



THE CAPITAL CRISIS IN BIOTECH AND THE INVISIBLE COSTS OF REGULATION

Citation

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THE CAPITAL CRISIS IN BIOTECH AND THE INVISIBLE COSTS OF
REGULATION

Food and Drug Law
January 27, 1995
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Today only a handful of people are privy to the secret of life and how to manipulate and change it... It is now only a matter of years before biologists will be able to irreversibly change the evolutionary wisdom of millions of years with the creation of new plants, new animals and new forms of humans and post-human beings.

—Ted Howard and Jeremy Rifkin, *Who Should Play God?*(1977)

A. Introduction

To the Rifkins of the mid-70s, the threat of biotechnology was as real as its promise. While enthusiasts for the new science certainly existed, it was the alarmists whose fears of new genes run amok shaped much of the contemporary thinking on the subject. These fears also shaped the regulation of biotechnology by the federal government—first NIH, then the FDA—to which critics looked for scientific guidance and regulatory restraint. During the twenty years since this debate began, Rifkin’s opinions have not changed dramatically (he now opines on the subject under the aegis of the oddly market-sounding Foundation on Economic Trends), but biotechnology has changed enormously. The field is no longer mere science: some 25 biotech products are now on the market for drug, environmental, and food applications; roughly 300 more are in various stages of the developmental pipeline. Nor is it fringe science:

more than 301 of the research budgets of traditional pharmaceutical companies are now devoted to biotechnological products. Yet like many other areas of government oversight where statutes and administrative regulations lag technological change, the Rifkin legacy of strict regulatory oversight has continued to be the dominant philosophy of governmental regulation of biotechnology. In many cases, biotech

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products continue to be regulated more extensively than identical chemical compounds.

Why should this bother us? As recently as 1993, when five hepatitis patients died after receiving the drug fialuridine, which had been engineered from recombinant DNA, biotechnology has demonstrated its relative immaturity as a science (modern chemistry is hundreds of years old) and the occasionally fatal risks that result. Human society has waited thousands of generations for the discovery of fialuridine. Why can't it wait a few more years while the FDA sorts out these risks and ensures that these new drugs are safe and effective?

This paper argues that while the approval process may be trivial in terms of geologic time, it is an eternity when viewed from the perspective of the biotech industry. A delay of even a few months can mean life or death for a nascent one-product biotech company. Spread over an entire industry over a period of years, such delays impose very real costs on companies which may be forced to curtail or eliminate valuable drug research. In the near term, such costs are borne by public shareholders and venture capitalists who voluntarily subject themselves to a risky market and seemingly do not deserve much sympathy. Annualized return rates do not seem to present a very compelling case when human life is at stake. But these same costs are ultimately borne by consumers in several more subtle ways that do put real lives on the line: (i) Consumers are denied use of drugs that are awaiting approval; (ii) When drugs finally do make it through the developmental pipeline, delays in the process increase industry costs and in the absence of governmental

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price regulation, those increased costs are passed along to consumers in the form of higher drug prices, raising issues of access and regressive taxation; and (iii) Most insidiously, consumers are denied the benefit of drugs that will never be discovered or whose discovery will never be exploited because increased industry costs imply reduced spending on research and development.

If these costs are so great why can't we see them? This crisis, if it exists, should be visible at both the industry and consumer levels. First, as to the industry, why have we not seen a wave of biotech bankruptcies if the industry is truly in crisis? The answer is that the industry has managed to keep itself out of bankruptcy (so far) by obtaining financing on highly discounted terms that are extremely unfavorable to issuing companies; in effect these companies are slowly giving away their equity in a way that is less visible, but no less profound, than a bankruptcy filing. Biotech firms have responded to this shrinkage of capital by reducing spending on new drug discoveries and development. Unlike traditional pharmaceutical firms like Merck which can cut marketing and other overhead costs before they cut R&D, biotech firms, which often are little more than laboratories dressed up in corporate form, rarely have infrastructure that can be cut temporarily to save money. As a result, we should expect to see markedly fewer drugs entering the developmental pipeline; since these drugs typically would not emerge from the approval process for five to ten years, it may be nearly that long before our society realizes that the promised flood of biotech drugs has slowed to a trickle.

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Second, why have consumers, who have the most at stake, not been more vocal in calling attention to the biotech crisis? To the extent they have been organized, consumers have tried to call attention to the crisis. Efforts by various AIDS groups and by the Cystic Fibrosis Foundation, for example, have helped draw scrutiny to the regulatory process at FDA. But constituencies are rarely this organized and the industry is therefore drafted as a stand-in for current and prospective ailing consumers. Yet the industry is in a remarkably precarious position: it may criticize the FDA, yet it must simultaneously depend on the FDA for approval. Since the agency notoriously (and unavoidably) exercises discretion within certain broad limits, biotech firms with just a few months' cash in the till fear that for all of the frustration they feel privately, they cannot criticize the agency publicly for fear of bureaucratic retribution.

Another way that we might be able to measure these invisible costs is to look at what consumers have gotten from the biotech industry. In the 20 year life span of the industry, with 1310 firms now in existence (many of them, admittedly, of recent vintage), fewer than 30 new biotech drugs have been approved by FDA for use by consumers.

Most commentators have pointed to health care reform as the main culprit in causing the capital crisis.¹ Yet the roots of this crisis also include a flawed regulatory philosophy at FDA. While recent critics of FDA have also pointed to the slow approval process as a source of

¹See e.g. Merrill Lynch, Biotechnology-Human Therapeutics, December 12, 1994, p.1.

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national competitive disadvantage,² they have not explicitly linked the approval process to the capital crisis. This paper argues that the FDA's cost calculus is flawed to the extent that it gives excessive weight to the risk of another fialuridine, yet puts very little value on benefits to the industry and its ultimate beneficiary, the consumer. That calculus should not be surprising given the kind of pressures under which the FDA operates; the agency is flogged publicly by congressional committees for lax oversight of drugs it has permitted to enter the market, but is rarely penalized politically for injuries and deaths attributable to natural disease. Nor is this calculus novel; the Hippocratic Oath instructs doctors to abstain from all intentional wrongdoing and harm. Yet this aversion to unclean hands is flawed: the FDA should internalize the costs of drugs left undeveloped and diseases left untreated because of excessive regulatory delays even if the agency risks a few more deaths in clinical trials. The FDA's regulatory calculus should be guided by a simple utilitarian weighing of harms that is admittedly easier for John Stuart Mill than Hippocrates and David

Kessler: Five deaths of willing patients (who understood and volunteered for the treatments they received) in the course of hundreds of clinical

²See e.g., The President's Council on Competitiveness, Report ~ National Biotechnolocxv Policy, February 1991. Ironically, while the Council on Competitiveness was patriotically concerned that European and Japanese companies would take advantage of regulatory handicaps in the US, the major efforts to capitalize on regulatory disparities have been made recently by American companies themselves. Many have begun to shift R&D to Europe where government oversight of R&D and clinical trials is less restrictive. It is unclear, however, whether safety has been compromised in the process since regulatory speed may suggest laxity as well as efficiency. If that is the case, then the FDA's overcautious approach (discussed below) may perversely lead to drugs that are less safe as US firms flock to Europe. (European development does not, however, skirt the US approval process entirely since FDA must still approve drugs for the U.S. market.)

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trials are inconsequential when compared to the benefits resulting from prospective and existing drugs.

B. Structure

Part I describes the current capital crisis in the biotech industry. Part II examines its consequences for R&D. Part III investigates various factors contributing to the capital crisis. Part IV describes the role of FDA regulation in causing the crisis and the effect of government regulation on industry and consumer costs. Part IV examines possibilities for reform.

Note that for simplicity, this paper simply discusses biotech drugs and ignores food and environmental applications which have similar characteristics.

Part I: The Capital Crisis

The paradox of biotech financing in recent years has been the appearance of prosperity. While various stock market indices of biotech performance have swung wildly from famine to feast and then back to famine (most recently with the assistance of alleged stock manipulator David Blech),³ the amount of money flowing into the industry has increased relatively steadily to \$4.7 billion in 1994 from \$3.7 billion in 1993.~ In the context of the debate on price controls, the current administration has pointed with apparent justification to these numbers as signs that the industry is healthy.⁵

This is misleading for two reasons:

(i) Rate of Spending. Biotech companies do not spend money at a constant rate. The burn rate of a biotech company, a widely used measure of a company's ongoing capital needs, is not a fixed number. As companies move from early-stage laboratory research to later-stage human clinical trials and manufacturing plant construction, its needs for capital increase. For example, the burn rate of Synergen, a late-stage biotech company, was \$140 million in 1993 while the burn rate for Icos, an earlier-stage biotech company, was \$20 million.⁶ Hence, we ought to

~8E1 of biotech stocks declined in value in 1994. Biotech Newswatch, January 16, 1995, p.3.

⁴These figures are for the fiscal years ended June, 1993 and June, 1994. (Ernst & Young, Ninth Annual Report on the Biotechnology Industry, 1994.)

⁵See e.g. Reginald Rhein, Is BIO Crying Wolf with Anti-Health Plan Lobbying?, Biotechnology Newswatch, March 7, 1994, p.1.

⁶Lehman Brothers, Bio-Financials, 1993, p.47.

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expect that as the industry moves from a predominantly early-stage group of startups to maturity, that its needs for capital will increase. That expectation is borne out by the industry median burn rate, which has increased—as the industry has aged—from \$6 million per year in 1991 to \$20 million per year in 1993.⁷ The conclusion: fixed capital inflows in conjunction with increasing capital needs will create a crisis.

(ii) More firms. The biggest problem with the steady cash stream is that there are more mouths to feed than there were five years ago. Emboldened by the success of Amgen, Genentech and other early biotech pioneers, a wave of startups went public during the period from 1991 to 1994. This period was a waterfall of money, one CEO nostalgically recalls. You held out your cup and it was full.⁸ Yet this waterfall creates an almost insatiable need for refinancing as soon the money raised an initial public offering (IPO) runs out. Since IPOs typically raise about \$23 million and since the burn rate for the median drug company is \$20 million⁹ (the average is \$26 million), a new biotech company will have only enough financing to last for about 14 months before it returns to the market for more money. (Note that this calculation is somewhat exaggerated because early-stage companies need less cash than later stage companies, as discussed above.) Whereas a handful of firms competed for funding in the early 1980s, now 1310 firms vie for funding. As a result, roughly 501 of the industry is within two

⁷Bio-Financials, p. 47. This is the burn rate for the universe of public companies. When non-public companies, which outnumber public companies are included in this calculation, the average burn rate in 1993 was \$665,000 per month or about \$8 million annually. (Ernst & Young, p. 54)

⁸Daniel Green, Survey of Venture and Development Capital, Financial Times, September 23, 1994, p. iv.

⁹Bio-Financials, p. 47.

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years of bankruptcy or flameout at current burn rates.¹⁰ If the pool of new capital remains constant, as it has in recent years, then the industry will die a slow (and perhaps unspectacular) death due to capital deprivation.

One sign that something is amiss is the diversion of money earmarked for biotech from the US to foreign biotech firms. Investors increasingly frustrated by returns on domestic drug development, yet still confident in the future of the industry, are shifting funds to Europe in particular. If US investment prospects were attractive, the funds would remain at home.

A more subtle, but no less important, sign that something is deeply wrong is composition of the \$4 billion flowing into the industry. Unlike the euphoria of the IPO market in the late 1980s and early 1990s in which the public markets pumped money into startups at inflated prices that subsequently have fallen dramatically, much of the current investment is coming from later-stage venture capital firms and from institutional private placements (largely from insurance companies). These investors are more demanding than the credulous public IPO investor: they require extensive equity in return for their investment, often in the form of shares that are discounted from the publicly quoted market price of the stock. (Private Investment in Public Enterprise financings (Pipes) are the most recent incarnation of this trend.) Biotech companies would prefer to raise funds in booming biotech markets when stock prices are high and equity is therefore relatively less¹⁰Ernst & Young, p. 54.

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costly. But given their burn rates, these companies' need for cash is immediate and they cannot afford to wait. Bank financing is not an alternative for all but a few of the largest biotech firms. Desperation therefore forces them into the arms of venture capitalists and insurance companies who extract equity from them on highly unfavorable terms. This equity is not given away lightly: in most cases, even where companies are already public, the largest shareholders (sometimes the majority shareholders) are the companies' founders whose personal assets and self-worth are inextricably bound up with the company's. Their choice—bankruptcy or dilution—is only made, therefore, out of desperation.

Part II: Implications of the Capital Crisis

The immediate consequence of this severe capital shortage is that R&D will suffer. Capital inflows have risen steadily, yet the pace of scientific discovery has risen much faster. Currently, although the industry is receiving funding of \$4 billion annually, the industry is spending \$7 billion annually on R&D. (That gap understates the extent of the problem since all biotech companies make cash expenditures on overhead, and the later-stage companies have manufacturing and marketing expenses as well.) This extraordinary deficit cannot continue. In the absence of additional financing—which does not appear to be forthcoming—biotech companies will have no choice but to cut R&D expenditures to survive. This will likely occur in several ways as companies focus their spending on drugs that have the highest probability of winning FDA approval in the shortest period of time. Companies first will stop research on drugs in early development since

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they will not generate cash for five to ten years. Hence we ought to expect that numerous potentially life-saving compounds will go unexamined in the future. Second, a shortage of R&D funds discourages innovation and experimentation in later development. Companies with drugs in clinical trials will no longer be able to afford to undertake multiple trials with varying levels of dosages, in varying forms, and for varying indications. Since they do not have sufficient funds to attempt a trial-and-error approach to see what works, they will make an educated guess based on what little data is available. Uncertainty is not necessarily problematic, but the history of biotechnology (and indeed science) is that many discoveries (insulin) were serendipitous. Serendipity has no place in the new capital-poor regime, and society will lose the benefit of what might have been discovered as a result. Finally, decreased funding for development efforts means not only that these companies will have to constrict the scope of their clinical trials, but that scale will suffer as well. While the cost of such trials varies according to duration and the intensity of patient monitoring (among other factors), clinical trials—particularly in phase III—are as a general matter, extraordinarily costly. Cash-poor companies will have little choice but to reduce the number of patients enrolled in trials. This raises the possibility that dangerous side effects, invisible on a small scale, but visible on a larger scale might slip past the clinical testing process. Hence, FDA's justified

There is already indirect evidence that this is occurring to the extent that venture capital investors are shifting their interest and resources from early-stage companies with distant prospects (historically their main focus) to later-stage companies that are closer to market (via mezzanine funds) . Consequently, the number of startups has fallen for the first time since the industry's inception, although the absolute amount of cash inflow has increased. (Ernst & Young, p.28)

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insistence that clinical trials meet minimum statistically significant thresholds. But the more serious problem is less a safety issue than an effectiveness issue: it is more difficult to show effectiveness the smaller the patient sample. Hence, the real risk here is that drugs which may help only a small subsegment of a larger population may appear to be ineffective and therefore will be rejected entirely. This may be one explanation for the string of recent failures among new biotech drugs. For all of these reasons, then, diminished R&D expenditures will likely lead to fewer drugs reaching ailing consumers who need them.

Part III: Factors Contributing to the Capital Crisis

Why are investors so reluctant to fund an industry that may ultimately replace stodgy traditional pharmaceutical companies as the source of new drugs? The main reasons are risk and timing. The returns that investors demand are affected both by the likelihood that projected cash flows will occur and by the immediacy of the flows. Drugs score poorly on both counts: returns are highly uncertain and cash flows do not begin until the distant future.

The combination of riskiness and time to market is devastating because each problem compounds the other. In order for an investor to break even on a relatively risk-free drug, he would require a return of 2601 over a 10-year drug development horizon at a discount rate of 10%. However, drugs are crapshoots: only one in ten² entering clinical trials makes it to market and some companies have only a single drug in ²G Kirk Raab, Embryonic, *The Economist*, August 27, 1994, p.6.

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their portfolio. By some estimates that raises the discount rate to between 15% and 35%¹³ Assuming a relatively conservative 20%, our company must now return an astounding 6201 over its 10 year development cycle.

Not surprisingly, once-euphoric investors who plowed considerable funds into biotech startups during the boom over the past decade have been sorely disappointed. While several companies' drugs have made it to market successfully, the overwhelming majority have remained in the product pipeline. As a result, even companies with highly promising drugs are unable to attract capital. Are investors simply displaying a superstitious aversion to throwing good money after bad? While the markets' occasional inefficiency and vulnerability to psychology may explain some market phenomena, investors' hesitation here is the result of several factors, some well-documented, each of which affects the risk and timing elements of investors' calculations:

(i) Price Controls. Industry banking analysts frequently cite the prospect of price controls as the source of the industry's capital crisis. Since the cost of a drug ranges from \$200 to \$350 million by the time it gets to market (including direct R&D, marketing, and manufacturing costs as well as the indirect cost of failed drugs),¹⁴ prices must compensate for development costs. If prices are regulated,

¹³See e.g., E.M. Hurwitz et al., *Biotechnology 1993 Review/1994 Preview*, Smith Barney Shearson, January 20, 1994, p.26. Fidelity uses a discount rate of up to 401. George Anders, *Power Player*, *Wall .r. Journal*, May 20, 1994, p.R16.

¹⁴Estimates vary here. See e.g. Office of Technology Assessment, Pharmaceutical R&D: ~ and Rewards, 1993, which found a fully-loaded cost of \$194 million.

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therefore, drug companies (and hence investors) will be unable to recoup their investment. The threat of health care-related price regulation thus increases the riskiness of drug approvals. But this mantra-like insistence on price controls as the reason for biotech financing problems is probably overstated. Health reform might actually encourage the use of biologically-derived drugs—even at premium prices—because many act as substitutes for more costly chemical therapeutics or surgical procedures, and thus result in the kind of net savings that health reform is attempting to promote.

(ii) Weak Patents. Publicized disputes such as Amgen's EPO battle illustrate the fragility of patents. Ignoring the costliness of patent litigation which is not inconsequential, the uncertainty of patent protection simply increases the riskiness of an already risky drug approval process. The risks are twofold: first, that a company may not have any rights to its discovery altogether; or second, that a company's patent may be construed so narrowly as to weaken the monopoly it grants during the patent's life. Investors may also legitimately fear that the resolution of patent questions will take place late in the developmental process, after extensive research, developmental and manufacturing costs have been sunk. Weak patents therefore increase the riskiness of drug investments.

⁵In an unfortunate burst of regulatory zeal, the Patent and Trademark Office (PTO) has interpreted a judicially required practical utility test to mean that it must scrutinize the efficacy of biotech drugs and precursor substances before patents can be granted. As a result, the PTO has begun to look very similar to FDA. Under pressure, PTO agreed to reexamine its standards, and recently agreed to accept less comprehensive test data to show that a substance has a plausible use. Drug Patent Rules Will Simplify Process for Biotech Concerns, Wall Street Journal, December 23, 1994, p.B5.

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(iii) DruQ Failures. The prospects for biotechnologically-derived drugs are intrinsically unpredictable. Efficacy and safety can be projected in a lab setting through animal testing, but such projections rarely are definitive. As a result, numerous promising products fail at the clinical stage. Recent examples include Centocor's Centoxin, Synergen's Antril, and Gensia's Protara.⁶ Leaving aside for the moment whether the FDA's hurdles for safety and effectiveness are reasonable, the possibility of drug failure is very real and increases the risk level borne by investors. Nonetheless, this factor is also easily overstated since the uncertain prospects for traditional chemically-derived drugs have been known for some time, and it is difficult to imagine that investors would fail to anticipate the same would be true of biologically-derived drugs. Many investors in fact ought to have anticipated a high failure rate by consciously diversifying their biotech holdings in order to create a portfolio affect. Hence, the high failure rate for individual biotech firms does not necessarily create problems for investors holding larger portfolios as long as the winners more than compensate for the losers. While some drug companies ought not to get funding because their drugs truly lack merit—a judgment communicated through by venture capitalists—most drug companies have sound ideas, but do not offer investors sufficient returns to entice investors.

⁶Rhonda Rundle, Biotech 'Jinx' Strikes the Hope of San Diego, Wall Street Journal, October 18, 1994, p. B1.

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(iv) Time to Market. Some drug companies (notably Genzyme) record positive cash flow from drug research done on a contract basis. Leaving aside the question of whether this is simply accounting gimmickry to recognize as revenue that which is really expense, this is the only operating cash flow that companies receive until their drugs reach market. Since this money, along with outside financing, is spent entirely on drug research and development, companies generate no positive cash flow until the drugs themselves reach the end consumer markets. Because this process can take from five to eighteen years,⁷ investors will need to wait that long for returns on their investment. But investors are impatient since money tied up in drug development cannot be invested in commensurately risky investments elsewhere. They therefore demand returns to compensate them for the delay.

Part IV: FDA

Congress last visited the topic of regulating biologically-derived substances in 1902 when it passed the Biologics Act after a batch of contaminated vaccine reached the market. In the interim years, with the nation's vaccination programs proceeding smoothly, Congress surprisingly has not revisited the topic legislatively despite innumerable hearings. As a result, the FDA has enjoyed enormous discretion in regulating biotechnology as the field has emerged. Although it shares jurisdiction over biologics with EPA, USDA, OSHA, DOT and several other agencies,

⁷One recent Tufts University study found that the pipeline from discovery to market lasted between 11 and 17.8 years. Ted Bunker, A New Prescription for Biotech, Investor's Business Daily, November 4, 1994, p. A1.

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under the Coordinated Framework, FDA is uniquely responsible for regulating drug development. The agency consequently has wide latitude in setting standards and procedures for biotech drug approvals, as it does for ordinary drugs.

(i) Approvals

The time-to-market problem is well-known, but what has been less clear is the role that FDA regulation has played in deterring capital from entering the industry. FDA views its role as ensuring safety and efficacy. Time is therefore relatively unimportant to the FDA since delays in the approval process do not make drugs any less safe or effective when they finally emerge. The FDA's calculation thus places an almost infinite value on preventing a fialuridine or a thalidomide from penetrating the approval process and a very low priority on accelerating approval for everything else.

Until recently, FDA typically required two years to evaluate New Drug Applications (NDAs) after three years of clinical trials had been completed. After industry pressure, Congress passed the User-Fee Act in 1992, under which industry effectively agreed to pay its own way in the approval process. In return, FDA pledged to streamline the process. Whether this has actually happened is unclear. The agency proudly points to reduced approval times as evidence of improvement. Indeed, agency figures show that median approval times have been cut in half from about

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two years to one.⁸ Yet these statistics are deceptive: the agency approved just one new therapeutic biological drug in 1994. More importantly, the agency measures its performance only when the review process formally starts. The problem: before the official stopwatch begins, the agency has begun to demand even more data from drug manufacturers.⁹ Hence, PLA's have decreased significantly, miraculously clearing the backlog which has bedeviled FDA for the past decade. While the formal review stage may be shorter, drugs will not get approval any more quickly.

Until recently, to outsiders such as those sitting on Congressional committees, this was as it should be: speed was equated with a lack of caution. But speed and caution are not incompatible. Delay imposes costs of foregone drug development that are indirect and less visible than fialuridine deaths, but are no less real. These costs are twofold:

(a) Current Patients. Until recently, this group was denied access to as-yet-unapproved drugs unless patients were participants in clinical trials. Even then, access to experimental drugs was not assured since the decision to administer placebo or drug to a patient in a clinical trial was left to the discretion of the designer of the study. These

⁸Lisa Piercey, FDA Review Times, Approvals are Down, Bio World Today, January 19, 1995, p.1.

⁹Drug User Fee Review Times May Be Ripe for Oversight From Republicans, Pink 56 (46), November 14, 1994. While the FDA has not been publicity-shy in announcing the speed (nine months) with which it approved Genentech's Pulmozyme, the company spent more time than would ordinarily be the case in Phase III trials in order to bring a stronger case to FDA. Pulmozyme Development May be Prototype for Other Biotech Products, 56 (1), January 3, 1994.

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restrictions have been lifted slightly to permit patients with serious or immediately life-threatening disease to receive the drug concurrently with the clinical trial as long as alternatives are not available (which, presumably they are not, since by definition, a new drug is unlikely to be developed if comparable products are already on the market) . Of course, this only applies to a narrow class of patients. Others are denied access to experimental drugs awaiting approval even if they consent after being informed of the risks. Although there is a real possibility that manufacturers will exploit this exception to sell unapproved drugs and make and end-run around the historically sacrosanct notion of FDA pre-market approval,²⁰ it seems more problematic for the agency to deny drugs to chronically ill patients who want them. This is particularly the case because patients have precisely the incentives to correctly evaluate drugs that the risk-averse FDA lacks: they may be willing to accept a risky drug as long as its expected benefits exceed its expected risks. This does not solve the paradox of informed consent: while consent may be informed to the extent that a patient understands that a drug is risky, how can a non-expert patient truly assess a drug's risks if it takes two years of analysis by FDA experts who have made such investigations their life's work? The counterargument is that patients make such decisions every day when deciding to take over-the-counter drugs, a risk-benefit decision made on the fly at the

²⁰FDA attempts to limit this risk by prohibiting the manufacturer from promoting the drug and requiring the manufacturer diligently to seek approval for the drug while the back-door sales are occurring. These limitations seem rather hollow: the manufacturer might attempt to promote the drug through the news media, although the government has restricted that kind of behavior as to unapproved uses of approved drugs. Similarly, a manufacturer can skirt the diligence requirement by insisting on more tests. This would put the agency in the politically incongruous position of insisting on fewer tests and complaining about approval delays.

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drugstore. Though the risks are admittedly less serious for these kinds of drugs, our treatment of over-the-counter drugs nonetheless suggests that we have permitted patient choice in other contexts and should extend it here, although not in a cavalier way. (In this case, unlike over-the-counter drugs, unapproved drugs ought only to be available after meeting the scrutiny of a doctor who must prescribe them.)

(b) Prospective Patients. Ultimately the more insidious impact of delay is on prospective patients who likely would not even know that a drug would have been available to them. Returning to our familiar perspective of the impatient investor, delay costs fledgling biotech companies in two ways. First, delay diminishes sales from the new drug which would have occurred during the approval period. Note that these sales are foregone, not simply postponed, because under ordinary circumstances (for non-Orphan drugs), the patent clock continues to tick irrespective of the speed of approval. Since a patent ordinarily lasts 17 years and the time elapsed from drug inception to approval can range from 5 years to 18, the market monopoly conferred by the patent may last just a few years, although the stridency of current regulation deters generics from entering as effortlessly as they do in the synthetic drug context.²¹ By the FDA's own conservative estimate, every month that a drug is withheld from the market represents foregone income of \$10 million.²² Reducing the FDA's approval period from 23 months to 12

²¹Generic biologic manufacturers must meet safety and effectiveness requirements that would not otherwise have to be met if the drug is chemical.

²²This estimate is conservative because it implies annual sales of \$120 million for a given drug. Revenues are higher for so-called blockbuster drugs. The top ten best-selling biotechnology drugs each averaged \$430 million in sales in 1993. (Ernst & Young, p.14). This estimate is also

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months, as the FDA says occurred in 1994, would therefore result in \$120 million in revenue for each manufacturer- -enough to keep the average biotech company alive for six years. Second, delay costs biotech companies that must continue to service carrying costs during the approval period. These carrying costs are not simply the company's actual cash outlays for overhead which together constitute the burn rate. They also include the imputed cost to investors' capital. If for example in our earlier hypothetical, the return period were shortened from 10 years to 9, the total return that investors would require to finance the project would fall by 1001.23

In the immediate term, these added costs (or potential savings, depending on one's perspective) are either absorbed by consumers in the form of higher prices or by investors in the form of lower returns. In the longer term, if such costs are not passed along to consumers, then investors will respond by contributing less financing to biotechnology ventures and companies will respond by developing fewer drugs.

(ii) Clinical Trials

The fialuridine case illustrates what happens when a clinical trial goes awry. First, there are deaths—in this case from unexpected

conservative because it apparently fails to take into account worldwide drug sales, which account for about 20% of drug revenues, by one estimate. Robert Bohrer, What is Biotechnology, 55 University of Pittsburgh Law Review (1994) 607, 608. Although other nations have independent drug approval processes, since these nations honor the findings of the FDA as they would their own, some companies wait for FDA approval before seeking approval abroad. 23(12)~9...516% vs. (1.2)'~10=619%.

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liver toxicity. Then, there are recriminations: was the manufacturer careless in conducting the tests? Was the FDA lax in overseeing them? Pressure builds, then the agency responds with new regulations designed to prevent a recurrence.²⁴

This now-familiar pattern of legislative and regulatory response to tragedy has been repeated—in 1813, in 1902, and again in 1938—with favorable results, suggesting that scandal and tragedy are valuable prods to a sleepy Congress and FDA. But in this instance, FDA is not sleepy; its thousands of regulators are wide awake. The fialuridine scare unfortunately pushed the FDA further in what is already the wrong direction. FDA responded by requiring additional reporting of adverse effects—in effect, attempting to require vigilance.²⁵ Taken alone these new requirements sound sensible. But they add to what already is a crushing administrative burden on small biotech firms racing against time through the approval process in order to test products that may save thousands of lives—not just the five involved in Phase I clinical trials. Under FDA's oversight, the size—and therefore the expense—of clinical trials grew significantly in the 80s.²⁶ Not surprisingly, therefore, the proverbial struggling biotech firm may run out of cash before even reaching Phases II and III if Phase I is too costly. Once

²⁴John Schwartz, FDA Moves to Improve Safety of New Drugs, WashinQton Post, p. A10. Federal ReQister, vol. 59, No. 207, p. 54038. ²⁵Ironically, while an FDA investigation squarely blamed the trial researchers for failing to spot early warning signs in the incident, the NIH (which had equally self-serving motives) subsequently cleared its own researchers, concluding in effect that no amount of additional prudence or analysis would have saved patients' lives. Eliot Marshall, Drug Deaths Deemed Unavoidable, Science, June 10, 1994, p. 1530. ²⁶Off ice of Technology Assessment, Pharmaceutical R&D.

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again, the agency has made a poor calculation between lives lost to experimental drugs and lives lost to prospective drugs left undeveloped.

(iii) Discrimination

While the FDA's approval delays occur irrespective of whether the product in question has been biologically or chemically derived, other aspects of FDA regulations treat biologicals more stringently than their chemically-derived counterparts. The discriminatory treatment is a legacy of early fears from the Rifkin era about biologicals that have not been borne out. Although many of the original ethical questions remain unresolved, these issues should not be under the purview of the FDA in any case since they are political questions. By contrast, the earlier fears about safety, are clearly in the FDA's bailiwick, but have been largely answered. Consequently, to a limited degree, the FDA has recognized its anomalous treatment of biological drugs and has moved to equalize treatment with traditional pharmaceuticals. In 1986, the agency adopted a Coordinated Framework for Regulation of Biotechnology under which it agreed to assess drugs according to their product characteristics (presumably use, side effects, novelty) and not according to the process by which they were made (biotechnology). This outcome recognized that biotechnologically-derived substances in many instances are indistinguishable from their chemical counterparts. In some cases, biotechnology simply permits a known substance to be manufactured cheaply on a large scale, a feat which may have been impossible with chemical methods that could produce quantities too small to be commercially viable. The agency also recognized that as with

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traditional drugs, some are riskier than others; the level of risk depends on the drug's novelty and application.

Unfortunately, that philosophy has been applied inconsistently. For example, for conventional chemical drugs, the FDA has waived the onerous NDA requirements in favor of a shortened and much less time-consuming Abbreviated NDA (ANDA) in instances where new drugs are chemically equivalent to listed drugs that have already been approved. Nonetheless, for biologically-derived drugs with identical chemical structures, the agency has required applicants to go through the full NDA process. Since time-to-market is such a crucial determinant of a biotech company's willingness and ability to begin development efforts, this kind of discriminatory treatment may act as a significant deterrent to drug development.

Discrimination is more overt in manufacturing certification. Although the probability of success for a drug increases as the drug nears final approval, a high level of uncertainty remains. This poses a problem for the drug manufacturer which must decide at what point it should create a full-scale manufacturing facility in anticipation of approval. This is not an obvious decision: if it waits too long to create a factory, it has wasted part of the precious and fast-closing window of opportunity between approval and patent expiration. Yet if it builds the factory too soon, it runs the risk that the drug fails clinical trials or that its approval is significantly delayed by FDA while more tests are run. An idle factory increases the company's burn rate; a dedicated facility that will never be used is an investment that

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will never be recovered.²⁷ This is also not a trivial decision: because of the sophistication of the equipment, the costs of constructing a drug factory are enormous.

Although all drug manufacturers face this predicament, biological drug makers are at an enormous disadvantage. Although drug manufacturers must include similar plant information in their new drug application (NDA) and are subject to inspection,²⁸ they do not have to be precleared. By contrast, biological drug manufacturers cannot wait to build until a drug's chances of approval have improved because under the Biologics Act of 1902, the FDA requires that biotech companies seek premarket certification of their manufacturing facility (ELA) concurrently with the drug approval application (PLA). The corollary of the rule is that if the manufacturing process or facility is changed, the approval process must be repeated. The rationale: what makes biologics unique is the process by which they are derived. Since potentially harmful bacteria and viruses are often present throughout the manufacturing process, slight changes in the manufacturing process can cause significant contamination in the output of the process and the FDA believes consistency and therefore safety can only be ensured by prior certification.

²⁷This became painfully clear recently to Centocor which had put the finishing touches on an enormous factory in Leiden, The Netherlands, shortly before the failure of Centoxin, its sepsis drug. Udayan Gupta, *Now or Never*, Wall Street Journal, May 20, 1994, p.R12. ²⁸Regulation of chemical and biotech plants has converged in recent years as FDA scrutiny of chemical facilities has increased.

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Taken together these manufacturing restrictions impose disproportionate costs on biotech companies—the very companies that can least afford to bear them.²⁹ Biotech companies, living precariously close to their flameout date, must incur enormous manufacturing costs during Phase III tests even though these expenditures might be wasted entirely if a drug fails FDA approval. The restrictions also raise the same dangers that Good Manufacturing Practices (GMPs) pose for ordinary pharmaceuticals. First, there remains an intractable conflict between narrowly specifying what the standards should be and in doing so stifling innovation, or permitting innovation but inviting agency discretion by leaving the rules deliberately vague. In the biotechnology context, the risk of reduced innovation is particularly problematic. Once a process has been certified as complying, the FDA rules create enormous disincentives for process innovations since sufficiently significant innovations can trigger the approval process again. Such innovations not only include improved processes that save the company money, but also innovations that improve drug consistency by lowering defect rates. These kinds of innovations which benefit consumers will not be made by companies who cannot afford to stop production for facility recertification while the patent clock continues to tick. At an industry wide level, therefore, the incentives are quite perverse: since the FDA's definition of industry standards is tautologically dependent on what good manufacturers do in practice, since no company has the

²⁹Regulation proponents point out that biotech companies can subcontract their factory to more experienced drug manufacturers. This makes considerable economic sense since expertise will likely reduce costs, but it does not eliminate the costs of a dedicated facility. If these costs are born by the contract manufacturer, the biotech will have to pay for them, either in cash (unlikely) or by giving away royalties to the drug if it reaches the market.

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incentive to improve its practices, the industry standard will never change. Conversely, no company has an incentive to innovate and therefore deviate from the industry standard since non-conformity suggests to the FDA that a company's practices might not be good.

Discrimination will become increasingly anomalous as the distinctions between traditional drug and biotech companies blur. A biotech company is a pharmaceutical company, one industry advocate has observed, only not encumbered with revenue.³⁰ Already, 30% of pharmaceuticals' research is biotechnology-based.³¹ As biotech companies desperate for cash surrender control to pharmaceutical companies, that percentage will grow. This highlights the inequity in treatment between two disciplines whose work is scientifically comparable, yet treated differently by the FDA. Nonetheless, simply because companies merge does not mean as a logical matter that science must be merging also. But that is in fact what is happening: biotechnologists have increasingly turned to chemistry during the development and manufacturing process. The FDA should recognize the collapse of its already artificial distinction.

Part V: Reform Proposals

Several kluge solutions to the current capital crisis have been proposed:

³⁰Carl Feldbaum, as quoted in Mario Aguilera, Biotech's FDA Gripes Reported, San Diego Daily Transcript, October 6, 1994, p. A1.

³¹PMA Warning on Future of Biotechnology, Marketletter, September 27, 1993.

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(i) Defer to the Market. After biotech firms have exhausted private equity—even on unfavorable terms—and in order to preserve their companies, if not control, many have begun to sell out to traditional pharmaceutical companies. While these combinations are appealing to pharmaceutical makers (they help replenish depleted research pipelines) and to biotechs (they help achieve economies of scale in marketing and manufacturing and give biotechs much-needed expertise in navigating the regulatory process) and are becoming more prevalent, they do nothing to solve the industry’s fundamental problem. Whether biotech companies are owned by shoestring entrepreneurs or by Merck, returns for new drug R&D remain unattractive because of risk and timing. Pharmaceutical combinations do not change this.

(ii) Provide tax breaks for biotechnology investors. This proposal recognizes correctly that unless investors achieve higher returns, money coming into the industry will continue to be inadequate. Tax benefits effectively lower these investors’ capital costs. But because this proposal treats symptoms rather than disease, it is inefficient: by providing subsidies to investors the government effectively pays twice—once in forgone tax revenue, and again for an expensive FDA scrutiny of drug approval applications. Meanwhile, while tax breaks solve the investment and R&D problem, they do nothing to speed access to drugs by current patients since drug approvals will continue to be delayed. Additionally, they are inequitable, since the same financing characteristics and regulatory concerns apply to ordinary pharmaceuticals as to biotech products; if one receives preferential

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treatment, they both should. Why should Icos be treated more favorably than Merck?

(iii) Create an exception to new accounting rules. Proponents of this plan, including the Biotechnology Industry Organization (BIO), seek to exempt the industry from new Financial Accounting Standards Board (FASB) rules that compel companies to estimate and reveal the value of stock options doled out to executives and to dock earnings accordingly. This proposal seems superficially appealing since cash-poor biotech firms frequently prefer to pay executives in stock not cash. Yet the proposal ignores the behavior of venture capitalists and other investors who look at cash flows and burn rates not at accounting earnings. Biotech earnings are already so depressed as to be meaningless. Few would be deceived by phony bookkeeping. Further, the proposal's aim is simple deception since it would allow biotech firms to make less disclosure than firms in other industries—a situation that is both inequitable and unethical.

(iv) Create a private-sector alternative to FDA. This proposal, contemplated by several conservative Washington think tanks,³² would create a shadow FDA comprised of private sector physicians and academics drafted for the purpose of evaluating drug approvals. These free-market proponents argue that constructing a private-sector approval organization to compete with FDA would create a market in drug

³²Interview, Geoffery Pierce, Citizens for a Sound Economy, January 23, 1995. As of this writing, none of these think tanks, which also include the Cato Institute and the Gingrich-affiliated Progress and Freedom Foundation, have published their proposals on FDA reform.

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approvals, and would thereby create incentives for FDA to reduce approval times to stay competitive. While a shadow FDA directly addresses the underlying problem, it goes too far: it would not be difficult to imagine a race to the bottom in which the two organizations compete not only by accelerating approvals, but by lowering safety standards. The approval panel with the most porous safety standards likely would attract the most takers in this artificial marketplace. The industry should get speed, but not permissiveness. Think-tank staffers have not yet come up with a coherent answer to this problem.³³

On the other hand, while they lack the ideological purity of free-market polemics, direct regulatory reforms are a more sensible way to correct the regulatory crisis:

(i) Approvals

Given the enormous costs in foregone drug development that result from the long approval process, FDA should do what it can to shorten the process. The final clinical trial phase probably cannot be substantially shortened for two reasons. First, clinical trials must be performed sequentially, not in parallel, so that the knowledge gained from earlier trials can determine the design of later trials or whether they should be held at all. Second, since there is a minimum latency period for some toxic effects of various drugs, there is a minimum natural limit on the duration of clinical trials. To shorten the trials below this limit

³³Interview, Geoffery Pierce.

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would be to lower the FDA's hurdle for effectiveness and safety. We would prefer instead to increase speed without decreasing safety.

It is no coincidence that to the extent there has been discussion of this problem (in debates over the User Fee Act), the focus has been on shortening the approval phase. No viruses incubate during this part of the process; on the contrary, the approval period is simply an opportunity for the FDA to review the voluminous statistics submitted by the manufacturer. Since the agency by its own estimate will collect \$343 million in user fees in 1995,¹³ it cannot plead inadequate resources as a barrier to reduced approval times. Rather than gaming the approval process to present rosy statistics for public consumption, the FDA should continue to make meaningful reductions in approval times.

(ii) Availability for Unapproved Drugs

The agency should make all unapproved drugs available during the clinical trial process. Provisional drug distribution would ensure patient access to new drugs and that the agency does not interfere with patient choice. This would also eliminate inequities as between patients with ailments the agency deems serious and life-threatening and those whose ailments are merely painful and chronic. FDA would no longer engage in a comparative victimization analysis under which it decides which diseases (particularly those with political glamour) outrank others; the patients themselves would do it. As under the current system, manufacturers would be barred from promoting the new drugs, ¹³ Biotechnology Law Report 489 (Number 4, July-August 1994).

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either in the press or elsewhere. To ensure informed consent, FDA would require patients to sign a consent form and to be told the probability of drug disapproval, based on historical tallies for unapproved drugs at a comparable stage.³⁵ Only seriously desperate patients would likely want to play those kind of odds.³⁶

(iii) Manufacturing

FDA should end the disparity between its treatment of chemical and biological manufacturing facilities. By requiring biotech companies to clear these facilities concurrently with the drug to be manufactured there, the agency is effectively requiring such firms to substantially increase their ante when virtually all of their chips are already on a product with an unavoidably high risk of failure. Allowing biotech companies to wait to exercise their option on plant construction would effectively raise returns to investors and encourage investment.

* * *

The unavoidable reality is that no amount of regulation will fully eliminate risk from what is an inherently risky process. The incremental reductions in risk that result from succeeding waves of FDA regulations

³⁵This goes further than a proposal by the Competitive Enterprise Institute, a conservative think tank, that would simply require a drug's label to state that the drug is unapproved. Group Calls for FDA Reform, BNA Health ~ ~ January 13, 1995.

³⁶This type of pre-approval distribution would be advantageous to the extent that it effectively extends the scope of testing. While these patients would not be subjected to the same kinds of rigor as clinical trial patients (control groups, monitoring), this group could provide valuable supplementary information on safety and efficacy.

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are more than offset by the costs of delay from an already highly scrutinized process. By removing unnecessary regulatory requirements, the FDA would contribute significantly to rejuvenating the capital markets' interest in the biotech industry, an outcome that would encourage R&D spending and therefore innovation. We would then expect to see a wider range of new drugs available to consumers at lower prices.