Data Exclusivity for New Biological Entities

Henry Grabowski
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Abstract

Congress is current considering legislation that would create a regulatory pathway for follow-on biologics. One critical issue in this regard is the issue of data exclusivity for innovators. This is an important form of intellectual property that complements patent protection. Data exclusivity is the period of time before a follow-on competitor can enter the market with an abbreviated filing that relies in whole or in party on the innovator's data on safety and efficacy. From the standpoint of economic theory, industries where the R&D process is costly and risky need longer exclusivity periods to realize innovation benefits, compared to those industries where innovation is easier and less costly. Similarly, when the output of innovation has important external benefits to society – as in the case of new medicine and new indications for existing medicines – this also supports a longer exclusivity period.

An analysis of these characteristics for new biological entities provides support for a substantial data exclusivity period. The R&D process for new biopharmaceuticals is long, costly, and risky. The market sales distribution for those molecules that do reach the market is highly skewed, with long payoff periods to profitability. Recent new biological entities also have resulted in several leading therapeutic advances, with important attendant benefits for human welfare. New biological entities have accounted for a disproportionate share of novel and "best in class" therapies in areas such as oncology and rheumatoid arthritis.

This paper also considers what time period might be appropriate to ensure adequate data exclusivity protection for innovators. This is based on a specific analysis of breakeven lifetimes for new biologicals. In this regard, a simulation analysis is undertaken of a model portfolio of biotech products with sales that are representative of the actual historical distribution. The breakeven lifetimes were found to be between 12.9 and 16.2 years at alternative discount rates of 11.5% and 12.5% respectively. This breakeven economic analysis, while preliminary in nature, also provides support for legislative proposals that include a substantial data exclusivity period for new biologicals.

I. Introduction

Congress is currently considering legislation that would create an abbreviated regulatory pathway for follow-on biologics, which are sometimes referred to as biosimilars. Most biologicals are regulated through the Public Health Service Act, which does not presently contain a mechanism for an abbreviated application like that which exists for chemical drugs under the Hatch-Waxman Act[1]. In considering such legislation, Congress must balance the objectives of innovation incentives and price competition, as was the case when it created a regulatory pathway for generic chemical drugs.

One critical decision for legislators involves the issue of a data exclusivity period for innovators. Data exclusivity is an important form of intellectual property (IP) for innovators. It is the period of time after U.S. Food and Drug Administration (FDA) approval before a follow-on competitor can enter based on an abbreviated filing that relies in whole or part on the innovator's data on safety and efficacy. Without a data exclusivity period, there would be little incentive to invest in developing and marketing new product candidates with few remaining years of patent protection or with uncertain forms of protection. In addition, newly approved products with substantial commercial sales would be exposed immediately to legal risks associated with patent challenges and early generic entry.

Data exclusivity and patents are complementary forms of IP for new pharmaceuticals and biologics. The importance of patents to R&D innovation for new pharmaceutical therapies has been demonstrated in several economic studies. (Mansfield, 1986; Scherer, 1996) Patents are a reward for innovation based on the criteria of novelty, utility, and non-obviousness. Innovators generally apply for patents on compounds in the pre-clinical or early clinical phase of the development process. In the period after a patent is granted, but before a product can be marketed, innovators

[1] For a discussion of the scope of the Hatch-Waxman and the Public Health Service Acts, see Mossinghoff (1999) and Grabowski, Cockburn and Long (2006).

must generally perform a long, risky, and costly investment process to demonstrate a product's safety and efficacy. Data exclusivity recognizes the substantial investment that innovators have to make in the data which demonstrates safety and efficacy to gain FDA regulatory approval. Ideally, data exclusivity would delay abbreviated filings and patent challenges until innovators have had an opportunity to earn a positive return on the new therapeutic candidates which successfully complete the lengthy and costly R&D process.

The Hatch-Waxman Act provided for a 5-year data exclusivity period for new chemical entitles (NCEs) before an abbreviated new drug application could be submitted, and 4 years with a patent challenge. By contrast, the European Union (EU) recently harmonized across member states, enacting a ten-year data exclusivity period for both new chemical entities and new biological entities (NBEs) before generic copies or biosimilars can be approved.[2] In addition, the EU provides for an additional year of data exclusivity for entities with significant new indications that are approved within the first 8 years after approval. (Verheugen, 2004; Towse, 2004)

Current U.S. legislative proposals contain widely different provisions regarding data exclusivity. At one extreme, a bill introduced by Representative Henry Waxman[3] would not provide for any data exclusivity for new biological entities. On the other hand, the bill recently introduced by Representatives Jay Inslee, Gene Green, and Tammy Baldwin[4] provides for fourteen years of data exclusivity.

[2] Generic firms can submit abbreviated applications to the regulatory authorities eight years after approval of the original molecule, but the earliest these applications can become effective is when the ten-year exclusivity period expires.

[3] Representative Waxman introduced H.R. 1038, The Access to Life-Saving Medicine Act in the House and Senators Clinton and Schumer introduced an identical companion bill in the Senate, S. 623.

[4] H.R. 1956, Patient Protection and Innovative Biologic Medicines Act.

This paper presents some of the key factors that influence the optimal length of the data exclusivity period from an economic perspective. It then applies this analysis to current policy issues involving data exclusivity for new biologicals. The next section provides an economic framework to assess the relevant factors in determining an optimal exclusivity period. The following two sections discuss the risks, development times, and costs of new biological entities (Section III) and the importance of biological innovation to social welfare (Section IV). Section V discusses the funding process in this entrepreneurial industry and the importance of IP protection for various private and public equity partnerships. Section VI considers prior research on net present value (NPV) breakeven lifetimes for new drugs. It also provides a preliminary simulation analysis of this issue for new biological entities. The paper concludes with some important policy lessons from the Hatch-Waxman Act and suggestions for future research.

II. Perspectives on Optimal Exclusivity Times From Economic Analysis

Beginning with the pioneering work of William Nordhaus (1969), economists have developed conceptual models to determine the socially optimal exclusivity time. Exclusivity can originate from patents and from complementary forms of IP protection such as data exclusivity. The basic tradeoff is between incentives for new product development versus more intensive price competition after exclusivity expires. In particular, longer exclusivity times encourage increased development of NBEs and NCEs as well as additional research on new indications for established products. But longer periods can also postpone the onset of generic competition. When the additional benefits from expected development of more new medicines are just equal to the additional costs of postponing the onset of generic competition, the exclusivity time is considered optimal from an economic perspective.

While this theoretical modeling has not yielded a specific value for the optimal exclusivity time for biopharmaceuticals (or any other industry), it does provide a framework to assess which industry characteristics are relevant to current policymakers' decisions in this regard. In particular, industries where the R&D process is costly and risky need longer exclusivity periods to realize innovation benefits, compared to those industries where innovation is easier and less costly. Similarly, when the output of innovation has important external benefits to society – as in the case of new medicines and new indications for existing medicines – this also supports a longer exclusivity period. (Scherer and Ross, 1990)

In the next two sections I review what is known about the basic characteristics of innovative activities for new biologicals. These characteristics provide support for a substantial data exclusivity period. I then turn to an analysis of breakeven times for new chemical drugs and biologics. Breakeven occurs economically when the present value of net revenues equals the present value of R&D costs (or equivalently, where a firm's risk-adjusted return on its R&D investment is equal to its cost of capital). A preliminary simulation analysis indicates that the breakeven times for new biologics are lengthy, generally well in excess of 10 years. This also provides support for a significant data exclusivity period.

III. Characteristics of Innovative Activity for New Biopharmaceuticals

A. Sources of Risk for New Biological Drug Candidates

1. Technical Risks

The R&D process for new biological entities is fraught with many different kinds of risk. It is common for the development of a new biological entity to originate in a start-up company financed through venture capital (VC) financing. At this early stage of development, there is a high

degree of scientific risk associated with proof-of-concept. Pre-clinical data are used to gain insights into expected efficacy, toxicity, and pharmacological effects once a lead compound is identified. Even when animal studies indicate promise, they imperfectly predict human response concerning safety and efficacy. This is one important reason for high attrition in clinical trials.[5]

As a biological candidate moves through the clinical trial process, there are additional risks of failure due to difficulties involving formulation, manufacturing scale up, or inconvenient dosing regimes. Since biological drugs are complex molecules produced from cultures of living cells, manufacturing and engineering process issues at the R&D stage can pose greater challenges than for chemically synthesized compounds. Process specifications and manufacturing know-how are critical elements for new biologics. Validation of a biological manufacturing process involves many complex activities and even minor changes in this process can affect a product's quality and properties that necessitate additional testing. [6]

2. Regulatory Risks

Another risk is regulatory: the risk that after spending hundreds of millions of dollars in biologics development and investing in manufacturing facilities, a firm may not receive FDA approval to market a product. The biopharmaceutical industry offers scores of examples of products that showed promise but failed to gain FDA approval. One highly publicized set of cases involved a trio of biopharmaceutical drugs to treat sepsis. Centocor, Xoma Group, and Synergen all developed drugs into Phase III testing to treat this important medical problem that affects 500,000 patients

[5] For a general description of the discovery and development pathway for new drugs and biologics, see U.S. FDA (1999).

[6] As Dr. Janet Woodcock (2007), Chief Medical Officer of the FDA, emphasizes, "Even well-characterized, highly purified recombinant proteins may exhibit minor degrees of structural variability from lot to lot resulting from variants in the manufacturing process. The quality and nature of natural source products can vary depending on the condition of the source material, processes used to extract and purify the product and other factors."

annually, and from which one-fifth of all those afflicted die. In each case, the drug failed to garner FDA approval. Two of these companies had already built expensive manufacturing facilities in anticipation of market approval, while the third had built up a large sales force that had to be dismantled after the FDA rejected the project. (Robins-Roth 2000, p. 186)

A related risk involves regulatory delays and the fact that FDA requirements and attitudes evolve and change over time. The last decade has been characterized by increased regulatory turbulence, spurred by legislative concerns and a few high profile product withdrawals. Products are also subject to liability risks and labeling changes as they are utilized by larger populations after approval. Relatively rare risks, not observable in clinical trials, can emerge from post-marketing surveillance adverse drug reports. This can result in black box warnings or, in rare cases, a product can be recalled from the market.

3. Competition and Reimbursement

Competition for new biological entities is dynamic, and typically there are several firms simultaneously developing biologics and new classes of biologics to treat the same condition. Dr. Joseph DiMasi (2001) has examined the basis for research terminations for new drug candidates that first entered clinical trials between the early 1980s and 1990s. His study found that efficacy is the most frequent reason for project termination. Economics is the next most cited reason, with comparable numbers of terminations as efficacy for the most recent time period analyzed. The study also found that economic considerations were the most frequent determinants underlying decisions to terminate late-stage clinical research. Economic considerations involve an evaluation of the costs versus returns from further investment activity. This economic calculus is affected by many determinants including manufacturing and engineering issues, competitors' products and R&D activities, reimbursement policies and formularies, and other market related factors.

DiMasi's analysis of research terminations is consistent with the increasing importance from a competitive standpoint of introducing a molecule that can demonstrate some therapeutic advantage *vís a vís* existing products. This is the key to obtaining favorable formulary placement and reimbursements from payors, whether public payors or managed care organizations. In addition, later entrants in a therapeutic class are typically introduced at a discount to established therapies. This can also affect R&D termination decisions, given that the relevant market size may commercially support only a certain number of competitors.

4. Economic Analysis of Success Rates

Several economic studies confirm that the R&D process for new biologicals is subject to large risks from scientific, regulatory, and economic factors. A recent analysis of the probability of success of 522 biologic candidates at various stages in the development process by DiMasi and Grabowski (2007) found that the overall probability of success in clinical development was 30% (i.e., the success rate of candidates that make it as far as human trials). While biologicals had higher overall success rates than drugs, they have had lower success rates in the most expensive Phase III trials, indicating that biologics that fail in clinical trials often do so only after high development costs have been incurred.

A recent study by Goldman-Sachs reported in Parexel's statistical sourcebook (2004) also found that Phase III biological success rates from 1995 through 2003 are lower than those of pharmaceuticals, and have exhibited a significant downward trend over time. This downward trend is consistent with the fact that the complexity of biological products under development has increased, a phenomenon also reflected in longer development times.

B. Development Times

The development process for a new biological is lengthy and typically spans more than a decade. The discovery and pre-clinical process is subject to considerable uncertainty and variability, especially when a new class of compounds or new target receptor site is being investigated. This is illustrated by the development process and timeline for Avastin, the first of a new class of drugs to treat colorectal cancer. It took 15 years from the initial discovery of this compound in 1989 to regulatory approval in 2004. (See Exhibit 1)

Exhibit 1: Case Study on the Development of Avastin

Almost two decades ago, in 1989, Dr. Napoleone Ferrara, a scientist working for Genentech, made a discovery that would ultimately lead to the development of the first anti-angiogenesis treatment for cancer. Angiogenesis refers to the formation of new blood vessels, and anti-angiogenesis is a targeted therapy to prevent tumors from creating new blood vessels in order to stop tumor growth. The critical finding by Dr. Ferrara was the existence of a specific angiogenic growth factor known as vascular endothelial growth factor (VEGF), which is secreted by some cancer cells. VEGF was found to attach to a protein and then signal the cell's control centers to begin growth and formation of new blood vessels. Four years later, in 1993, Dr. Ferrara and his team published a key study demonstrating that an anti-VEGF antibody can suppress angiogenesis and tumor growth in preclinical models. However, it was not until three years later, in 1996, that Genentech scientists were able to humanize an anti-VEGF antibody. As a result, Genentech submitted an investigational new drug application for Avastin to the FDA in 1997. The first clinical trial, a Phase I trial, for Avastin began that same year and was followed by a Phase II trial in 1998. In 2000, a Phase III trial began to evaluate the use of Avastin to treat first-line metastatic colorectal cancer. This trial alone took three years. Finally, in February 2004, 15 years after Dr. Ferrara discovered the existence of the angiogenic growth factor VEGF, FDA approved Avastin as the first angiogenesis treatment for cancer.

Source: M. Flanagan (2006)

Clinical development for new biologics proceeds through well defined stages, and it takes many years to gather the necessary data to gain FDA approval. Figure 1 shows the total clinical development time to FDA approval for new chemical and biological entities from the DiMasi and Grabowski 2007 study. The starting point is the initiation of Phase I trials by the company performing the clinical investigations, rather than the filing of the investigational new drug application, which is often much earlier in the timeline.

We found that the average development time for a new biological was 97.7 months, compared to 90.3 months for small molecule or chemical drugs. As shown in Figure 1, a significant part of the difference is associated with a lengthier phase I process for biological entities. After a new pharmaceutical or biological is approved, there is frequently substantial additional R&D activity involving investigations for new indications or formulations. In addition, the FDA may require post-approval Phase IV studies as a condition of approval.

Figure 2 shows that mean development times for new biological entities have increased steadily since the early 1980s. New biological entities are defined here as new protein therapeutics, including new recombinant proteins, monoclonal antibodies, and non-recombinant proteins. This is based on data collected by the Tufts University's Center for the Study of Drug Development from several time cohorts of FDA approvals. At the beginning of the 1980s, the majority of new biological products receiving marketing approval were proteins with well understood functions. As this initial group was exhausted, the industry has turned to more complicated, less well-understood targets, and development times have steadily increased.

C. Development Costs

DiMasi and I have also analyzed R&D costs for new biological introductions. We collected data to estimate the expected costs at each phase of the cycle. These data were then risk adjusted for the expected probability of success at each stage of the development lifecycle. Using this approach, we found that total out-of-pocket costs for the preclinical and clinical periods exceed $500 million. We also take account of time costs by capitalizing out of pocket costs to the date of marketing approval. We find that the capitalized R&D costs for a representative new biological entity range from $1.24 billion to $1.33 billion when the real cost of capital is 11.5% to 12.5%.[7] As discussed below, the average cost of capital for new biological entities in early stage companies will be much larger than this 11.5% - 12.5% range that is estimated for a small set of established biopharmaceutical firms. (Grossman, 2003) (Myers and Shyum-Sunder, 1996)[8]

We found that R&D costs for new biologics are comparable in magnitude to our earlier estimates involving chemical drugs (DiMasi et al., 2003) when the latter estimates are time-adjusted to take account of differences in the time periods analyzed. However the underlying cost components differed significantly. As noted, biologics have higher probabilities of clinical success

[7] A real cost of capital adjusts for the effects of inflation. Assuming a historical rate of inflation of 3 to 3.5%, the corresponding nominal cost of capital would be approximately 15%. Our cost of capital estimate is based on a capital asset pricing model analysis for a small set of biotech firms with a history of profitability based on multiple marketed products. These companies also had an extensive portfolio of new biological product candidates over the period 1990-2003. (DiMasi and Grabowski, 2007)

[8] Grossman (2003) estimates that biotechnology firms without a marketed product but with one or more drug candidates in phase II or III trials have an average *nominal* cost of capital of 27.4%. He also estimates a *nominal* cost of capital for biotechnology firms with at least one drug approved have of 18.l7%. Myers and Shyum-Sunder (1996) estimated a 14% real cost of capital for a group of publicly traded biotech firms for an earlier period. As noted, our 11.5% *real* cost of capital is based on a smaller group of biotech firms that have multiple products and a history of positive operating profits over the past decade.

overall, but lower probability of success in the more expensive Phase III trials. Biologics also have higher discovery and pre-clinical expenditures and longer mean clinical development times.

Chemistry, manufacturing and control costs related to development and incurred during clinical development are included in our cost estimates for the clinical phase. We found the development of biologics involve higher development costs associated with process engineering and manufacturing than is true for chemical drugs. This reflects the need to resolve novel manufacturing challenges at the R&D stage. As discussed, biologics generally involve more complex molecules that are produced from large scale cultures of living mammalian, microbial, or yeast cells. By contrast, manufacturing process issues in R&D typically are more straightforward for drugs based on chemical synthesis.

It is important to note that the costs of constructing a new manufacturing facility or retro-fitting an existing plant for large scale commercial production are not included in the R&D cost estimate. The cost of a new multi-product manufacturing plant is substantial in the case of biologics. In particular, it has been estimated that a new manufacturing plant can take three to five years to build, and cost $250 million or more. (Molowa, 2001) Even retrofitting an existing plant can cost between $50 - $100 million.

D. Market Structure and Skewed Sales Distribution

The sales of new biological entities that do make it to the market exhibit tremendous variability. As is the case for chemical drugs, the sales distribution for new biological entities is highly skewed, with relatively few compounds accounting for a disproportionate share of sales and profits. An analysis of 30 new biologics introduced from 1982 to 1994 indicated that the top one-fifth ranked entities accounted for roughly 70% of the total 2002 sales. (Grabowski, 2003)

Biologicals that rank in the top few deciles of the sales distribution are frequently "best in class" or "first in class" therapies. In addition to direct competition from new molecules in the same class, they also would be the primary targets of generic biologic firms.

Given this skewed distribution, the prospects of high returns from a few blockbuster compounds is a key driver of the R&D decision process and is essential to sustaining investments for the full range of drug candidates from private and public equity sources. Venture capitalists in particular recognize that a majority of their high risk early stage investments will fail, but strong returns on a few successful projects are often enough to justify investments in high risk endeavors that entail many losses. Similarly, biotech and pharma firms pursue a portfolio approach and pursue partnership arrangements in an attempt to diversify risks from such highly variable and skewed distribution, as well as to fill in gaps in capabilities such as manufacturing and marketing.

E. Competition Within a Therapeutic Class

Even when a pioneering new drug theory is introduced that offers a novel approach to treating a particular illness, it is typically subject to rapid competition from new entities with the same general mode of action. Recent research by DiMasi and Paquette (2004) has shown that the number of first-in-class drugs that are sheltered from competition has declined precipitously since the 1970s, reflecting a decline in the barriers to entry for new molecules launched into established therapeutic classes. The authors identify both supply side factors, such as technological advances in basic biomedical research, and demand side factors, such as the increased price sensitivity caused by the spread of managed care, as explanations for the decline in the time that first-movers enjoy before competitive entry.

Booth and Zenmel (2003), in an analysis of 1991-2000 introductions also find that the "best in class" compound in most therapeutic areas is usually not the first mover, but a subsequently introduced product that improves the efficacy or reduces the side effects of existing compounds. Significant medical progress, therefore, occurs both from the introduction of novel new classes and the entry of competitive products into those classes. Berndt, Cockburn and Grepin (2006) also find that new indications and formulations play an important role in expanding therapeutic choices and improving patient welfare. This phenomenon is discussed further in the next section on innovation for new biological therapies.

F. The Risk of Early Generic Firm Entry

Some of the proposed legislation (for example, H.R. 1038), would allow generic firms to challenge patents of new biological entities from the date of market approval, and if successful, enter with an abbreviated application.[9] The resulting uncertainty and litigation expenses would add to the scientific, regulatory, and economic risks already present in the R&D process. This would adversely affect R&D investment in the biotech industry where most firms have no profitable products and therefore must rely on outside sources for investment funding. This would be a particularly undesirable outcome for this industry, given the large potential social benefits from new therapies for unmet medical needs.

IV. Importance of Biological Innovation

As discussed in Section I, when innovation has important benefits for overall social welfare, this provides support for a longer exclusivity period. There is accumulating empirical evidence that

[9] For an analysis of competition in the generic market, see Grabowski, Ridley and Schulman (2007)

new medicines and therapies have played an important role in increased longevity, enhanced quality of life, and improved labor force productivity. (Lichtenberg, 2001) (Calfee, 2007) Furthermore, recent studies have attributed up to half of all welfare gains worldwide during the 20th century to the introductions of new medical knowledge and technologies, including drugs. (Nordhaus, 2003) (Becker et al, 2005)

The biotech industry is a relatively new source of medical innovation. It had its first new drug product approvals only in the early 1980s. However, it has become a major source of novel drug introductions and overall industry growth in recent years. In a recent paper, Richard Wang and I (2006) examined the quantity and quality of worldwide new drug introductions between 1982 and 2003. We found that biotech drugs are the fastest growing segment of new therapeutics. They accounted for 4% of new drug introductions in the 1982 to 1992 period, but this has grown to 16% in the 1993 to 2003 period. Furthermore, U.S. firms are the dominant source of biotech drugs, originating more than half of all worldwide biopharmaceutical introductions from 1982 to 2003.

Although not the only measure considered in our analysis, one of the key indicators of drug quality or novelty was first-in-class introductions. New biological entities had a significantly higher likelihood of being a first-in-class or novel introduction compared to new drug introductions. New biologicals have been particularly focused on oncology and immunologic areas in recent years. Given the increased knowledge of the molecular bases for cancer, the oncology class has been characterized in recent years by introduction of breakthrough monoclonal antibodies and other targeted biological agents. These include rituximab (Rituxan), trastuzumab (Herceptin), and bevacuzimab (Avastin).

Several new biological entities have had rapid diffusion and are among the leading drug therapies in their class from a therapeutic perspective. Furthermore, these products are being

investigated for a number of new indications at the present time. Substantial improvements in survival, morbidity, and patients' quality of life have been documented in diseases previously resistant to successful treatment, including cancers such as aggressive HER-2 positive breast cancer (Smith et al., 2007) and gastrointestinal stromal tumor, or GIST (ASCOG, 2004), as well as in preventing the disease progression, functional decline, joint destruction and disability associated with rheumatoid arthritis. (Weaver, 2004)

The prospects of future advances are further enhanced by a strong pipeline of more than 400 biotech drugs under development in a variety of therapeutic areas (PhRMA 2006). These include novel approaches to conditions with large disease burdens including 200 biotech drugs for cancer alone. Early stage R&D of a novel character is fraught, of course, with high risks, but also can yield both high potential rewards to investors as well as large therapeutic benefits to patients. It is important that such high risk endeavors have sufficient economic prospects for returns to undertake the long, costly, and risky investment process.

In a recent paper, Calfee and DuPre (2006) pointed out two important features of competition involving new biological entities. First, after proof of principle has been established for a new biological, multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (e.g., a particular receptor or dysfunctional enzyme). In the case of Herceptin for example, there are more than 10 targeted drugs currently in Phase II or III for breast cancer targeting the HER-2 receptor, other members of the HER family, or one of the other proteins downstream from HER-2. The INF inhibitors for rheumatoid arthritis and the angiogenesis inhibiting drugs for cancer are also experiencing similar forms of competition involving the same targeted pathways, but with different modes of action.

A second important feature of competition for new biological entities involves new indications associated with the same or related pathways. For example, drugs that were initially approved for rheumatoid arthritis are being investigated for a number of anti-inflammatory conditions that may be related to the same dysfunctional pathway. Two of the leading rheumatoid arthritis drugs have already received subsequent approval for psoriasis (Enbrel) and Crohn's disease (Remicade). At the current time, Avastin (see exhibit) has more than 20 clinical trials in progress for different types of cancer and different stages of cancer. (Flanagan, 2006)

The development of new indications for established biological therapies would be particularly vulnerable to early patent challenges by generic firms seeking to enter based on an abbreviated pathway. This is because obtaining approval for a new indication post-approval can take several years and involve large scale patient trials and significant costs. The uncertainty surrounding early patent challenges may tilt the risk-return against otherwise economically viable investment programs for new indications. In this case, patients would be deprived of health benefits from new indications that in many cases are equivalent to or surpass those of the original approved indications. (Berndt, Cockburn and Grepten, 2006; Calfee and DuPre, 2006) While it might be possible for a firm in this situation to get a use patent for the new indication, these patents are difficult to impossible to enforce against a generic entrant that manages to get an approved label for a more limited set of indications.

V. Financing of Biotech R&D Projects.

In the case of biopharmaceuticals, early stage development is frequently done in private firms supported by VC funds. Venture capital firms specialize in high risk-high return ventures and utilize a variety of controls to assess and monitor their investments. These include extensive due diligence

and multi-stage financing with milestone targets. Risk capital is supplied in exchange for equity positions at high implicit costs of capital. Returns are realized by the VC firms when a firm in their portfolio has an IPO or is acquired by a larger entity. The returns distribution for venture firms is highly skewed. While many of their projects are terminated at a loss, a few highly successful projects can yield a significant return to the overall portfolio to justify investments in these risky enterprises. (Scherer and Harhoff, 2000)

Intellectual property is a key dimension of the decision to invest in life science companies that have little other tangible or intangible assets and a lengthy period of clinical trials prior to marketing approval. Success in the biopharmaceutical area is ultimately predicated on the fact that when firms develop novel and useful therapies for diseases with unmet needs, they will be able to earn significant profits over a product life that justifies their lengthy and costly R&D investments and that offsets many projects that fail after large investment. If these profits are endangered by uncertainty about the prospect of generic entry through patent challenges early in the product life cycle, it will lead to a shift in VC portfolios away from biopharmaceutical firms. Venture capital firms are agnostic about which industries they invest in, and can shift to information technology companies or even a new fast food chain if there is heightened uncertainty about returns from biopharmaceutical firms.

Typically, even after a biopharmaceutical firm goes public, it will need to raise additional funds to finance clinical trial activity. This generally occurs through secondary financing in the public market and/or partnerships with larger firms. In this latter regard, a rich market exchange for new technologies has emerged in the life sciences area over the past two decades. A prototypical development stage agreement would involve payments for reaching particular milestones in the exchange for rights by the licensee to develop and/or market the new products covered under the

agreement. (Danzon et al., 2005; Simpson, 2000; Cockburn, 2004) The extent of integration varies, ranging from joint development agreements to transfers from licensor to licensees, to marketing options in exchange for R&D funding and future royalties.

Given the characteristics of the R&D process, some important implications follow for the financing of R&D investment in an innovative entrepreneurial industry like biopharmaceuticals. First, in the early stages of development, it is crucial to have the support of financial institutions like VC firms that can take a long-run view and a portfolio approach to such risky investments. Second, if the relatively few large successes experience increased uncertainty due to patent challenges and the potential for early generic entry, higher risk-adjusted rates of return will be demanded by VC firms, yielding fewer leads that meet this standard. Early stage R&D will be the most adversely affected segment. Such a prospect is a particularly unfavorable outcome for firms and industries whose products contribute to important long term advancements in public health.

New biological entities that are developed internally by large, established biotech or pharmaceutical firms also must confront similar considerations in their portfolio decisions. Product candidates with significant uncertainty from expected legal challenges soon after marketing launch would have diminished economic prospects relative to other investment-stage candidates.

VI. Breakeven Lifetimes for New Drugs and Biologicals

In this section, I consider what time period might be appropriate to ensure adequate data exclusivity protection for innovators based on analysis of breakeven lifetimes for new drugs and biologicals.

A. New Drug Introductions

It is instructive for the current analysis to examine the time required by a new therapeutic agent to achieve breakeven status from an economic perspective – that is, to cover its R&D costs and earn a risk-adjusted return on capital. To do so, one needs information on R&D costs and other cash outlays and inflows over the full product life cycle. To date, this issue has been investigated in a comprehensive way for new molecular entities introduced in the 1980s and 1990s. The sample of drugs investigated has consisted primarily of new chemical entities. A few of the initial biological entities that were introduced in the 1980s and early 1990s were included in the analysis.

The breakeven lifetime is illustrated in Figure 3 for the cohort of 1980 to 1984 new chemical entities. (Grabowski and Vernon, 2000) The analysis combines data from analysis of R&D costs and cash flows from this cohort of 1980-1984 introductions. The breakeven lifetime for this cohort is just over 16 years. In particular, this is where the present value of cumulative after-tax cash flows just intersects the present value of after-tax R&D investment (all measured in 1990's dollars), signifying the fact that the firm has recouped its investment plus a return equal to the industry's average cost of capital for that period.

A similar analysis for the 1990-1994 cohort of new chemical entities gives a breakeven lifetime of 15 years. (Grabowski, Vernon, and DiMasi, 2002) As noted, the distribution of NCEs is highly skewed. A few blockbuster new drug introductions earn several times the mean R&D costs and can achieve a break-even point much faster. But it must be kept in mind that only 30% of the sample of NCEs has positive net present values (NPVs). Hence, the blockbuster products with large commercial sales compensate for the large number of products that never break even from an NPV standpoint.

With the high degree of risk and uncertainty that exists for R&D in new therapeutics, particularly biologics, it is difficult to predict in advance which or whether any products in a

particular portfolio will be big winners. Many products start with this objective but end up as incremental advances or fall by the wayside. This is why VC firms and biopharmaceutical firms take a portfolio approach. In effect, the few highly successful new biologic entities play a key role in covering the large fixed costs of R&D and enable the entire portfolio to achieve a positive risk adjusted rate of return.

B. New Biological Entities

Only a few biological entities have been included in prior analyses of R&D returns, given the long time frames of several decades that these studies require. This reflects the fact that the biotech industry is still a relatively young industry. However, for current purposes, it is instructive to undertake a preliminary analysis which simulates the breakeven lifetimes for new biological entities launched in the present time frame with different projected sales revenues.

As discussed, the recent DiMasi and Grabowski study of R&D costs found that the typical biotech entity introduced in recent years had a capitalized cost of $1.24 billion to $1.33 billion, measured in 2005 dollars, and utilizing a discount rate of 11.5%, to 12.5%. These cost estimates account for both the R&D costs of success and failures, since all these costs must be recouped from the sales of approved products. However, the analysis involved only pre-approval R&D costs, and did not include the substantial post-approval costs associated with new formulations and indications or include the often substantial pre-approval investment in constructing manufacturing facilities.

In the breakeven lifetime analysis, I utilize the annual R&D costs for a new biological molecule from the DiMasi-Grabowski (2007) analysis for the pre-approval period. This is combined

with a plausible estimate of post-approval R&D costs for new indications and formulations.[10] Using this R&D investment information, I consider the breakeven lifetimes for a portfolio of new biotech products with peak sales of different values. In particular, to construct this model portfolio, I utilize values on peak sales that approximate the distribution on sales revenues for 30 mature biotechnology products analyzed in my studies published in the *Georgetown Public Policy Review* (2003) and by the Dallas Federal Bank Reserve (2003).

In Figure 4, the peak revenue values are shown for a four product "stylized" portfolio. This portfolio reflects the mean values observed for the top four ranked quintiles of the sales distribution of established biotech drugs. In particular, biotech drugs in highest ranked 20% cohort had a mean sales of approximately $2 billion. The next three quintiles had means respectively of $500 million, $250 million, and $100 million. The bottom quintile, accounting for the lowest ranked 20% of the products in the sales distribution, is excluded because many of these small selling biologics were approved under the Orphan Drug Act and may not have representative R&D cost profiles. However, excluding all the biologics in the lowest tail of the distribution makes the current analysis conservative and biases breakeven lifetimes downward.

We can focus on a stylized portfolio of four products without loss of generality since peak sales are based on historical values for the top four quintiles of the sales distribution. To construct a representative sales life cycle for these four marketed products, I utilize as a template the annual

[10] It is important to include post-approval R&D costs in the breakeven analysis, given that sales values in the analysis include revenues from new indications and formulations as well as the original indication. To take account of post-launch R&D expenditures, I assume they will be 35% of the out-of-pocket expenditures for pre-approval R&D costs. This yields total cash outlays of $195.6 million spread evenly over the first eight years after launch ($24.5 million per year). These assumptions are consistent with our analysis of new drug introductions (Grabowski, Vernon, and DiMasi, 2002). It is reasonable to assume that expenditures on new indications and formulations for biotech drugs are proportionately as large as for new drug introductions, given R&D pipeline data and the analysis of Calfee (2007).

sales profile realized by the average new drug introduction in the 1990s. (Grabowski, Vernon and DiMasi, 2002) Based on this profile, sales are observed to peak in year 9-10 and then decline at a 3.5% annual rate due to product obsolescence and therapeutic class competition.

Figure 5 shows the corresponding life cycle profile for the mean biotech drug in our stylized portfolio. The mean drug in this portfolio has peak sales of $712.5 million. This is the average peak sales for the four products in Figure 4. In particular, we observe that sales increase at a rapid rate during the early years of the life cycle, reach a peak in years 9-10, and then slowly decline due to product obsolescence. Generic competition of course would cause a much steeper decline in sales than that shown in Figure5. However, this is not included in the life cycle profiles because our basic objective is to understand how many years are typically required for an innovation to breakeven before generic entry occurs.

Given this highly skewed distribution shown in Figure 4, the mean is heavily influenced by the top decile product. In particular, the mean peak sales value for the four product portfolio of $712 million is larger than three of the four products in the portfolio. This underscores the importance of a portfolio approach to product development to obtain an occasional significant commercial success. Most VC firms that specialize in early stage companies will invest in a large number of firms and investment projects. Most of these candidates will fail, but there is a chance to obtain one or more highly successful products that will drive positive overall returns. Similarly, established biotech companies will also carry a number of pre-clinical and clinical projects at different points in the life cycle with a similar strategy in mind.

It is also instructive to model the development process underlying this stylized portfolio, utilizing industry averages for development times and successes. The four product model portfolio shown in Figures 4 and 5 would first require four to five years of pre-clinical R&D to generate

several lead candidates. The clinical process would then span an average of about eight years, and require approximately 3.3 product candidates in clinical trials for every product introduction (i.e., a 30% success ratio). However, one can still expect substantial year-to-year variability around these averages even for firms with large diversified portfolios, given the skewed distribution of outputs. (Scherer and Harhoff, 2000)

With respect to capital expenditure requirements, I assume in the present analysis that firms can utilize an established plant for the commercial production of the biological products in this stylized portfolio.[11] In particular, rather than undertake a net cash flow analysis associated with the production of a new manufacturing facility, I assume capital costs are captured by depreciation charges that are subsumed in the contribution margin. This approach is conservative, since some new plant construction or retrofitting of an existing plant is normally required in association with significant new product introductions. A correct financial cash flow analysis would yield lower returns and higher breakeven lifetimes, given that cash flow outlays for new plant facilities precede in time any recovery of cash flows from net income and depreciation charges. [12]

For the current analysis I also assume risk discount rates in the range of 11.5% to 12.5%. This is reflective of the equity cost of capital for larger publicly listed biotech firms with multiple products on the market in recent periods. However, as discussed above, smaller publicly traded companies and non-listed private biotech firms would generally have much higher cost of capital, given the lack of historical track record of profitable marketable products and pipelines that are concentrated in higher and riskier early stage R&D.

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[11] Based on prior work, I assume there will be $25 million in plant validation costs per product introduction ($12.5 million per year), since these costs are not captured in our R&D cost estimates.

[12] Alternatively, this approach is akin to assuming production is outsourced with a contract manufacturing charge equal to book depreciation charges. This also would be a conservative assumption since contractors would have to obtain a margin above depreciation costs to be a viable business.

In this analysis I use a steady state contribution margin of 50%.[13] This value is obtained after a two year transition period, during which extra launch costs related to market introduction are concentrated.[14] This 50% contribution margin is in line with the contribution margins realized by the eight largest biotech firms with multiple products on the market. (Centers for Medicare and Medicaid Services, 2003) However, it must be kept in mind that there are few biotech companies that are profitable, and the universe of biotech firms is populated with development-stage companies whose principal assets are their human capital and intellectual property. They would be expected to realize higher costs to launch a new product than a firm with an established line of approved products.

The results of our model portfolio analysis are shown in Table 1. Breakeven lifetime for the portfolio occurs at 12.9 years in the case of an 11.5% real cost of capital. When a 12.5% real cost of capital is utilized, the breakeven lifetime is increased to 16.2 years. This illustrates the strong sensitivity of breakeven lifetimes to the discount rate. This sensitivity reflects the lengthy R&D investment periods associated with pharmaceutical and biopharmaceutical investments. Figure 6 shows the cash flow patterns for the mean product in this portfolio analysis from the initiation of R&D to payback. When the net present values of inflow just equals outflows, one is at the breakeven point where a firm recovers its R&D investment and earns a risk-adjusted rate of return. This breakeven time is 12.9 years for a discount role of 11.5%, and 16.2 years for a 12.5% discount rate.

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[13] Contribution margins are defined as sales minus the costs of good sold (including depreciation charges for plant and equipment), marketing, promotion, and administrative costs in the numerator. This is expressed as a percentage of sales in the denominator.

[14] I assume that total expenses exceed sales by 30% in year 1, and the contribution margin in year 2 is equal to 20%. In addition, in the two years prior to market introduction, I assume there are launch related expenditures equal to 10% and 20% of the first year's sales. These values are based on information collected in conjunction with new drug introductions. (Grabowski, Vernon, and DiMasi, 2002)

This illustrates the importance of a data exclusivity period to the incentives for innovation in the pharmaceutical industry. Even diversified portfolios that achieve substantial commercial outcomes, including a blockbuster product, require lengthy payback periods. If the patents of the most successful products are subject to legal risk and uncertainty early in their product life cycle from follow-on generics, the likelihood of positive returns on investments becomes problematic. Consequently, VCs and other investors would be less willing to bear this risk along with the other significant risks associated with the biotechnology R&D process, and would substitute other venture projects with better benefit to risk profiles.

VII. Lessons from Hatch-Waxman

Since biologicals are regulated under the Public Health Service Act, they currently do not receive any data exclusivity. When a regulatory pathway was created for new chemical entities, a 5-year data exclusivity period was put into the Hatch-Waxman Act to provide incentives for innovators faced with little or no remaining patent exclusivity time at launch. The NCE data exclusivity period under Hatch-Waxman affords branded products a floor of effective exclusivity of five to seven and one-half years, depending on how long courts take to resolve patent suits.[15] Even the upper bound of seven and one-half years is an insufficient time for new drugs to recoup the upfront R&D costs and earn a positive return on this investment. (Grabowski, 2004)

The Hatch-Waxman Act also includes a provision, a so-called "paragraph IV certification," that allows generic firms to challenge the patents on an approved product on the basis of invalidity or non-infringement, and another provision to encourage such challenges. In particular, the reward to being the first to challenge the patents is a 180 day exclusivity period. Even if the odds of

[15] The Hatch-Waxman Act has a stay on generic entry of up to 30 months while court cases are in progress, and longer than 30 months if the patent is challenged after 4 years.

winning are low, the reward for successfully challenging a patent is large. There have been an increasing number of patent challenges undertaken by generic firms early in the innovator's product life cycle. Grabowski and Kyle (2007) find that this is contributing to a shortening in the average time that innovators have to recoup their R&D investment.

Multiple law suits involving infringement have become the rule for the commercially important drugs early in the brand product's life cycle. As a percentage of ANDA filings, they have increased from 2% during the period 1984-89, to 12% from 1990-97 to 20% from 1998-2000. (Berndt, 2007) Most of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an ANDA filing with a paragraph IV certification. (Grabowski, 2004) As of June 2002, the FTC reported that generic firms had won the vast majority of suits, but most of the cases with outcomes at that time involved late-stage patent challenges. (FTC, 2002) While all patent litigations are costly, the negative consequences for R&D incentives of the increasingly prevalent early stage patent challenges are especially troublesome because they occur many years prior to the breakeven lifetimes for new drug entities.

A patent can be challenged on grounds such as of obviousness, anticipation by the prior art, or double patenting. A court may determine, for example that a drug invention was "obvious," allowing the generic challenger to enter if the data exclusivity period has expired. The issue of patent type is also relevant from a policy standpoint. Process, method of use, and formulation patents have less breadth than product compound patents and may be more vulnerable to challenge, although each situation must be evaluated on a case by case basis. It is worth noting that many important biotech products rely on process and formulation patents rather than compound products, and this could intensify the scope of litigation challenges.

From a strategic perspective, generic firms can be viewed as "prospecting" in patent suits. They are investing money in filing and litigation fees with a portfolio of patent challenges for the rights to obtain a very large payoff from the exclusivity period if they win a few of these suits. However, this wave of lawsuits crowds the courts and creates uncertainty around the commercial viability of the innovator's product. Furthermore, this uncertainty adversely affects research-based pharmaceutical firms. It can cause firms to abandon R&D projects on future drug candidates with uncertain patent prospects. Early patent challenges also can have a chilling effect on the development of new indications and formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval.

VIII. Conclusions and Further Research Topics

Over the coming decades, biopharmaceutical innovation can provide major improvements with respect to quality and length of life over an expanding set of disease areas. As Dr. Woodcock (2007) emphasizes, "It is important to ensure that facilitating the development of follow-on products through abbreviated pathways does not discourage innovation and the development of new biological products."

Biopharmaceuticals possess demand and supply side characteristics that support a substantial data exclusivity period. On the supply side, early stage research is concentrated in start-up companies that are typically financed by venture capital firms and partnerships with larger entities. The R&D process for new biopharmaceuticals is long, costly, and risky. Most candidate molecules never reach the market. The market sales distribution for those molecules that do reach the market is highly skewed, with long payoff periods to profitability. With respect to medical demand and

patient care, recent new biological entities have resulted in several leading therapeutic advances, with important attendant benefits for human welfare. New biological entities have accounted for a disproportionate share of "first in class" and "best in class" therapies in areas with high unmet needs such as oncology and rheumatoid arthritis.

One approach that policymakers could follow that is based on basic economic principles would be to align data exclusivity periods with the time necessary for the representative new biologic entity to earn a positive risk adjusted return on the large upfront R&D investment. This paper presents a preliminary analysis of breakeven times for new biologicals to gain insights into this issue. In this regard, a simulation analysis was undertaken of a model portfolio of biotech products with sales that are representative of the actual historical distribution. The breakeven lifetimes were found to be between 12.9 and 16.2 years at alternative discount rates of 11.5% and 12.5% respectively.

Proposed legislation without any provisions for a data exclusivity period or only very nominal periods of exclusivity would have adverse effects for these biological innovation activities. Under these legislative scenarios, there would likely be an explosion in patent challenges shortly after a new product is introduced. The resulting uncertainty and litigation costs would increase risks and diminish R&D investment funding sources for this sector, especially for early-stage R&D in companies without any profitable products (the majority of biotech firms). As a consequence, the future introduction of important new medicines could be delayed significantly or deterred altogether. This would not be a desirable outcome for policymakers who must balance the terms of competition between innovators and imitators. It is important to avoid these unintended consequences for an innovative industry with strong entrepreneurial roots and important expected benefits for human health and welfare.

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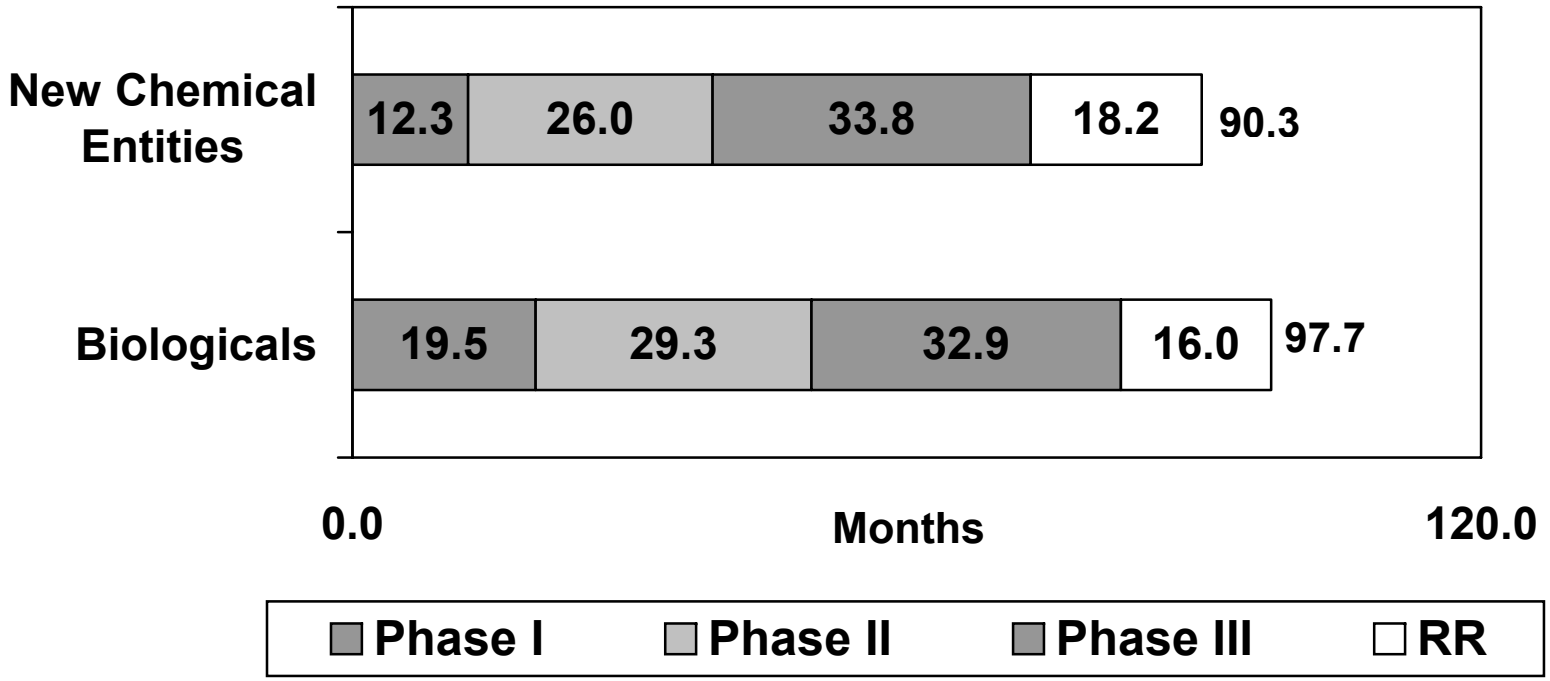
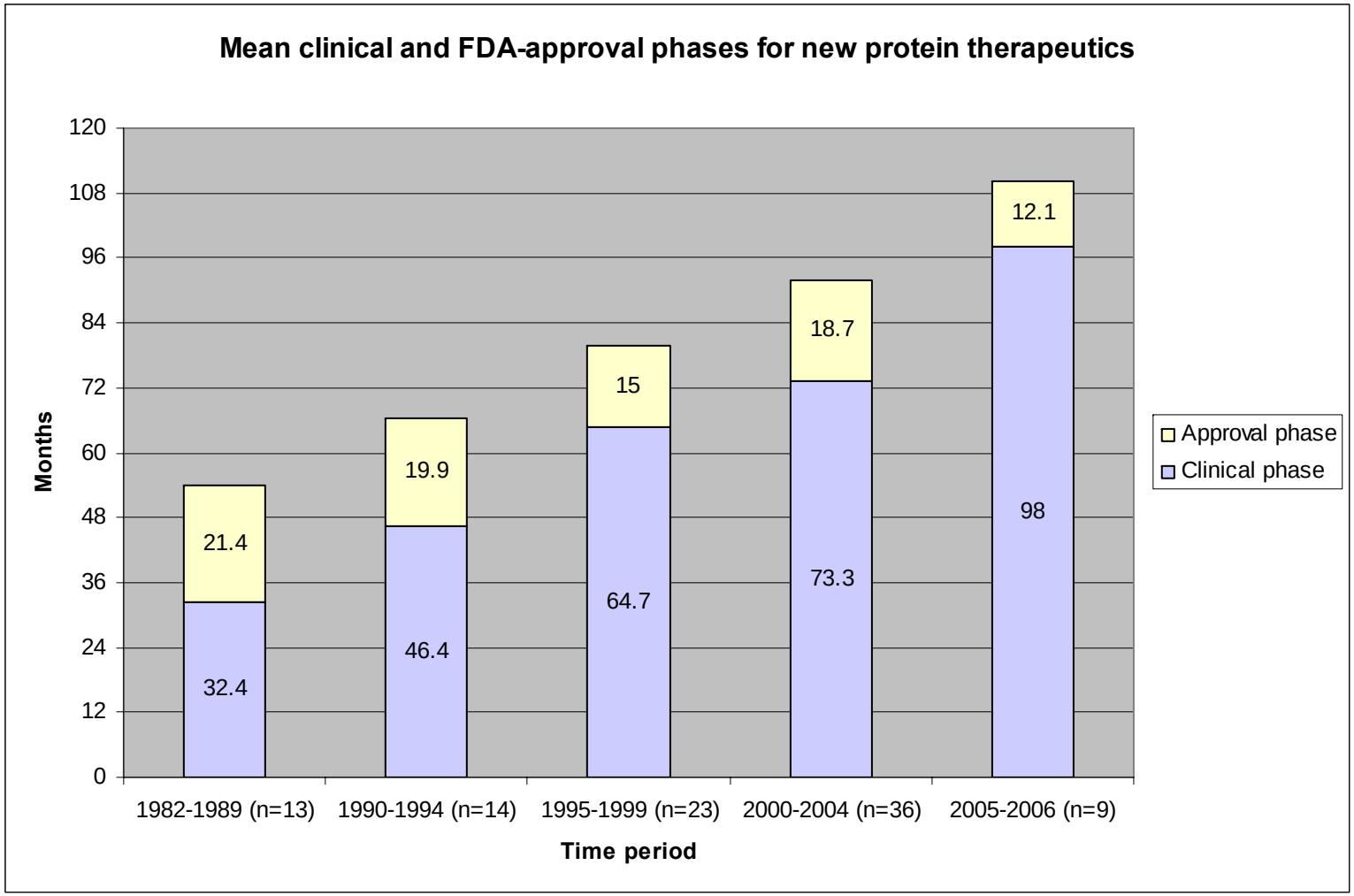
Figure 1: Clinical development and approval times for chemical drugs and biologicals



Note: Development times include only clinical phases and regulatory review (RR) periods. Pre-clinical times are not included.

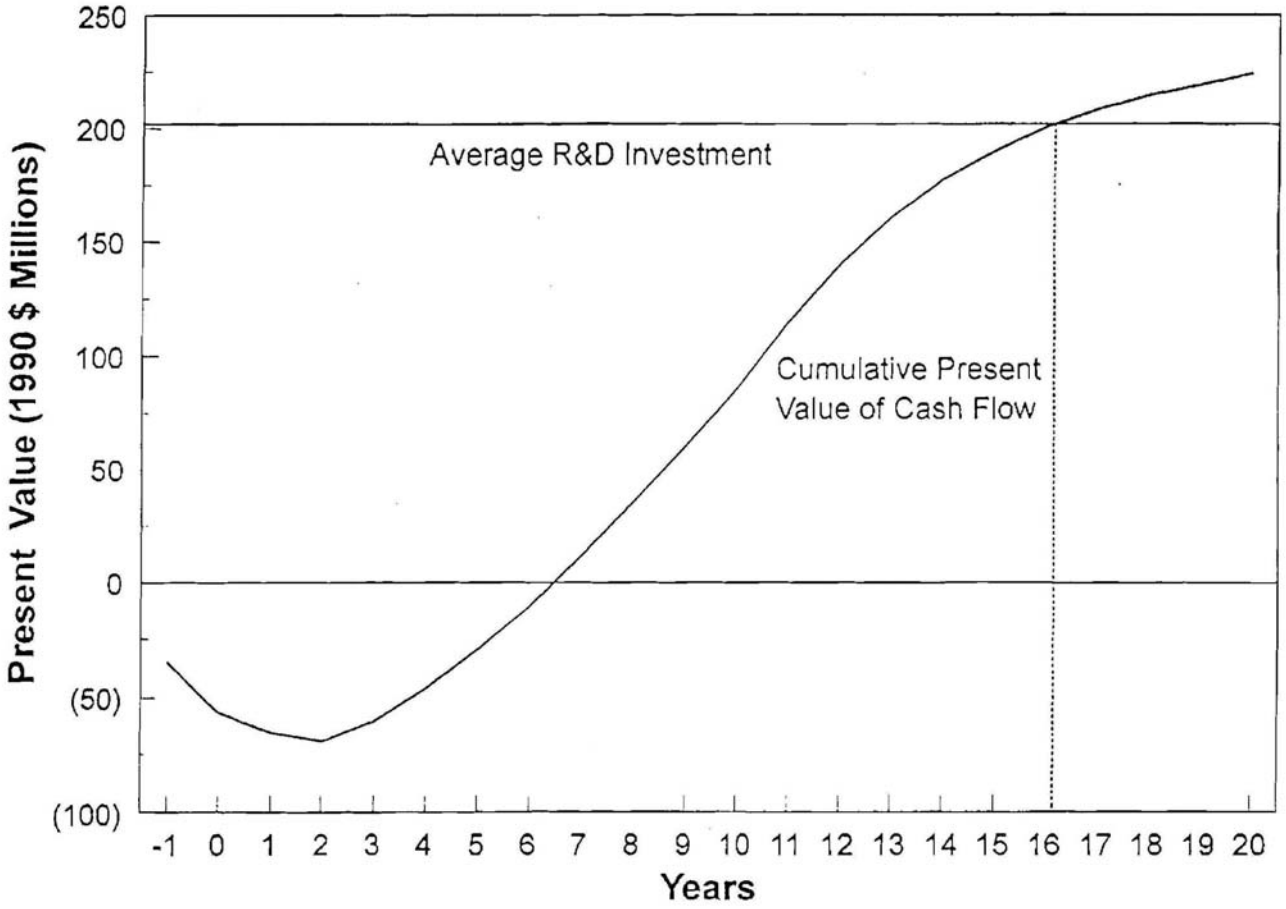
Source: DiMasi and Grabowski (2007)

Figure 2: Development times for new protein therapeutics



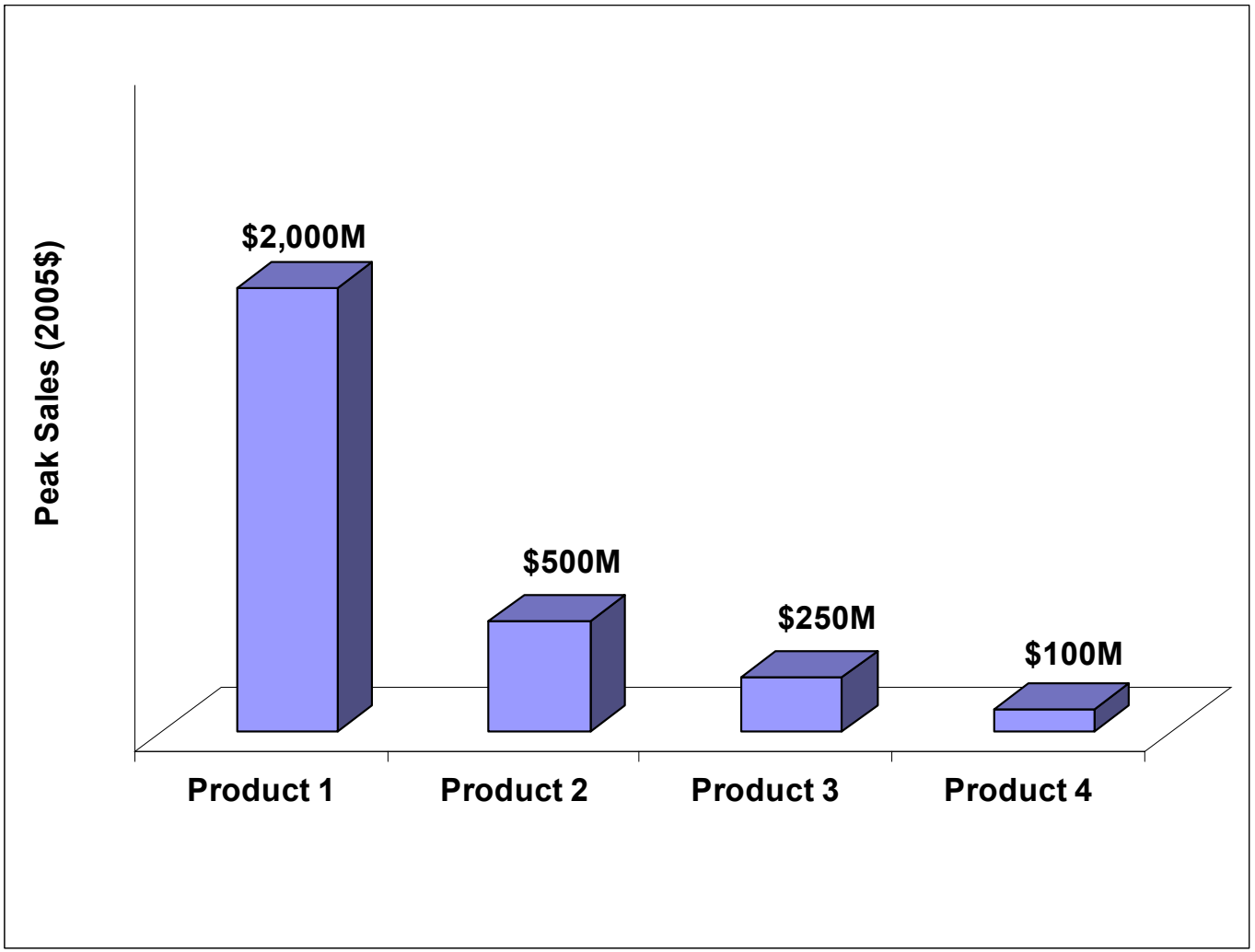
Source: Tufts Center for the Study of Drug Development (2007). Private correspondence

Figure 3: Cumulative present value of cash flow versus R&D investment for the mean new chemical drug introduced between 1980 and 1984



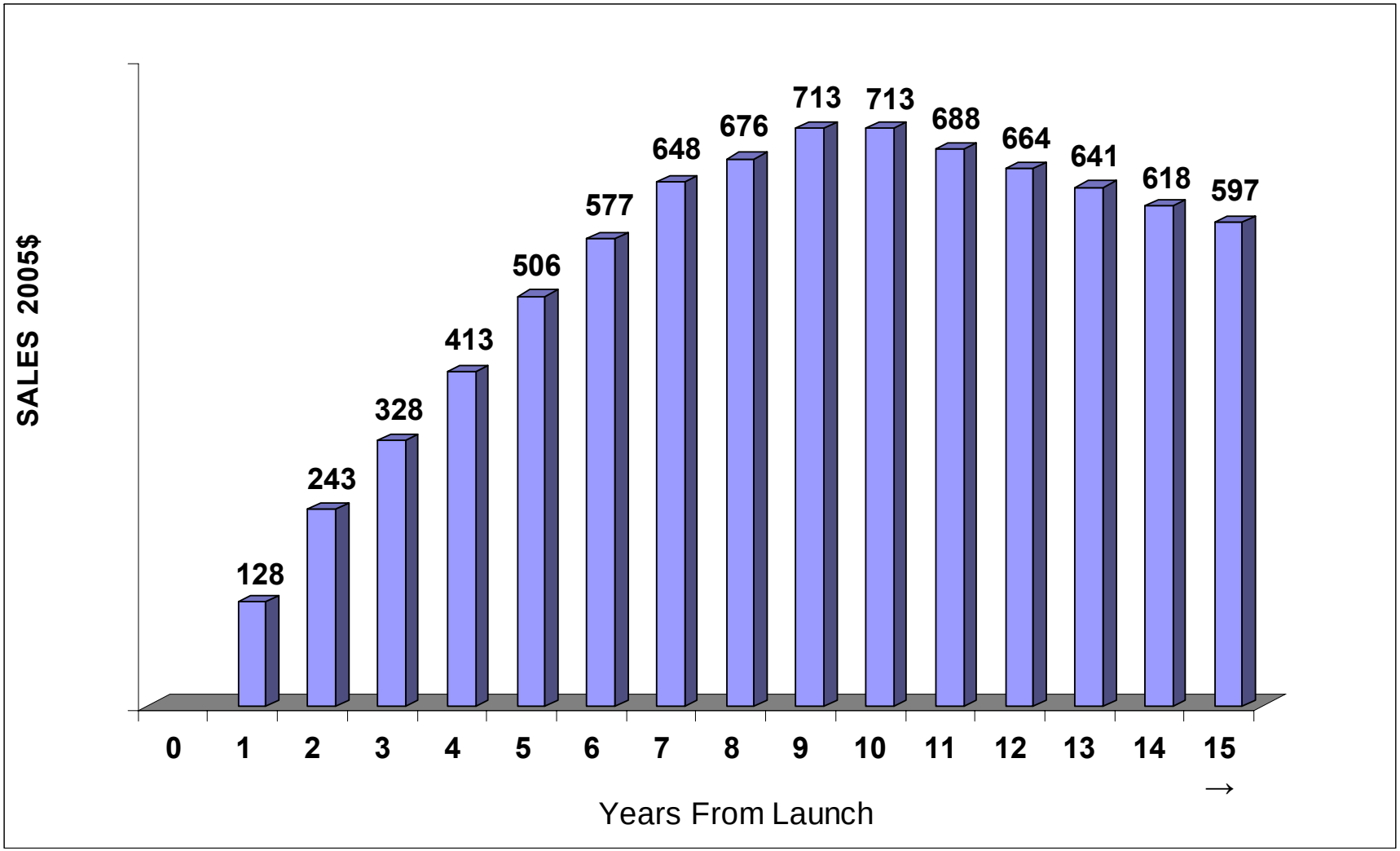
Source: Grabowski and Vernon (2000)

Figure 4: Model portfolio based on sales distribution for established biological products



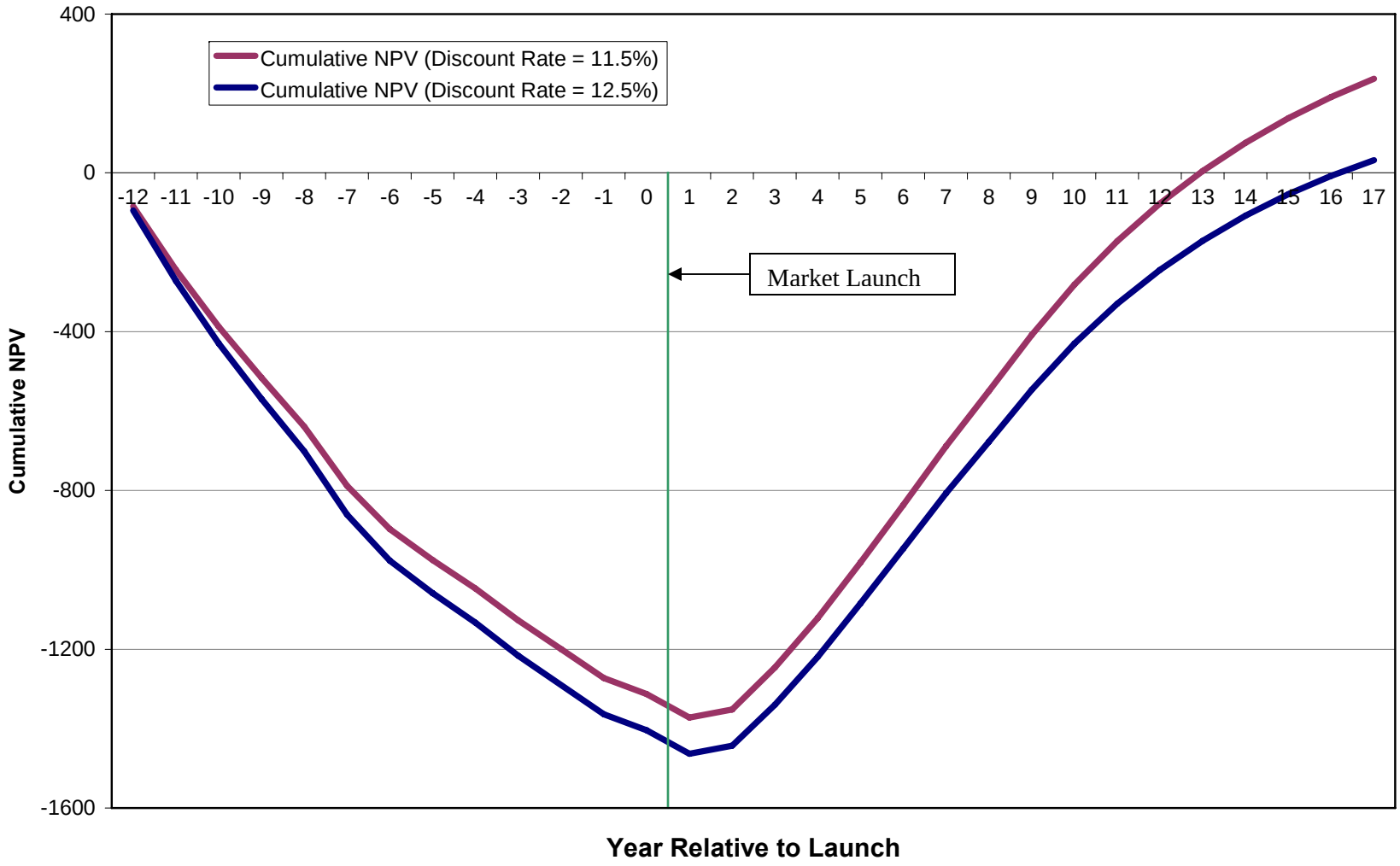
Source: Grabowski (2003) and author's analysis

Figure 5: Life Cycle Profile for Mean Product in Model Biologics Portfolio



Source: Author's analysis

Figure 6: Estimated Cumulative Net Present Value for Average Biological Drug



Source: Author's analysis

Table 1: Breakeven Lifetimes for Biotech Products With Different Peak Sales Values

Discount Rate	Breakeven Lifetime
11.5%	12.9 years
12.5%	16.2 years

Key Assumptions:

1. Pre-approval R&D costs are based on DiMasi and Grabowski (2007)
2. Post-approval out-of-pocket costs equal to 35% of pre-approval costs
3. Post-approval R&D costs are spread evenly over the first eight years after launch
4. Sales are based on historical distribution of successful biotech market introductions
5. Pre-tax contribution margin of 50%
6. All sales measured in constant 2005$

Source: Author's calculations; DiMasi and Grabowski 2007

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