that these fees will be used to increase expenditure on staff and equipment to reduce review and approval times.

As with success rate, we find substantial variation in times to market across drugs with different characteristics. For example, thrombosis drugs take about 9.5 years to go from Phase I to market and 5 years to go from Phase III to market. Yet AIDS drugs take approximately 5.5 years to go from Phase I to market and less than 2 years to go from the start of Phase III to market. The FDA has allowed AIDS drugs to go through an accelerated approval process, resulting in a very short time from the start of Phase III to market.²³ This means that AIDS drugs are able to apply for marketing approval prior to completing Phase III clinical trials.²⁴

We find little variation in times to market for drugs with different materials of origin. For example, biological drugs take slightly less than 8 years to go from Phase I to market while chemical drugs take slightly more than 8 years to go from Phase I to market. There also seems to be little difference in time to market for drugs with different routes of administration. We do find, however, that topical drugs move through the earlier phases more quickly than average, but then slow down in Phase III, with an average of 4.5 years from the beginning of Phase III to market. Also, our regression analysis suggests that an indication for Parkinson's diseases is likely to increase a drug's time to market, all else equal, while an indication for AIDS or hypertension will reduce a drug's time to market.

There are two important caveats. First, there is no average drug, and even within categories there can be variation in both success rates and time to market. Still, we argue that it is important to understand the empirical facts of pharmaceutical development to put facts and arguments into context. The second caveat is that our analysis is based on observed data, which are affected by the strategic decisions of the pharmaceutical firms themselves. Pharmaceutical firms are constantly assessing the likely cost and benefits of developing different drugs. When we observe that a drug ends development in Phase II, we are unable to determine whether that "failure" is due to some adverse event, like a serious illness among patients, or due to a change in expected profits caused by entry of a similar drug (for example).²⁵

Assuming that anything greater than a one in two chance is "reasonably likely" and anything less than three years is "foreseeable," these results suggest that on average, only drugs in Phase III or beyond will satisfy the Gotts and Rapp criteria. However, enough variation exists to suggest there exist exceptions. For example, AIDS drugs in Phase II can be satisfy the criteria while Alzheimer's drugs cannot until they have finished Phase III trials and are under regulatory review. If "reasonably likely" is anything greater than a four in five chance of success, then most drugs would need to be under review to qualify. A notable exception again would be AIDS drugs, where

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²² 21 U.S.C. § 379.

²³ See Dep't of Health and Human Services, Food and Drug Admin., Expanded Access and Expedited Approval of New Therapies Related to HIV/AIDS (Jan. 1996), available at <http://www.fda.gov/oashi/aids/expanded.html>.

²⁴ Michelle Meadows, *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FDA CONSUMER (July–Aug. 2003), available at http://www.fda.gov/fdac/features/2002/402_drug.html.

²⁵ One survey of firms finds that 34% of trials are abandoned for "economic" reasons, 38% for "efficacy," 20% for "safety," and 9% for "other." See Joseph A. DiMasi, *Risks in New Drug Development: Approval Success Rates for Investigational Drugs*, 69 CLINICAL PHARMACOLOGY AND THERAPEUTICS 297 (May 2001), available at http://www2.us.elsevierhealth.com/scripts/om.dll/serve?action=get-media&id=a115446&trueID=pdf_115446&location=jcp010695&type=pdf&name=x.pdf.

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drugs in Phase III would satisfy the criteria. If “foreseeable” is less than five years, then some drugs in Phase II may satisfy the Gotts and Rapp criteria.

Actual Competition for Potential Goods. An important issue in *Genzyme* was whether the merger would lead to a reduction in “research competition.” Commissioner Thompson stated that the merger would reduce the number of active programs researching a cure for Pompe disease from two to one.²⁶ In particular, there was concern that there would no longer be a “race to market” in Pompe disease.²⁷ The effect of a reduction in the number of pharmaceutical firms on research and development seems to be an open question in economics. According to an FTC Staff Report, “economic theory and empirical investigations have not established a general causal relationship between innovation and competition.”²⁸

When firms competing in research and development merge, the merger could reduce the incentive to be first to market, but it could also bring together scientists working on different approaches and improve the productivity of the research programs. If the first effect dominates, then we might expect mergers to reduce spending on research and development. One recent study analyzing the financial effects of mergers in the pharmaceutical industry finds some decrease in research and development spending for smaller firms that merge, but no change in research and development spending for larger firms that merge.²⁹ If the second effect dominates, it would be because there are “spillovers” in research and development, with larger research and development programs having greater success. Another study finds some empirical evidence that there are indeed “spillovers” in research and development programs in the pharmaceutical industry. The study finds that larger firms seem to have more productive research efforts.³⁰

Our analysis also suggests that larger firms are more productive. We find evidence that firms with a large number of drugs in development have higher success rates and shorter times to market. This seems to be particularly true for drugs in Phase III of the development process. Using our sample, we compare the success rates of the drugs originated by the top ten pharmaceutical firms by revenue against the all other drugs. We find that the probability that a drug from a large firm successfully gets from Phase III to market is 69 percent compared to 54 percent for all other drugs. However, the success rate from Phase I to market is almost identical, at 25 percent and 26 percent, respectively. With respect to the duration of time from Phase I to market, we find drugs from the large pharmaceutical firms take about 7 years, while other drugs take approximately 8 years. These differences are consistent with our regression results, suggesting that larger firms are more productive.

²⁶ Dissenting Statement of Commissioner Mozelle W. Thompson, *supra* note 5.

²⁷ For a detailed discussion of the case see Balto & Sher, *supra* note 4.

²⁸ 1 FEDERAL TRADE COMM’N, ANTICIPATING THE 21ST CENTURY: COMPETITION POLICY IN THE NEW HIGH-TECH, GLOBAL MARKET PLACE ch. 7, at 16 (1996), available at http://www.ftc.gov/opp/global/report/gc_v1.pdf. But see FEDERAL TRADE COMM’N, TO PROMOTE INNOVATION: THE PROPER BALANCE OF COMPETITION AND PATENT LAW AND POLICY (Oct. 2003) (“Competition can stimulate innovation. Competition among firms can spur the invention of new or better products or more efficient processes. Firms may race to be the first to market an innovative technology.”), available at <http://www.ftc.gov/os/2003/10/innovationrptsummary.pdf>.

²⁹ PATRICIA M. DANZON ET AL., MERGERS AND ACQUISITIONS IN THE PHARMACEUTICAL AND BIOTECH INDUSTRIES (National Bureau of Econ. Research Working Paper 10536, June 2004), available at <http://www.nber.org/papers/w10536.pdf>.

³⁰ Iain Cockburn & Rebecca Henderson, *Scale, Scope and Spillovers: The Determinants of Research Productivity in the Drug Industry*, 26 RAND J. ECON. 32 (1996).

An important caveat is that our method of measuring firm size may not be independent. In particular, we measure firm size as of 2001, and all of the drugs that are with the large firm are assumed to have always been with the large firm. This is a problem because a number of mergers occurred during this period, and so the positive relationship between success and firm size may mean that firms merge to improve their drug development pipelines. If firms are merging to purchase drugs that will improve their pipelines, then it may be that successful drugs *cause* large firms rather than the other way around.³¹ ●

³¹ See DANZON ET AL., *supra* note 29, for a more detailed discussion of the motivation behind pharmaceutical mergers.