



Avoiding no man's land
Potential unintended
consequences of follow-on
biologics

After years of ongoing debate, Congress has brought forward legislation to create a regulatory pathway for the approval of “follow-on biologics” (FOBs) – drugs envisioned as the biotechnology equivalent of generic drugs in the chemically-based pharmaceutical industry. Two bills have been introduced addressing the issue of FOBs, and each is based at least indirectly on the model of the Hatch-Waxman act of 1984 that created an abbreviated approval process for chemical generics.

Patient Safety

- What will constitute threshold “biosimilarity”? Specifically, what type and length of clinical trials will be required to establish that a new FOB is sufficiently similar to a currently approved and marketed “branded” biological drug, and thus permit the FOB a relatively quick path to market? Under what circumstances would a new FOB be considered “interchangeable” with a currently approved drug?¹

Industry Economics

- How can new regulations most appropriately encourage competition while also maintaining sufficient economic incentives to foster scientific innovation? Specifically, what should be the appropriate period of time granted to a branded biological drug for protection of its underlying intellectual property prior to the approval and entry of an FOB?

Given the pivotal importance of both patient safety and economic viability to the future of the global biotechnology industry, observers and advocates have spent significant time – and reams of paper – deploying arguments on the impact FOBs would have on each. Advocates of a quick path to FOB approval note the rapid growth and high costs of life-saving biotechnology therapies in a time of cost constraints and successful biosimilar regulatory pathways elsewhere in the world;² skeptics note unproven clinical effects (how similar is similar enough?) and the effect a declining ROI would have on innovation.

At the heart of this debate is one key issue: How similar are the two underlying industries?

Proponents of the new legislation argue that, like the Hatch-Waxman bill of 1984, an abbreviated regulatory pathway for FOBs will reduce spending on therapies by increasing price competition in the highest-volume and highest-cost areas of drug therapy. Yet disagreement around the potential elements of FOB legislation is widespread; key issues are highly technical and analytically complex. Still, the essential debate encompasses two broad issues -- patient safety and industry economics:

¹ “Biosimilarity” and “interchangeability” are two separate but related concepts, with the former being necessary but not sufficient to establish the latter for a new FOB. The definition of biosimilarity is likely to involve standards regarding the degree to which a follow-on biologic has the same mechanism of action (i.e., if it targets the same molecular disease regulator) as the original drug, and if it passes efficacy and safety screens. Interchangeability goes a step further, and would mean that a patient could be switched back and forth between the FOB and the original drug without negative medical consequences. The mechanism for establishing these standards is likely to be addressed in the pending legislation.

² This paper will focus exclusively on the issue of FOBs in the United States. As of early 2009, the European Union has completed definition of a regulatory pathway for FOBs, and the first FOBs have been introduced into European markets; however, no clear regulatory pathway has been defined in Canada, Japan, India, China, or most other major world pharmaceutical markets.

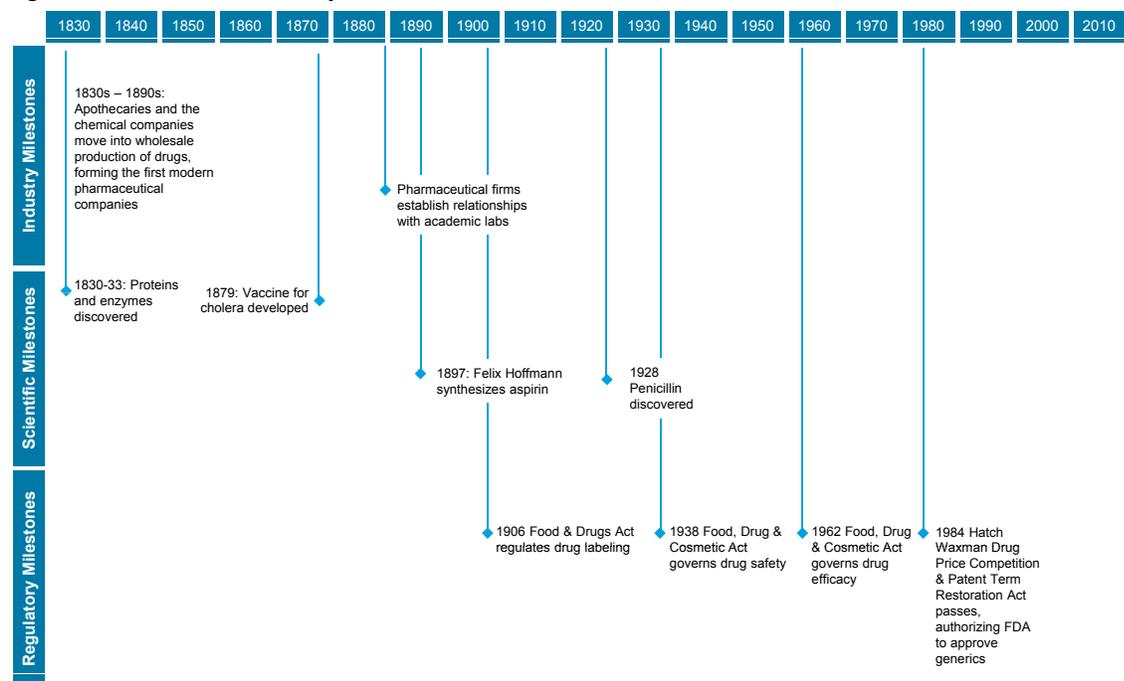
At the heart of this debate is one key question that has not been broadly discussed: given that Congress is considering similar legislation for biotech today as was passed for pharma in 1984, how similar are the two underlying industries? There are obvious similarities between the pre-Hatch-Waxman pharma industry of 1983 and the biotech industry of today – but there are also certain clear structural differences. How important are those differences? What impact would similar legislation have on the biotech industry? We believe the most logical way to answer these questions is to look at each industry as a business system – a combination of scientific, financial, and regulatory processes. We begin by considering how Hatch-Waxman reshaped the pharmaceutical business system.

The Pharmaceutical Industry *circa* 1983

By the time Congress was debating the Hatch-Waxman act, the chemically-based pharmaceutical industry was over a century old and represented a stable and mature business system:

- The **basic science** of the chemical pharmaceutical industry was mature: it relied upon chemical synthesis processes that, in many cases, had existed since the 19th century.
- The **industry business model** was mature as well: a small number of large, publicly traded companies were developing and producing most drugs that came to market, and just as important, self-financing drug development with internally available funds.
- The **regulatory regime** was mature: with the 1938 Food, Drug, and Cosmetic Act, the industry began to assume its modern form, in which a drug could only come to market after passing well-defined tests to establish its safety as a therapy.³

Figure 1: Pharmaceutical Industry Timeline ¹

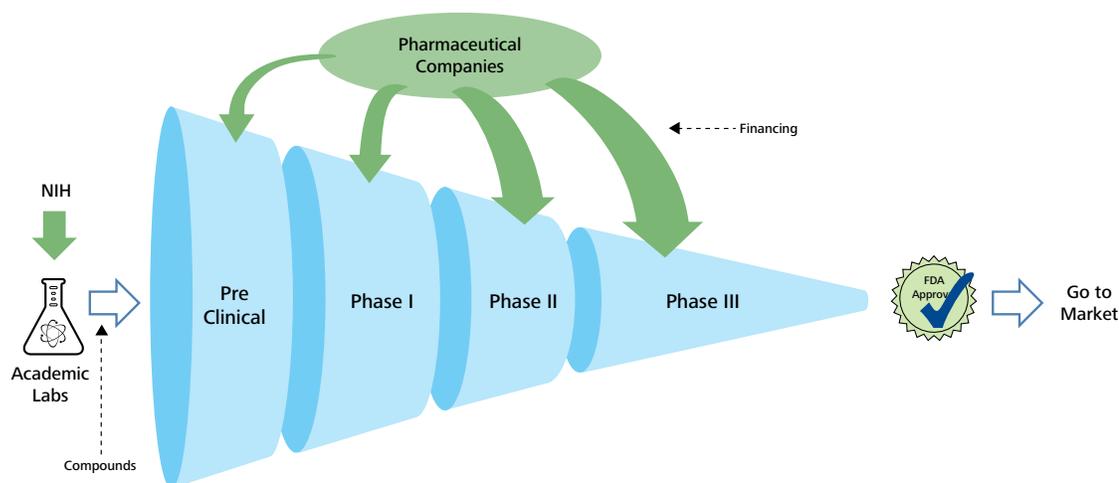


³ Tests for efficacy were added in 1962.

In its simplest form, that business system can be illustrated as a complementary set of flows of scientific development and capital necessary to finance it. As new compounds are discovered in the lab and journey toward the market, they must go through two related sets of gates. The scientific (and clinical) gates are often depicted as a funnel – broad on one end with a large number of chemically or biologically active compounds that show early promise as drugs, and narrow on the other, where a few compounds emerge as established therapies with proven safety and efficacy. It is well known that only a small number of early-stage compounds end up meeting the clinical standards required to become approved therapies. This funnel is commonly depicted, as in Figure 2 below, as several ever-narrowing sections, representing the established stages of drug development: Pre-Clinical, then Phase I, II, and III clinical studies that can lead to FDA approval and market entry as a drug.

Less often shown, however, is the parallel flow of capital that finances the various stages of drug development. Because most compounds never clear the clinical hurdles necessary to make it to market, investment in early-stage compounds is inherently risky – there is no guarantee of return on investment at any stage of the drug development process before final FDA approval. And because later stages of clinical testing are extremely expensive, investors in compounds that are in development must constantly weigh investments in each successive stage of clinical testing against the future market potential of the drug should it survive testing and get to market. The further the drug goes through the clinical pipeline, the lower the risk of failure, but the higher the stakes – more is known about the probability that it will be able to overcome the approval hurdles of safety and efficacy, and more and better assumptions can be made about the compound’s full commercial potential, but each phase of clinical trials is increasingly costly. This means that, in effect, most drugs in development actually face two sets of hurdles: one set is clinical, the other financial. A drug in development may be delayed or abandoned if it fails to clear either hurdle.

Figure 2: Pre-Hatch-Waxman Pharmaceutical System

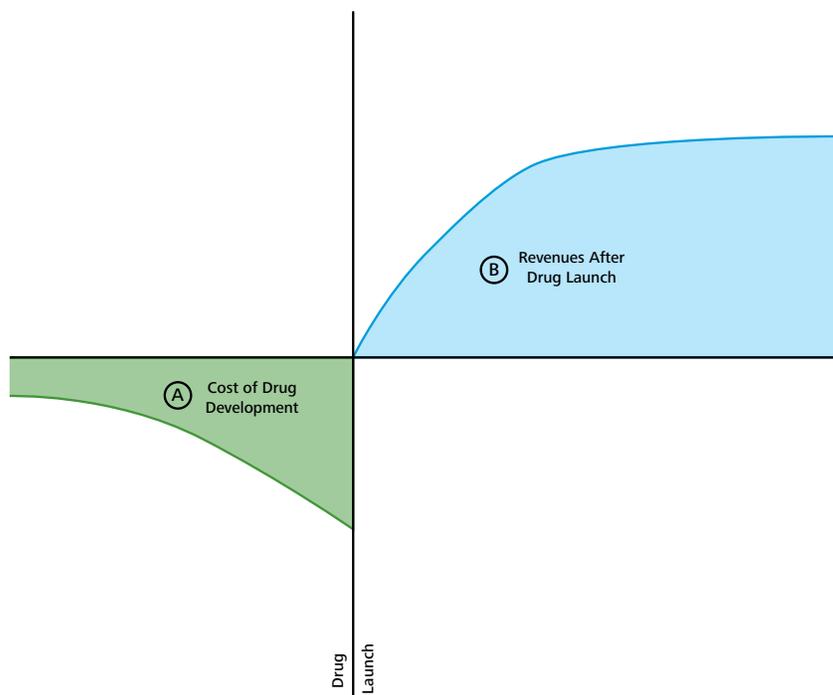


The business system for the pharmaceuticals industry in 1983 is illustrated in Figure 2, showing both sets of flows, clinical and financial. Note that there are two major sources of funding: government and private. Government funding then constituted well over half of total investment in the industry, and it was weighted toward the early and most risky stages of discovery and pre-clinical drug development. Private investment mainly came from the large corporations that made up the pharmaceutical industry, and it was focused in the four stages of pre-clinical and clinical development.ⁱⁱ Taken together, these two sources comprised more than 90% of all funding for drug development. In this pre-Hatch-Waxman system, the decision criteria for pharmaceutical manufacturers were relatively simple. The drugs under development in their pipelines represented a portfolio of assets, each with its own probability of success, and its own estimated market potential. Because the riskier, early stages of basic science drug discovery tended to be funded by government research grants, it was possible for a company to estimate the scientific and commercial risk associated with a specific compound. Investments in development, and the pace of bringing products to market, depended on their own cash flow and their targeted return on investment.

In simple terms, drug companies make decisions about investment in the development of any specific compound according to hurdle rate economics: they choose to fund a project (i.e., a potential drug) based upon the likelihood it will receive approval, and be able to achieve total return on investment that exceeds their cost of capital. Prior to Hatch-Waxman, an FDA-approved drug could enjoy a differentiated position on the market for many years, and therefore companies could afford to plan for longer payback periods for any individual drug than the drug's patent protection alone would imply.

A successful drug can have a material impact on the share price of a publicly traded company. Because share price is strongly correlated with both the profitability of a company and the company's projected growth, then and now pharma companies have to manage their drug portfolio to produce an appropriate level of profitability (or ROI – tied to their hurdle rate), and a growth in total earnings over time. The provisions of Hatch-Waxman would have a significant impact on how pharmaceutical companies manage their drug portfolios against these two financial objectives.

Figure 3: Economics of Drug Development

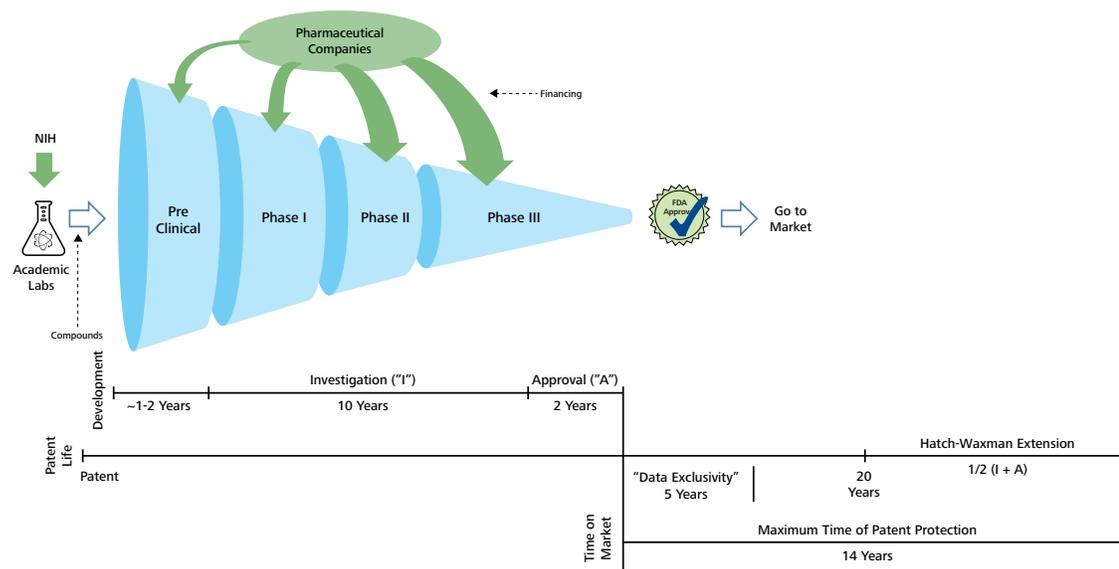


What Hatch-Waxman Did

The Drug Price Competition and Patent Term Restoration Act, as it is formally known, sponsored by Representative Henry Waxman (D – California) and Senator Orrin Hatch (R – Utah), fundamentally altered the 1983 pharmaceutical business system by changing both sets of hurdles: clinical trial requirements and market economics. The aim of the bill was to foster price-based competition, and therefore to reduce public expenditures on prescription drugs.ⁱⁱⁱ In order to accomplish this, it created an abbreviated regulatory path to market for generic drugs. At the same time though, it established mechanisms designed to provide protection for the economics of innovator companies, largely through a set of rules that allowed drug companies to extend the patents on drugs they brought to market.

In order to speed entry of generic drugs and create price competition, the Act created a path to market that allowed companies that developed generic versions of existing drugs to receive FDA approval to market generic versions without conducting their own lengthy clinical trials. In essence, they were allowed to borrow the clinical data that the innovator company had originally gathered during the development of its branded compound. All that was required of the generic producer was to demonstrate that their version of the drug had the same chemical properties as the original drug.⁴ This abbreviated path to approval meant that generic producers could avoid the previously required expense of conducting their own Phase I, II, and III clinical trials. Since clinical studies are

Figure 4: Hatch-Waxman Provisions for Patent Protection



⁴ More specifically, the legislation instructed the FDA to evaluate generics based only on the chemical equivalence of their active ingredient, assuming that bioequivalence was an adequate substitute for directly demonstrated safety and efficacy. In fact, the only test the FDA is allowed to apply to a chemical generic is bioavailability (the amount of active ingredient in the bloodstream over a period of time), and that only needs to be within a plus-or-minus 20% range of the innovator's molecule.

typically the most time consuming and expensive phases of drug development, skipping them dramatically shortened generics' time to market and reduced their development costs. But Hatch-Waxman also recognized that a company that had developed and produced an innovative drug had a legitimate expectation for return on its investment. The legislation recognized that without adequate returns, incentives to fund innovative (and thus inherently risky) inventions would be dampened across the entire industry. Accordingly, the Act granted innovators a pair of mechanisms to extend the time approved branded drugs would have on the market prior to the entry of a generic competitor: extended patent life, and data exclusivity. These provisions are complicated, but they are important, because they are central to the debate about FOBs.

As shown in Figure 4, Hatch-Waxman allowed innovators to extend the life of their patents by allowing them to recapture some of the time lost to the FDA regulatory process. The formula for this is arcane, but essentially

manufacturers were allowed to add onto their patents about half the time it took from the outset of clinical trials in humans through the time of final FDA approval. (This is shown in the chart as $\frac{1}{2}$ of Investigation + Approval, or $\frac{1}{2}(I+A)$.) There were limits: patents could be extended for no more than five years, regardless of how long development had taken. And the maximum period a drug could enjoy patent protection after approval was set to 14 years.

At the same time, Hatch-Waxman also introduced a parallel protection known as the data exclusivity period. The innovator drug was permitted a minimum of five years post-approval on market before a generic competitor could use the original manufacturers' clinical trial data to establish the generic's safety and efficacy.

In sum, then, Hatch-Waxman gave something to both sides: it provided a path to market for generic drugs, and gave a window to innovators of at least five but no more than 14 years of patent protection.

Economics of the Generic Chemical Pharmaceutical Industry

While the concept of generic copies of branded prescription medications has existed since the 1960s, the industry came into its present form following the passage of the Hatch-Waxman act in 1984. The industry, which realizes revenue of nearly \$60 billion per year, captures 70% of prescriptions and 20% of pharmaceutical spending in the U.S. Generic manufacturers are able to address patient safety concerns by demonstrating chemical equivalency with a branded compound and implicitly "piggybacking" on the clinical trials done by the innovator. Meanwhile, generic manufacturers are able to capture substantial market share immediately upon market entry by selling chemically equivalent drugs at a fraction of the branded price. These companies bear few costs of research, development, or clinical approvals; generally speaking, the cost of raw materials and manufacturing is low; and generally marketing to physicians or patients is not required as the branded compound has built awareness for the chemical and mechanism of action. In sum, generic chemical pharmaceutical manufacturers are able to offer safe, effective drugs with wide room for price arbitrage at the same return on invested capital as a branded pharmaceutical company.

The results of Hatch-Waxman have been striking. Consistent with its intent, it did succeed in creating price competition in the market. The Congressional Budget Office (CBO) estimates that by 1994, ten years after passage of the legislation, US consumers were saving \$8 - \$10 billion dollars per year through the introduction of generic alternatives to branded drugs.^{iv} But the Act also produced unintended consequences. Some of these were positive. Surprisingly, after Hatch-Waxman, R&D investment among the innovator companies increased sharply.^v However, even as generic prices dropped after the Act, prices for new branded drugs increased substantially faster than baseline GDP growth.^{vi}

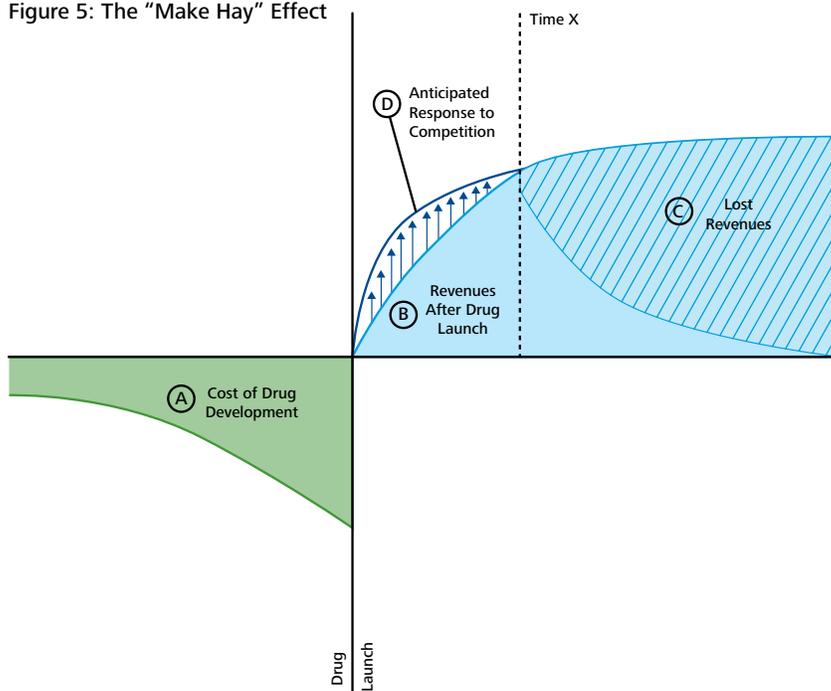
We believe it is important to understand these unintended consequences, because they may shed light on what we might expect if an abbreviated approval pathway is created for FOBs. And we believe they can largely be explained by looking at the economic incentives created for innovators as a result of Hatch-Waxman. We see three separate effects caused by the Act, which we call the “make hay effect,” the “blockbuster effect,” and the threat of “no man’s land.” All three of these effects influence the planning for a drug innovator. The first also has a bearing on how it commercializes drugs. Together we believe they explain the unintended consequences of Hatch-Waxman. Let’s review each in turn.

As seen in Figure 5, the introduction of a generic competitor radically alters the economics of development and commercialization for the innovator organization. Recall that for an innovator, the costs of development are significant, and increase right up until launch (the area under the curve labeled “A”). Once a drug goes on market, the innovator begins to earn revenues over time, which grow as the drug gains wider adoption, and then tend to peak and slowly decline as new innovator therapies appear.

This revenue curve is labeled “B.” During the life of each product, the revenue earned on the drug pays for its development costs, and the innovator’s return on investment depend on the how much revenue it can generate, and how quickly.

When a generic competitor enters the market (at time X) it quickly takes market share, and that share grows over time, reducing the innovator’s revenues (the hatched area in the curve labeled “C”). These lost revenues mean lower return on investment for the innovator, and faced with that prospect (i.e., once the innovator knows there is an approved route for generic entry), they will try to maximize the revenues they can realize ahead of the onset of generic competition (the area marked with arrows and labeled “D”). They can do this in two ways: 1) raise prices; and 2) invest more in the marketing of the new drug at launch to drive earlier adoption. This is exactly what happened in the wake of Hatch-Waxman.^{vii} In this respect, Hatch-Waxman arguably worked counter to its original intent.

Figure 5: The “Make Hay” Effect



Revenues lost to generic competition not only reduce the return on investment of the individual drug – they can also affect the stock price of the innovator company, because they are lost future earnings upon which enterprise value is based. So innovators need to both increase their revenues in the short term, and replace those revenues in the long term. One obvious way to do this is to invent new drugs and bring them to market as soon as possible. This helps explain the increased investment in R&D by innovators that followed Hatch-Waxman, which was arguably a positive, if unintended, consequence of the Act.

It's not hard to see, then, how the new avenue for competition would reshape the planning process for pharma innovators. Given an ever-increasing cost for drug development, but a capped period of patent protection during which to achieve most return on investment, innovators will concentrate on the development of drugs with the highest revenue potential, i.e., blockbusters. Several analysts have done sophisticated work exploring the payback periods for drug development, but this is a point that is relatively easy to illustrate with simple numbers as well. Once a compound is patented, it has a limited amount of time to get to market and earn a return – under Hatch-Waxman, assuming patent extension, this period is roughly 25 years. If this seems at first glance to be a long time, subtract from those 25 years the time it takes on average for a compound to move from the lab through pre-clinical and clinical development and receive approval

(an average of roughly 12 years). What remains for the average compound is roughly 12 years to recoup the cost of investment in its development. Add to this equation the average cost of developing a novel drug: roughly \$1 billion. Further adding to the calculation a conservative cost of capital over the 25 year span shows that just to break even the average drug must achieve average annual revenue of roughly \$150 million.⁵ That much revenue cannot reliably be achieved unless a drug targets a large population of patients, or comes at a high cost per treatment. This blockbuster effect has led pharma companies generally to focus development efforts on only the largest potential indications.⁶

Finally, there is the issue of “no man's land.” As soon as a company has patented a novel compound, the clock begins ticking. Working from the same timeline in Figure 4, each year a patented drug waits to go into development is a year it loses of on-market revenues. This means that for each compound waiting to be developed, there is a point at which it will never earn sufficient return to fund its development, because if too much time elapses, there won't be enough time remaining on market for it to generate sufficient sales. Crossing that point is what we call crossing into “no man's land,” because after that point it will never pay back for anyone to develop the compound. Given the overall economics of producing a financially viable drug, we estimate that no man's land appears very quickly for a new compound – within as little

⁵ Assuming a 12% cost of capital, reasonable within the 11.5% - 12.5% range defined by Ibbotson Associates for the pharmaceutical industry.

⁶ To some extent, the Orphan Drug Act of 1983 ameliorated this issue for conditions affecting less than 200,000 people in the U.S., allowing seven years of market exclusivity and some limitations on clinical trial requirements (e.g. size of Phase III trials). However, there are still potential drugs with a broader market than 200,000 but not sufficient revenue potential to overcome the financial hurdle – which leaves them stuck in the middle and unable to reach market.

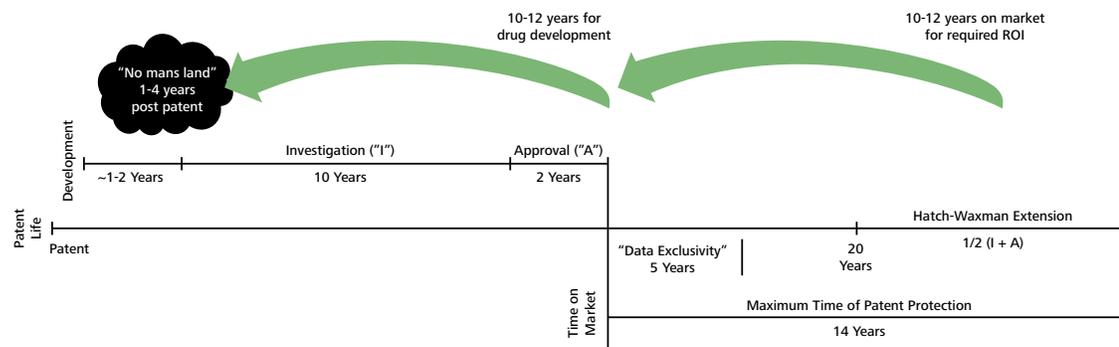
as one year of receiving a patent.⁷ We also speculate that this effect contributed to the increase in R&D spending by innovator pharma companies after Hatch-Waxman – once the Act had passed, there was a strong economic incentive to get any promising compound approaching no man’s land into development and onto market.⁸

In sum, then, Hatch-Waxman fundamentally altered the economic incentives of the pharma industry. It is worth noting that in doing so, the Act implicitly recognized the mature state of the pharma industry in 1983. In recognizing the relative ease for generic producers to demonstrate bioequivalency of their generic drugs, it relied upon

the maturity of chemically-based pharmaceutical science. And by providing economic incentives for new entrants, it relied on the mature structure of the existing big pharma industry cluster. Even in making those two assumptions, it produced some unintended consequences, both positive and negative.

It is not clear whether either of these assumptions holds true for today’s biotechnology industry cluster, and it is worth exploring the potential impact of similar potential unintended consequences in light of the differences between pharma then and biotech today.

Figure 6: “No Man’s Land”



⁷ If we assume a total patent life, including extensions, of roughly 25 years and work backwards, we subtract 10-12 years of time on market to earn required ROI, and 10-12 years for drug development, for a total of 20-24 years after the issue of a patent. This leaves between only one and four years to begin the development of a drug in order for it to have commercial viability. While many on-market drugs are able to subsequently extend their patent lives through additional indications, that cannot be guaranteed in advance – and what is at issue with “no man’s land” is the decisions made early in the life of a compound to fund its development. This effect could be even more pronounced for a biologic. (For the time required for an average biologic to earn sufficient returns, see H. Grabowski, G. Long, and R. Mortimer, “Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques,” Duke University Department of Economics Working Paper, No. 2008-10, Dec. 22 2008, and the previous articles that the authors cite therein.)

⁸ It is interesting to note that there was a large spike in drug approvals during 1995 and 1996 that has now fallen off. (See for example “New Drug Application Approvals and Receipts, Including New Molecular Entities, 1938 to Present,” U.S. Department of Health and Human Services, (2007). <http://www.fda.gov/oc/history/NDApprovals.html>.) This is often cited as evidence that R&D productivity is dropping in the pharmaceutical industry, but it might also be seen as the result of pharma companies seeking to avoid “no man’s land” just after Hatch-Waxman – the spike appears 11-12 years after the passage of the Act, which is just where it would be expected if companies expedited the development of compounds that had been ‘on hold’ in their pipelines.

The Biotechnology Industry Today

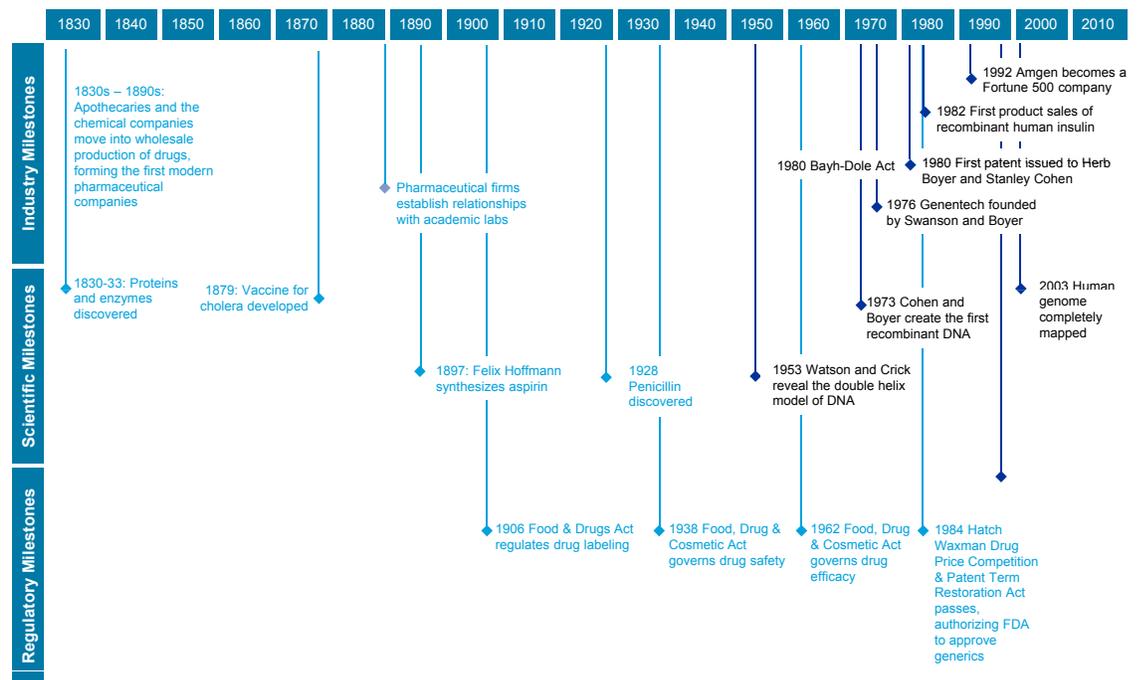
The biotech industry is comparatively young, and in contrast to pharmaceuticals in 1983, the overall business system that drives it is immature in two of its three key dimensions:

- The **basic science** of biotechnology is far from mature: While biotechnology has led to breakthroughs in therapy for life threatening diseases such as cancer, most scientists agree our knowledge of biology and genetics is now only scratching the surface of its potential promise.
- The **business model** is less mature: It is more fragmented and more heavily reliant on risk capital (in the form of venture capital) than was its 1983 pharma counterpart. In fact, despite some famous success stories, in the aggregate the biotech industry is barely profitable.

- The **regulatory regime** for the industry is arguably its most mature feature, and is nearly identical to that governing pre-Hatch-Waxman pharmaceuticals.

It is not surprising that biotechnology as an industry is less mature than its earlier chemical-science based pharma counterpart. While advanced organic chemistry is over a century old, biotechnology as a scientific discipline is young. As shown on the timeline below, DNA – the very building block used in the industry’s science – was first described by Crick and Watson in 1953. The first patent issued to a biotechnology start up is now only 29 years old.⁹ The first marketed product is only 27 years old. By each measure, this is a young industry based on a nascent science.

Figure 7: Biotechnology Industry Timeline



⁹ The 1980 patent issued to Herb Boyer and Stanley Cohen for gene cloning is widely regarded as the founding event of the biotechnology industry.

And yet it is a young science with enormous potential. Though the industry is young, it has already discovered major breakthroughs in the treatment of many types of cancer, cardiovascular disorders, diabetes, chronic kidney disease, and other debilitating or life-threatening diseases. The science of biotechnology often seems the stuff of science fiction: drugs are produced by splicing fragments of human DNA into cells, which themselves become the “factories” of proteins that are designed and engineered to attack disease at the sub-cellular or even molecular level.

The business model of biotech is more fragmented and more heavily reliant on risk capital than was its 1983 pharma counterpart.

The high specificity of the science increasingly means highly specific therapies based upon the genetic characteristics of individual patients – not just treating breast cancer, for example, but treating patients with breast cancer who have a certain genetic profile. Such a treatment relies on the science of genetics to develop both therapies and diagnostics for disease. As these two applications for biotechnology continue to complement each other and converge, the potential outcome is highly personalized treatment that has efficacy levels well beyond anything currently known in medicine.

But with this specificity comes enormous complexity. Many biotech products, for example, consist of a genetically engineered protein attached to a sugar. These molecules are as a rule vastly larger than the organic compounds produced by chemical pharmaceuticals. This difference in average molecular size and weight has two important implications:

1. Because these compounds are so large, in lay terms they tend to fold back on themselves, producing a wide range of different 3-dimensional configurations for molecules with the same chemical composition. These small differences in geometric configuration can produce large differences in the effects produced by the drugs in vivo – i.e., in patients. Often these different effects cannot be identified without clinical trials. ^{viii}
2. Similarly, and unlike chemical pharmaceuticals, owing to its complexity the composition of a biotech compound is generally only partially protected by a patent suite. In fact, many biotech patents are based upon the production process rather than the resulting molecule itself.

These differences between genetically engineered proteins and traditional small-molecule drugs have significant potential implications related to the impact of industry regulations, both on the safety and efficacy of drugs, and on the protection of innovators’ intellectual property.

Finally, because the science of biotechnology is earlier in its development, and because the complexity of the molecules is great, it takes longer and costs more to bring biotechnology drugs to market.¹⁰ This means that the risk associated with biotech drug development is, at least on the margin, higher than that associated with chemical drug development. This higher risk has contributed to the formation of a financial business system for the industry that looks quite different from that of its 1983 pharma counterpart.

The early-stage nature of the industry's science is mirrored by the early-stage nature of its business system. In the early 1980s, the pharma industry was dominated by 30 to 40 large vertically integrated companies who were self funding. Today, the biotech industry is made up of a handful of large publicly traded companies, and several hundred small companies. Most of these latter companies are not profitable – in fact, most do not yet have drugs on market earning revenues. On an aggregate basis, only in early 2009 did the industry cross into overall profitability.^{ix} The vast majority of these small companies are funded by venture capital, which has played and continues to play a seminal role in the industry.¹¹

¹⁰ Both the greater structural complexity and higher frequency of late stage failure compared to chemical drugs increases the development times for biologics compared to chemical drugs. For new chemical entities (NCEs), the average development time in terms of clinical phases and regulatory review is 90.3 months, whereas new biological entities (NBEs) have a significantly lengthier Phase I process and take an average of 97.7 months to develop. Source: DiMasi, J.A. & Grabowski, H.G. "The cost of biopharmaceutical R&D: is biotech different?" *Manag. Decis. Econ.* 28, 469-479 (2007).

¹¹ This is largely the (unintended) consequence of a piece of legislation introduced on the last day of the 1980 legislative session by Birch Bayh and Bob Dole which allowed universities to maintain or transfer ownership of intellectual property developed with U.S. government funding. Suddenly, ideas generated in the nation's universities had financial value – and could be brought to market profitably by the private sector. Prior to Bayh-Dole, academic work was adopted by the pharmaceutical industry through more informal mechanisms. (See Iain M. Cockburn, "The Changing Structure of the Pharmaceutical Industry," *Health Affairs* 23, Jan-Feb 2004, pp. 10-22). Without the Bayh-Dole Act, it is unlikely that the biotech industry could have taken off. It stands as an illustration of the potential power of Congress to shape industry outcomes in ways that are not completely foreseen at the time of legislative action.

Hurdle Rates and Home Runs

Like most public companies, chemical pharmaceutical manufacturers have historically invested in individual projects (new drugs) by evaluating the potential of each project to achieve a return in excess of the company's hurdle rate. If investment in a drug does not appear to be profitable for a company, the manufacturer will make a decision fairly early in the clinical development process not to proceed. This model is most conducive to investment in a set of potential therapies with fairly predictable markets and scientific mechanisms.

On the other hand, venture capital investments have historically operated by taking a portfolio approach where investors recognize not every project / company in a portfolio of investments will achieve a desired hurdle rate. Instead, the venture model is predicated on a small number of "home runs" in the portfolio which will raise the collective rate of return for the fund's investors to its expected level. This investment philosophy allows a greater degree of flexibility in new markets or new technologies, and has shown itself to be particularly compatible with the biotechnology industry.

Drug Producer

- Maximize shareholder value
- Long-term horizon: valuation based on current earnings and long-term growth of future earnings
- Criteria for individual investment:
 - Hurdle rate: projected return on investment greater than company's weighted average cost of capital (ROI > WACC)
 - Each project represents a large up-front investment in clinical development
 - Payback over several years only after a drug comes to market and earns significant revenues

Venture Capital

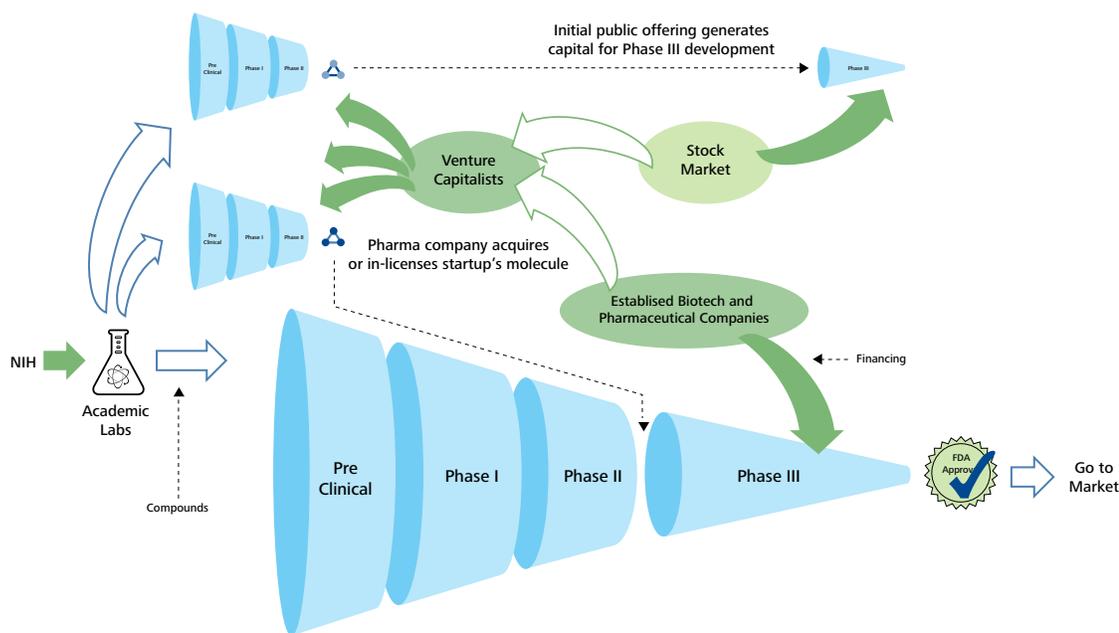
- Maximize internal rate of return (IRR)
- Each fund has fixed time period
- Criteria for individual investment:
 - Potential market size and protectable intellectual property
 - Possibility of large payback (aim for 5X to 10X return on capital)
 - Each project represents a relatively small investment
 - Exit within five to seven years by selling to established drug producer, or through IPO

Venture capital investment provides a bridge from the lab through proof of concept for many biotech inventions, and this means that early-stage molecules are funded with a different investment logic today than in 1983. Established biotechnology drug producers invest in their own portfolios with the same essential logic as established pharma companies do, using hurdle rate assessments to gate investment decisions. But venture capital investors behave very differently than the large industry players. Their window for return on investment is relatively short; the life of a typical venture fund is only five to seven years. The logic of their investment is not balanced development across their portfolio, but the expectation that only a few of their investments will ever provide them with a return. In order to compensate for that kind of risk across the portfolio, venture capitalists invest in projects only if they

have a chance to return five- to ten-times their original invested capital. So each individual investment entails a very high risk of failure, along with very high returns if it succeeds.

In order to achieve high returns when their investments succeed, VC relies on healthy returns in the industry overall. They have two ways to earn a return on their investments – industry and equity markets. The willingness of both to pay is driven by overall industry returns. If the industry is earning healthy returns, innovator companies are more inclined to purchase or in-license early-stage molecules, and stock market investors are more inclined to purchase the stock of a biotech startup through an initial public offering.¹²

Figure 8: Biotechnology System



¹² It is worth noting that the innovation coming out of biotechnology companies has become increasingly important not just to the biotech industry, but to the pharmaceutical industry writ large. As illustrated by recent significant industry developments, such as the acquisition of Wyeth by Pfizer, the announcement by Merck that it is investing heavily in biotechnology capabilities, and the effort by Roche to acquire complete ownership of Genentech, biotech is likely to become the main source of innovation for the development of *all* medicines.

The biotechnology business system of 2009 is much more complex than that of pharma in 1983:

- The main producers in the industry make investment decisions using criteria similar to those used by their 1983 counterparts, but their individual development projects cost more and take longer to come to fruition;
- Unlike the pharma industry of 1983, on aggregate the biotech industry is not self-funding. Many small companies are completely dependent upon venture capital or other sources of outside funding for their survival;
- Venture capital, in turn, is dependent upon healthy overall industry returns, which allow them to exit their investment positions within the time horizon of their funds, and to earn the rates of return expected by their investors.

Only in the context of this multi-layered business system can we understand the potential impact of the new legislation.

What the New Legislation *Might* Do

Given the significant differences between today's biotechnology industry and yesterday's pharmaceutical industry, what impact can we expect from the introduction of an abbreviated approval path for follow-on biologics? Obviously there is no certain way to forecast the future, as Hatch-Waxman itself illustrated. But it is worth revisiting the impact of the original Act within the context of the current biotechnology business system.

First, it is likely that follow-on biologics will introduce price competition and lower the overall cost within the specific treatment areas in which they are introduced. Competition generally lowers prices, but it is less clear how much of a price reduction the market can expect, due again to some fundamental differences between chemical-based drug manufacturing and biologic-based manufacturing. (See the box: "How Much Room for Price Reductions?")

How Much Room for Price Reductions?

There will be significant development, manufacturing, and marketing costs associated with introducing follow-on biologics, primarily due to the nature of their synthesis. Because follow-on biologics are more complex, the cost associated with their development is likely to be multiples of that required to develop small molecule generics. And though follow-on biologics may be therapeutically similar to the reference drug, establishing biosimilarity will also be costly, as each product will likely be judged on an individual product basis. Add to that the investment needed to construct a plant that will manufacture the drugs, which is estimated to be \$250-500M, and two things become clear: first, it is likely that only large, well capitalized companies will be able to produce FOBs; and second, on a drug-by-drug basis, it is likely that there will be less room for price reductions versus innovator's drugs than was true in chemical pharma after Hatch-Waxman. One study estimates that these effects will combine to lead to a price reduction of 10% – significant but not on the same order as the savings seen with chemical generics.^x

Second, it is possible that the introduction of a follow-on path could spur investment in the technologies required to make it work. This could include, for example, increased investment and therefore advances in genetic and molecular assay technology, required to assess biosimilarity. It could also spur investment in the process sciences required for faster and cheaper production of biologics. Both of these areas have enjoyed significant advances over the past few years, and the passage of FOB legislation is likely to continue if not augment this trend.

In these ways FOB legislation is likely to create effects similar to Hatch-Waxman, based upon the similarities between the two business systems. The remaining key question is: how will the *differences* between the systems play out? Let's begin with the issues related to the relatively early stage of the science of biotechnology.

The complexity of biotechnology will make it very difficult to establish standards for determining the biosimilarity of FOBs and innovator drugs. Yet the stakes involved are significant – set the bar too high, and each FOB will need to undergo costly clinical trials, working counter to one of the core purposes of the legislation; set it to low, and patients could be put at risk.¹³ We believe this is a debate better left to scientists and clinicians, but it is likely that the standards for establishing biosimilarity will need to be higher than those required for chemical pharma in Hatch-Waxman.¹⁴

However, there is a related and very pressing question with regard to biosimilarity that is central to the business system of the industry – and that is the question of patent protection for the intellectual property (IP) of innovator companies. Because the typical patent protection for biologic compounds is based either on a patent for part of the molecule (vs. all of its active ingredient), or on the process for producing it, many industry participants are concerned that innovators' patents will prove relatively easy to circumvent. The very size of these molecules opens the possibility that a very small change to the molecule that preserves the core design (i.e., keeping intact the portion of the drug that binds to a site in the body, while making minor changes to the parts of the molecule that are not clinically relevant) could circumvent the IP of the innovator company without technically infringing on its patent. Similarly, it is theoretically possible that an FOB producer could create a nearly identical molecule through a different process, and again be deemed technically to not be in violation of patents.¹⁵

It is clear that this is a contentious issue, but it is central to the eventual design of legislation. Much of the debate around the current legislation is centered on the length of the so-called data exclusivity period that will be granted to innovators, with different legislative proposals offering different durations. The relative strength of patents should be a critical part of this debate. As we saw in Figure 8, the time on market prior to the onset of competition is a critical factor in determining whether an innovator

¹³ A frequently cited example of this concern is Eprex, Johnson & Johnson's European label for erythropoietin, (which is marketed in the U.S. as Procrit by J&J and as Epogen by Amgen). Due to minor variations in the manufacturing process in this otherwise identical product destined for European and Canadian markets in the early 2000s, a significant number of patients receiving Eprex experienced red blood cell aplasia, a condition in which the body loses the ability to generate red blood cells, requiring a lifetime of blood transfusions. It took several years to conclusively identify the source of the difference, which was not easily detectable by chemical assays. It turned out to be organic compounds which leached from uncoated rubber stoppers in prefilled syringes. (See Boven K, Stryker S, Knight J, Thomas A, van Regenmortel M, Kemeny DM, Power D, Rossert J, Casadevall N.. "The increased incidence of pure red cell aplasia with an Eprex formulation in uncoated rubber stopper syringes," *Kidney Int.* 2005 Jun;67(6):2346-53.)

¹⁴ In our discussions with industry experts this has been a broadly held view, even among stakeholders with otherwise fundamentally different positions regarding the pending legislation.

¹⁵ For example, using mammalian ova rather than bacteria, or vice versa.

can recoup its investment in drug development, and it is clear that in practice it has been the patent protection of innovator drugs that has granted pharma innovators time on market to earn returns sufficient to fund new drugs. This means, with respect to fostering innovation, the debate around FOB legislation should focus first on whether biotech innovators will be able to recoup their investments, and secondarily on the mechanism for how to do that. Put another way: after 1984, pharma innovators earned sufficient returns to continue drug innovation, while generic producers enjoyed increasing volume growth and market penetration. This was accomplished because patents protected innovators' IP, and the data exclusivity period rarely came into effect.^{xi} For biotech innovators, if patent provisions are not sufficient to protect their IP, it may need to be the other way around. The key may be to avoid confusing the means with the ends.

What of the three effects that led to some of the unintended consequences of Hatch-Waxman? Will they create an impact under the new legislation, and if so, how? Let's turn first to the "make hay" effect – which provides an incentive for innovators to raise prices and make the most of sales and marketing efforts at launch, and to re-invest in R&D in order to speed time to market for drugs under development. We believe this effect is already in place in the biotechnology industry – that the precedent of Hatch-Waxman is well-recognized by biotech innovators. It is already standard industry practice to market aggressively at launch, and to move as quickly as possible to bring promising drugs to market.¹⁶ We envision little change in this regard following the potential passage of legislation, but it is a different story with the other two effects.

The logic of the blockbuster effect is almost inexorable. Since protected time on market is capped, the economics of drug development essentially forces innovators to focus

on drugs with the largest possible market potential – in this way, again, what was true for pharma innovators will be true for biotech innovators. But the risk here, which has not often been noted, is that this effect runs exactly counter to the direction and promise of the science of biotech, which has the potential to create more highly targeted and therefore more efficacious therapies. As therapies become increasingly targeted their commercial viability becomes increasingly uncertain, because while the size of patient populations gets smaller, the costs associated with drug development do not change. In order for

The blockbuster effect runs exactly counter to the direction and promise of the science of biotech.

personalized medicine to become a reality, drug innovators will need a regulatory environment that allows a return on their investments in research and development. It would be unfortunate if new regulations unintentionally circumvented the advances that now appear to be possible in medical science by putting in place economic incentives that rule out everything but blockbuster investments.

Finally, there is the risk of no man's land. The structure of the biotech industry is likely to make it much more sensitive to financial disruption than the pharma industry of 1984. This is because of the critical role played by venture capital in the early stages of both drug and company development. Take a hypothetical example: suppose for some reason the overall returns of the biotech industry were to drop 15%. (This could come about

¹⁶ In this way, established biotechnology companies behave in a fashion that is very similar to big pharma, and as the lines between these two industries continue to blur, we would expect their commercial practices to become even more closely aligned.

for any number of reasons, related or unrelated to the pending legislation. Patent protection could prove too fragile to provide sufficient periods for return; drug development costs could soar as the science seeks more elusive targets; or there could be an external shock, like today's economic crisis, for example.) In this circumstance, drug innovators will be forced to ratchet back their marginal investments in drug development. But venture capitalists will face an entirely different dilemma.

Recall that VC portfolios are based on high risk and high return. The typical fund expects around a third of its investments to be total losses, about a third to break even, and about a third to pay back at very high multiples of five to ten times the capital they invested. A simple mathematical illustration based on a 15% reduction in the investments that earn a return shows that in this circumstance, the IRR of the typical fund would fall from around 35% to around 25% – all while doing nothing to the underlying risk of the investments. This is probably not a sustainable situation for venture capital firms. In the short term, their commitments to their own investors would likely force them to continue with their current investment models as soon as the legislation is introduced. But with higher risks and lower returns, they would likely be forced to change their investing patterns; they would need to lower risk in order to balance against available returns.

There are only a handful of ways for venture capital firms to systematically reduce the risk in their portfolios. They could move development in their portfolio companies overseas in search of lower operating and capital expenditures. This would hardly be a good outcome for the US biotech industry, either in terms of its impact on the overall economy, or in terms of the concerns that could arise around drug safety. Indeed, a move overseas might simply

trade one type of risk for another. It is more likely though, that VC investment will shift to compounds in the later stages of development. Drugs that have been through proof of concept entail much less risk than drugs in pre-clinical or phase I. They also generally offer lower rates of return, but venture capital could counter this by taking larger stakes, or investing with more favorable terms, in their chosen companies. This potential shift to later stage investment is more than hypothetical – it is exactly what has been happening over the last few months of economic recession.¹⁷

In a circumstance such as this, a shift in VC investing would represent a systemic risk for the entire industry, because it would create the possibility of a very wide no man's land for early stage molecules. Venture capital has been the primary bridge for early stage biotech compounds since the industry's creation in the early 1980s.¹⁸ NIH funding is focused much earlier, typically on the academic lab. Larger innovator companies would not be in a position to fill the void, given the reduced returns that set the chain in motion. With lower total investment in pre-clinical and phase I development, we would likely never know which promising compounds had gone undeveloped, and which medical breakthroughs had not been brought to market, because once they entered no man's land, no one would have an incentive to move them forward.

In 1984 the pharmaceutical industry was a stable and mature business system, and Hatch-Waxman provided a catalyst that increased competition and fostered innovation. Today the biotech business system remains nascent and is relatively complex, both in its fundamental science, and in its financial underpinnings. In establishing a path to market for follow-on biologics, Congress may need to employ a different set of levers to achieve the same results.

¹⁷ This development has been consistently reported in our interviews in the preparation of this paper.

¹⁸ There are many examples of venture capital investment in early-stage biotechnology, but one of the classic stories involves IDEC Pharmaceuticals (now part of Biogen-IDEC), funded by the VC community with a lead candidate targeting non-Hodgkin's Lymphoma after being turned down by traditional pharmaceutical manufacturers as addressing too small a potential market. The result: Rituxan, the first new therapy for lymphoma in more than 20 years, and a \$2.5 billion product in the U.S. alone. The drug has transformed the standard of care for lymphoma and other cancers, extending the lives of thousands of patients around the world.

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Acknowledgements

The authors wish to thank the several executives and thought leaders in the biotechnology, pharmaceutical, and regulatory arenas who we interviewed during our preparation of this article. We agreed to keep the specific content of their interviews confidential, but we are no less in their debt. Additionally, we wish to acknowledge several colleagues within Deloitte who have supported the development of this paper:

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Mark Edwards, President, Deloitte Recap LLP

R. Terry Hisey, Vice Chairman and U.S. Life Sciences Leader, Deloitte LLP

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