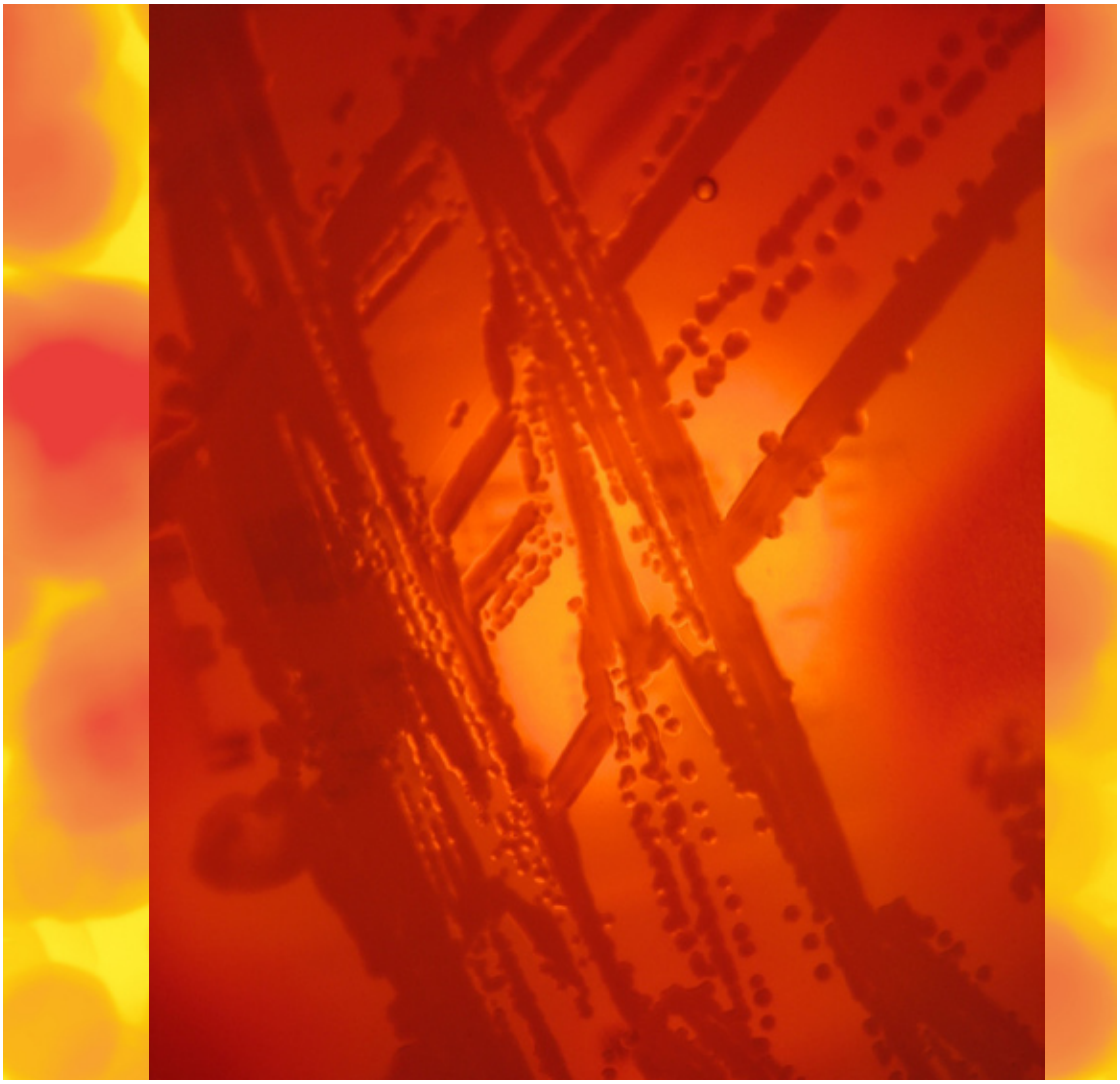

PROPER DURATION OF DATA EXCLUSIVITY FOR GENERIC BIOLOGICS: A CRITIQUE

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ABSTRACT

The future of improved quality and outcomes in healthcare will be dependent on the continued development and availability of biological drugs. Already, $75 billion in biologics are being sold around the world, and critical therapies from Actimmune to Zevalin are helping patients suffering from illnesses ranging from cancer to arthritis. Biologics, often the most expensive of health care treatment options, have now reached the point that many of them will be coming off patent and market participants are close to developing competitive alternatives, often known as biogenerics, follow-on biologics (FOBs) or biosimilars. In anticipation of these alternatives, a legislative process is under way in Congress to establish an abbreviated pathway for the FDA to grant approval to these biogenerics.

This paper discusses the importance of an appropriate duration for data exclusivity and critiques the recent work by Duke economist Henry Grabowski on this subject (Grabowski 2008). Grabowski estimates the number of years required for an average portfolio of biologic drug investments to recoup all development and fixed production costs and to also reward the investors their expected (double-digit) rate of return. This period of time economists refer to—tongue in cheek, perhaps—as a "break-even" point for the investment.

Grabowski (2008) estimates "break-even" to be between 12.9 and 16.2 years for a portfolio of biologics, and we examine this result and its implication for data exclusivity. First, using an alternative set of assumptions to the Grabowski model that we consider to be more plausible, we find that the "break-even" point drops to slightly less than nine years. Second, the "break-even" point is not the period for sufficient data exclusivity in this industry. Data exclusivity less than the "break-even" point is valid under any assumption in the Grabowski model as long as some economic profits continue to be earned by the innovator drug post-exclusivity; this is reasonable, given expectations for the effect of biogeneric competition on prices. Given our preferred model specifications, we show by example that seven years of data exclusivity would be sufficient in maintaining strong incentives to innovate while fostering a competitive marketplace.

INTRODUCTION

Biological drugs offer some of the most important innovations and benefits for disease treatment, yet are some of the most expensive medical treatments currently offered. While the rapidly rising cost of healthcare will pose a significant fiscal policy challenge in coming years, the therapeutic potential of biologics offers new promise to many of the most debilitating diseases. This dichotomy—critical potential benefit from this class of therapies in comparison to the high cost paid by consumers and, in the case of Medicare and Medicaid, taxpayers—elevates the importance of properly balancing a fundamental public policy tradeoff: policies to foster innovation (new products) against policies to foster competition (lower prices).

At present, the U.S. Congress is considering legislation to create an abbreviated pathway for the FDA to approve biogeneric[1] therapies. Such a pathway already exists for chemical drugs, created in the legislation known as Hatch-Waxman but biologics were generally excluded.[2] The differences in the manufacturing process for biologic drugs relative to chemical drugs, differences in the R&D expense and product cost, and the potential for both new therapies post-approval and second-generation innovations ("evergreening") are raising new questions about how to achieve the proper balance between innovation and competition.

One important policy for Congress to establish will be the number of years of data exclusivity awarded to the innovator drug. Data exclusivity rules control the amount of time after an approved drug enters the market that a biogeneric drug, relying on the innovator's data on drug safety and efficacy, must wait before entering the market. In the case of chemical drugs, that period is generally five years.

A recent article by Duke University economist Henry Grabowski (Grabowski 2008) offers the first attempt to quantify this innovation/competition tradeoff. Grabowski presents an analysis of a portfolio of biologic drugs based on clinical success probabilities, historical R&D costs, average historical sales data and an expected (i.e., "demanded") rate of return to investors to estimate the average number of years before all the development costs are recouped and a normal profit is earned (where normal profits are equated to the cost of capital for the biopharmaceutical industry). This analysis is referred to in accounting and economics as "break-even analysis" even though it includes profits in the calculation. Grabowski estimates that, given historical costs in the biologic drug industry, the time period in order to "break even" is between 12.9 years and 16.2 years. The variance is due to different assumptions about the cost of capital.

This paper provides an analysis of the Grabowski model and its assumptions. It demonstrates that with more plausible assumptions regarding the cost of capital and the contribution margin, the "break-even" period is considerably shorter. Furthermore, this paper explains that, as a general matter, the "break-even" point should be interpreted as an extreme upper bound for data exclusivity and not as an estimate of optimal duration of data exclusivity. In the case of the biologic drug industry, because innovator drugs can be expected to continue to earn economic profits in a market open to biogeneric competition, optimal data exclusivity will always be less than the "break-even" point. Many readers of Grabowski (2008) falsely interpret that paper's results.

The remainder of this paper is organized as follows. **Section 1** reviews the growth of biologic drugs in the U.S. and worldwide markets and discusses current developments in the rate of patent expiration for biologic drugs. **Section 2** outlines the theory of optimal patent protection. **Section 3** presents the finance theory used to evaluate business decisions in high-risk investments and explains how to estimate the "break-even" point for a portfolio of investments. **Section 4** presents the finding in Grabowski (2008). **Section 5** explores alternative specifications. **Section 6** discusses the interpretation of the Grabowski model for public policy purposes related to optimal data exclusivity, and **Section 7** concludes.

1 Throughout this paper we use the terms "biogeneric," "biosimilar" and "follow-on biologics" interchangeably.

2 For a discussion of the FDA approval process for chemical and biological drugs, see Crandall (2008).

1. BIOLOGICS INDUSTRY AND PATENT PROTECTION

Biologics and U.S. healthcare spending. U.S. healthcare spending reached $2.2 trillion in 2007, 16.3 percent of the total U.S. gross domestic product. Prescription drug spending in 2007 was $231.3 billion and has been growing about 7 percent per year since 2002 (Center for Medicare and Medicaid Services 2007). Biologic drug spending, roughly 18 percent of total drug spending, has been growing at a rapid 15–20 percent per year (Congressional Budget Office 2008) as new drugs enter the market and additional indications are discovered for existing products. Global sales of biologics were approximately $75 billion in 2007 (IMS Health 2008). New drug discoveries are increasingly biopharmaceutical products, and it has been estimated that half of all drugs approved in 2010 will be biopharmaceutical.

Biologic drugs offer some of the most promising benefits for a range of life-threatening and crippling diseases, including anemia, hemophilia, cancer, diabetes, HIV, rheumatoid arthritis and thrombosis.

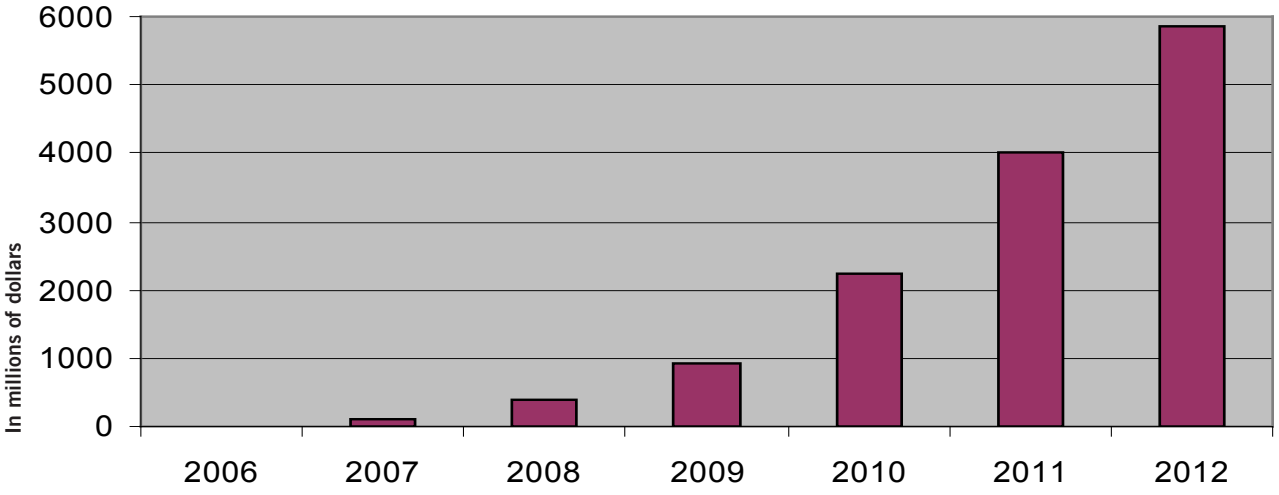
In the last few years, patents for Avonex, Epogen, Neupogen, Novolin and Procrit have expired. A number of biologics will lose their patent protection in the next few years, leading to potential rapid growth in the market for competitor generic drugs.

The world market for biogenerics has been projected to reach $5.8 billion in 2012. Three-fourths of that market will be the result of competition with biologic drugs for which patent protection has already expired. In addition, a number of drug patents, representing over $10 billion in annual sales currently, will expire over the next four years. Drugs such as Enbrel, Genotropin and Remicade will lose patent protection in the upcoming years and biogeneric research to replicate these products is currently under way (Crandall 2008). Figure 1 below presents the estimated world market potential for biogeneric drugs through 2012 according to research by Kalorama Information (Crandall 2008).

Needed legal framework for follow-on biologics. While nearly two dozen biologic drugs have lost their patent protection in the last few years and over 70 biologics will lose their patent protection soon, the Food and Drug Administration (FDA) currently does not have an established, abbreviated framework for permitting biogeneric drugs to enter the marketplace. This barrier to competition in the biopharmaceutical marketplace contrasts directly with the structure available for chemical drugs, as established in legislation referred to as the Hatch-Waxman Act[3]. Hatch-Waxman allows a generic com-

3 The bill's official name is The Drug Price Competition and Patent Restoration Act of 1984 (P.L. 98-417)

Figure 1: Total World Biogenerics Market Potential



Source: Kalorama Information, 2008

petitor to submit to the FDA proof of bioequivalence of the generic to the original drug, known as an abbreviated new drug application (ANDA), instead of being required to undertake a full set of clinical trials.

While the specifics of any legislation should be expected to lead to disagreement between advocates of the patent holder and those advocating for competitive products to come to market, a lack of any established pathway for biogenerics should be a concern for both sides of the debate as the current legal uncertainty creates a real risk that could be suppressing R&D of both innovator drugs and biogenerics. Beyond the importance of establishing *some* pathway for biogenerics, the precise rules and structure of that process will be paramount.

One point of contention among a handful of legislative proposals pending before Congress is the question of duration of data exclusivity. Data exclusivity guarantees that the FDA will not access the data from a drug's trial stages when examining an application of a competitor to sell an identical product. In effect, data exclusivity provisions provide a monopoly period to the drug's developer. Data exclusivity differs from patent protection, which is generally applied for in the preclinical stage and is generally valid for 20 years after the filing date, because data exclusivity is granted when a drug receives final approval from the FDA.

Recent legislative proposals vary along several dimensions, including differing durations of data exclusivity. Representatives Jay Inslee, Gene Green and Tammy Baldwin introduced H.R. 1956 and Senators Gregg, Burr and Coburn introduced S. 1505, which proposes 14 years of data exclusivity. S. 1695, sponsored by Senators Kennedy, Enzi, Clinton and Hatch, would allow for 12 years of data exclusivity. H.R. 5629, sponsored by Representatives Eshoo and Barton, would guarantee 12 years of data exclusivity, with an additional two years for a new indication and six months for pediatric exclusivity. In contrast, recent legislation introduced by Representative Henry Waxman would provide no data exclusivity for new biologics.

2. THEORY OF OPTIMAL PATENT PROTECTION

The purpose of a patent system is to ensure that the inventor of a patented product receives monopoly market conditions and can earn profit margins sufficient to induce the research and development costs associated with bringing the product to market. Nordhaus (1969) is credited with developing the economic framework for calculating optimal patent duration. More recent work, e.g., Tabarrok (2002), has discussed ideas such as varying patent life as a function of the sunk cost required to obtain the patent to yield more efficient outcomes. Lampe and Niblett (2003) discuss the theory of patent protection design broadly and explore game theory approaches in order to capture the dynamic environment when competing firms may be racing to discover and patent a product.

In general, however, the duration of the patent or other patent protections should be chosen to allow for the inventor to charge monopoly rents for a period of time sufficient to induce the initial R&D and other sunk costs.

Two separate intellectual property protections can be granted to new drugs: patent protection and data exclusivity. Their roles in encouraging innovation are different, but each serves an important purpose. Patent protection, granted by the Constitution, generally accrues for 20 years from the date of invention and is granted to an inventor as limited monopoly for new, useful and nonobvious discoveries. Data exclusivity is a definitive monopoly and a government grant, as it allows the innovator's data to be protected without challenge. In the case of chemical drugs, data exclusivity generally lasts for five years from the date a drug is approved by the FDA. Patents can, and frequently are, subject to legal challenge and therefore contain some amount of uncertainty for the patent holder. Data exclusivity is not challengeable in court and therefore is not uncertain.

Because a patent for a drug is granted prior to the marketing of that drug (usually years earlier), the effective patent life will be typically shorter than the statutory 20 years granted for new patents, and the exact effective patent life varies by drug.

One concern over the application and length of data exclusivity would be the determination of eligibility. The length and assignment of data exclusivity in this context could inhibit or encourage what has been described as "evergreening" practices. Evergreening is a process whereby the holder of the patents for a biologic drug, using incremental changes to its original product, is able to shift the market to a newer product so as to limit a generic competitor's market opportunity. If a long period of data exclusivity is applied to each incrementally changed version of the original product, it could result in biogeneric competition being consistently relegated to "older" versions where there is a diminished or exhausted market.

3. INVESTMENT THEORY

The same tools used by investors and corporate project managers to evaluate risky investment portfolios can yield insights for policymakers exploring the impact of data exclusivity rules, but the tools must be applied carefully. The total cost of developing a new biologic drug is driven by two factors: 1) the out-of-pocket R&D costs, including the costs for clinical trials, post-approval clinical costs and fixed costs for establishing the manufacturing facility; and 2) the time value of money driven by the long time periods involved in pharmaceutical R&D. Both factors introduce uncertainty into the total cost of the drug development process. However, the expected revenues from successful development of a biologic drug are, although uncertain, generally quite large. Integrating these expected costs and expected future rewards can be achieved through a cumulative net present value model. A positively valued portfolio is one that will be funded by investors.

By analyzing the expected R&D costs, time for development and approval of a new drug and the expected revenue of a portfolio of investments, one can calculate the number of years of data exclusivity that would yield a "break-even" result. This "break-even" point allows the innovator to earn its required rate of return (e.g., cost of capital) on the risky investment sufficient to induce the R&D.

This paper will focus on "break-even" analysis using a net present value (NPV) approach akin to the model employed by Grabowski (2008).

Net present value modeling of investment decisions. A simple NPV model allows for an analysis of a project that involves a series of fixed investment costs, k_t, at time $t < 0$—followed by a series of net future sales, s_t, at time $t > 0$.

By discounting the costs and future returns to the present using a discount rate that reflects the cost of capital for financing the project, the initial cost can be compared to the expected future returns to determine whether a project has a positive net present value. Box 1 provides an example of net present value modeling for investment decisions.

Box 1. An example of a cumulative net present value (NPV) decision model for the development of a new product.

Imagine for example, someone invented a product to automatically tie your shoes. The product took five years and $500 million to develop but is expected to produce $850 million in gross margin sales (net revenue) in the five years after it reaches market before becoming obsolete as a result of a new invention. The following table illustrates how to evaluate the expected return from years of development costs for a new product against the subsequent years of net revenues, all discounted (normalized) back to a single time period.

In this example, assuming a 10 percent discount rate, the project has a positive net present value in year 10. However, if one assumes a higher discount rate, say 15 percent, the value of the net revenues in the out years would be reduced and the cumulative net valuation would be negative. This illustrates the sensitivity of NPV calculations in the discount rate. We return to the point in Section 5.

Table 1. Example of NPV calculation

Year	Cost	Net Revenue	Net Present Value	Cumulative Net Present Value
1	-100	0	-100.00	-100.00
2	-100	0	-90.91	-190.91
3	-100	0	-82.64	-273.55
4	-100	0	-75.13	-348.69
5	-100	0	-68.30	-416.99
6	0	100	62.09	-354.89
7	0	150	93.14	-261.76
8	0	200	112.89	-148.86
9	0	200	102.63	-46.23
10	0	200	93.30	47.07

4. GRABOWSKI (2008)

Grabowski (2008) uses a cumulative NPV of discounted cash flows to analyze a portfolio of biopharmaceutical projects. The model is based on estimates of average costs and revenues associated with developing, marketing and selling an average new biologic drug, and the model incorporates average development times for a new product to reach clinical approval. Specifically, Grabowski employs estimates for the model from the following sources:

- Average pre-approval R&D costs from DiMasi and Grabowski (2007).
- Post-approval R&D costs based on Grabowski, Vernon and DiMasi (2002).
- A sales revenue distribution based on Grabowski (2003a, 2003b).
- A contribution margin based on Center for Medicare and Medicaid Services (2003).
- Net revenues and development costs are discounted using two alternative discount rates based on results from DiMasi and Grabowski (2007).

According to these specifications, a portfolio of biologics will have a positive net present value and the investment will break even (including necessary profits incorporated into the model as a cost of capital component) at a point between 12.9 and 16.2 years. Before discussing how this estimate relates to optimal duration for data exclusivity, the paper will next explore alternative specifications to the model.

5. ALTERNATIVE SPECIFICATIONS

Next we turn to a simple sensitivity analysis of Grabowski's results by altering two key variables: the cost of capital (which enters the model as a discount rate) and the contribution margin.

Cost of Capital. As noted in the discussion above, valuations are sensitive to discount rate assumptions. Grabowski's model discounts future cash flows and capitalizes R&D costs using the market-driven cost of capital as the appropriate discount rate. While this approach is valid in theory, we doubt the 11.5 percent and 12.5 percent real discount rates assumed by Grabowski. First, we draw on DiMasi and Grabowski (2007), who report multiple reasons why the real cost of capital for biopharmaceutical companies could fall within the range of 10 percent to 12.5 percent. Their own Capital Asset Pricing Model (CAPM) estimate from a sample of biotech firms (using the methodology explained in Myers and Shyam-Sunder (1995)) indicates that the cost of capital for biotech companies was 10 percent in 2004, the most recent year studied in that paper. Second, Grabowski, et. al. (2002) report that many large pharma firms in 2001–2002 were using *nominal* cost of capital estimates of 12–15 percent, which DiMasi and Grabowski (2007) equate to a 10–12 percent real cost of capital[4]. Third, using real cost of capital estimates compiled by Damodaran (2008) for biotechnology, based on analysis of 103 firms and using current long-term Treasury bill rates, the current real cost of capital for biotech firms is 10.25 percent. Taken together, a real cost of capital in the biopharmaceutical industry is reasonably 10 percent.

Contribution margin. The data for the contribution margin assumption used in Grabowski (2008) is taken from Center on Medicare & Medicaid Services (CMS) report titled "Health Care Industry Market Update: Pharmaceuticals," issued January 10, 2003. That report surveys eight large biotech companies and reports expense and income ratios for 2001. The non-weighted average contribution margin of these firms was 49 percent and Grabows-

4 DiMasi and Grabowski (2007) may have made an arithmetic error when they interpret 12-15 percent nominal cost of capital estimates to be equivalent to a 10-12 percent real cost of capital given an inflation assumption of 3 percent. The correct estimate would be 9-12 percent.

ki uses a similar value of 50 percent in his model. However, contribution margins vary over time and to focus only on 2001, a year in which the U.S. economy was in recession, fails to provide an accurate and current estimate of the contribution margin for the biopharmaceutical industry.

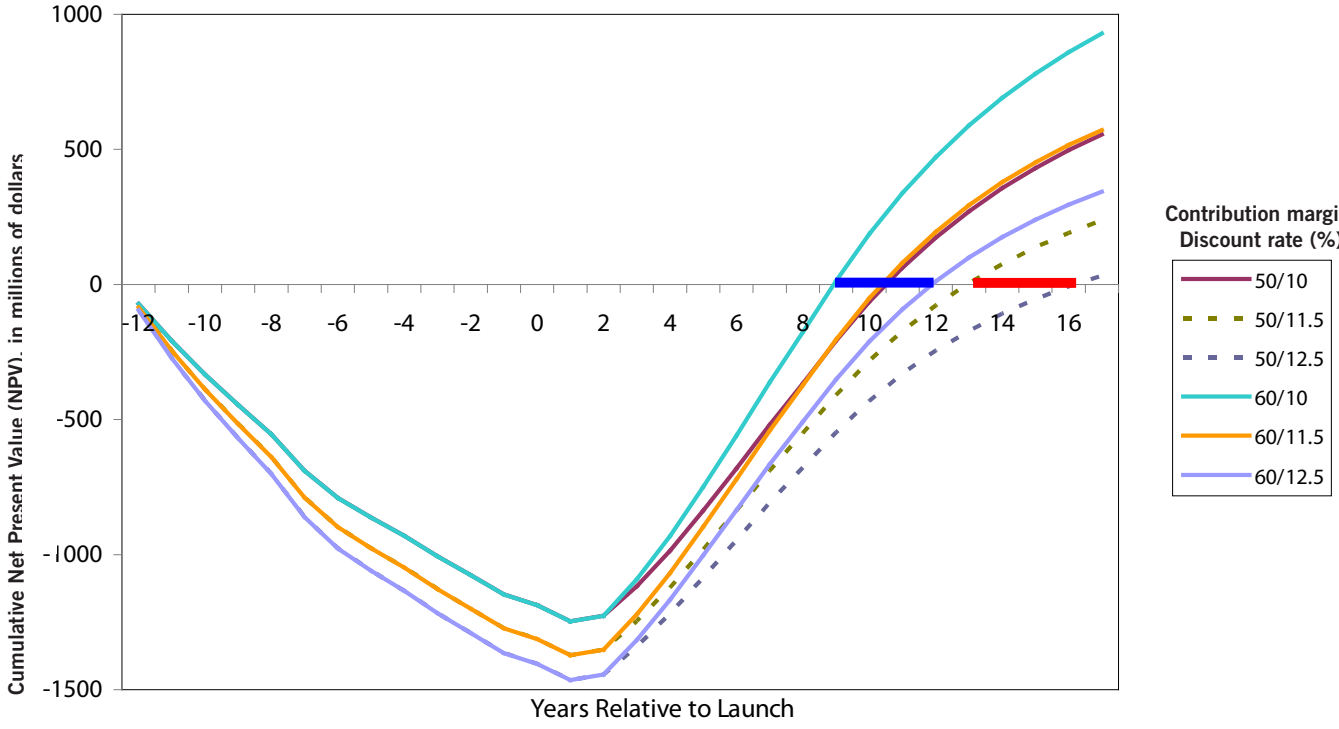
Using financial data reported by Bloomberg, we calculated contribution margins for each of the six largest biotechnology companies[5] in each of the years 2001 through 2007, in a manner similar to CMS (2003). We then calculated market cap–weighted contribution margin[6] averages for the industry for each year and average across years. We find that the weighted average contribution margin was 57 percent for all years and 61 percent for the most recent year, 2007. Therefore, we find that 50 percent is too low and consider a contribution margin of 60 percent a more plausible assumption.

5 The companies examined are Genentech Inc., Amgen Inc., Gilead Sciences Inc., Celgene Corp., Genzyme Corp., Biogen Idec Corp. and Biogen Corp. (Biogen is treated by Bloomberg as a separate corporation before its merger with Idec in 2003, so there are seven companies observed in 2001 and 2002.)

6 Contribution margins are calculated as the ratio of sales less cost of goods sold less selling, general and administrative expense (SG&A) less R&D to sales.

Results. Figure 2 below presents a range of results based on additional simulations of the Grabowski model with alternative assumptions. The two dotted lines on the right side of the graph represent the original Grabowski results; specifically a 50 percent contribution margin and an 11.5 percent or 12.5 percent discount rate. The four solid lines represent 50 percent contribution margin and a 10 percent discount rate; and a 60 percent contribution margin with a 10 percent, 11.5 percent or 12.5 percent discount rate. The new results range from just less than nine years to 12 years. Based on assumptions we view as most plausible, a 10 percent discount rate and 60 percent contribution margin, the best estimate of a "break-even" point is at just less than nine years.

Figure 2: Estimates of break-even lifetimes for new biologic drugs



6. INTERPRETATION AND IMPLICATIONS FOR DATA EXCLUSIVITY

Great care must be taken in interpreting the break-even result for public policy applications related to the optimal duration of data exclusivity rules. Data exclusivity duration should be set so that the portfolio of biologics has a positive expected net present value. Put in the terminology of Grabowski (2008), the portfolio should *eventually* reach a break-even point. Beyond the break-even point, the portfolio is earning profits that exceed the required rate of return expected by investors.

Importantly, the break-even duration will always be greater than the optimal duration of data exclusivity in a market such as biologic drugs, where it can be expected that the innovator drug will continue to earn economic profits following the entrance of biogeneric competition. A number of researchers have estimated the impact of biogenerics on prices and market share (Avalere Health (2007), Grabowski (2007), Express Scripts (2007) and CBO (2008)). In all cases, the prices will not fall to a point where no profits are earned, and in all cases, the innovator drug will maintain a significant market share. Thus, even post–data exclusivity, the innovator will continue to earn rents.

As a result of the fact that economic profits can be earned beyond the break-even point, optimal data exclusivity will be at a time prior to the break-even point. While Grabowski (2008) at no point claims that break-even should be equated with optimal data exclusivity, many readers of his work have made this assertion.[7]

Imposing data exclusivity and limited competition. To explore the impact of data exclusivity on the biopharmaceutical market, we re-estimate a break-even analysis assuming an impact of prices and market share from competition. We illustrate the effect of seven years of data exclusivity given our preferred assumptions about discount rate and contribution margin.

Additional assumptions about the effects of competition are required for this analysis, and we match our assumption about the effects of competition to the assumptions in CBO (2008)[8]. We assume that market share of biogenerics grows from 10 percent in the first year to 35 percent in the fourth year, and that price (sales-weighted) would decline 20 percent in the first year and 40 percent by the fourth year. The next chart adjusts sales revenues and contribution margins based on these assumptions and recomputes break-even points under the assumption of a 10 percent discount rate and 60 percent contribution margin. It is clear from the graph that investors will still earn their expected rate of return, as the NPV becomes positive in year 10, just one year later than without any competition. Depending on the application of data exclusivity rules, evergreening, the practice described earlier of making small modifications to the original product to extend market control, could further increase profits for the innovator drug but is not considered in this example.

While seven years of data exclusivity does slightly alter the trajectory of the line, the project does still continue to break even (again, this "break-even" point allows for double-digit real rates of return on investment, e.g., the cost of capital). In this case, the "break-even" point increases from nine to 10 years, after which considerable profits are still expected to be realized. Therefore, the incentives to pursue these investments remain.[9]

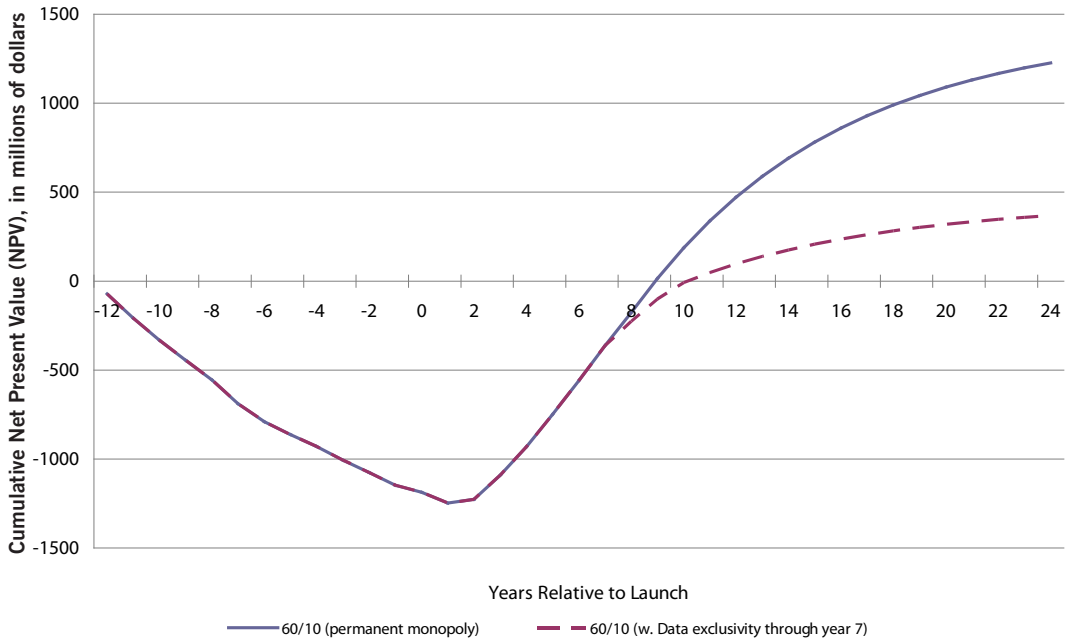
7 For example, Wyeth Pharmaceutical, in its letter to the Federal Trade Commission on September 30, 2008, incorrectly stated, "To address the concerns about patent challenges and exclusivity, Grabowski has determined that the appropriate period of data exclusivity for biologics should be 12.9 to 16.2 years." Amgen, in its letter to the FTC dated September 30, 2008, correctly describes the Grabowski results as relating to break-even analysis but falsely suggests that break-even is equivalent to optimal data exclusivity. Amgen writes, "The break-even point for biologics has been found to occur after it has been on the market somewhere between 12.9 and 16.2 years. Therefore, a 14 year period of data exclusivity is appropriate to recognize this increased cost and provide the proper incentives to invest in products which may fail at any stage in the research and development process." In testimony to the House Committee on Oversight (Grabowski 2007), Grabowski advocates for a data exclusivity period of "at least ten years in length," notably different than the position taken by proponents of Grabowski's work.

8 The CBO assumptions regarding the effects of competition on prices for biologics are more conservative than other reports such as Express Scripts (2007).

9 For the purpose of sensitivity analysis and to emphasize the result that data exclusivity should be less than the break-even point under any plausible assumptions, we also examined the effect of data exclusivity under alternative assumptions. Assuming a cost of capital of 11.5 percent, a seven-year period of data exclusivity still results in a break-even point.

Figure 3: Examining a 7-year data exclusivity period

Given a 10% discount rate & 60% contribution margin



7. CONCLUSION

Data exclusivity is an important protection awarded to biologic drug innovators and helps ensure adequate incentives for risky and expensive research on disease-curing drugs. However, excessive monopoly protection by the government creates windfalls to innovators, stifles competition and is costly to society. Establishing a pathway for follow-on biologics involves a multitude of policy decisions, and one important choice is the duration of data exclusivity to grant patent holders. Grabowski (2008) establishes a useful framework for estimating the average period of time required for a portfolio of biologics investments to recoup the development cost and reward investors their required rate of return.

We extend this work in two ways. First, we show that results are susceptible to considerable variation when tested with alternative assumptions. When two key variables, the cost of capital and the contribution margin, are adjusted with more current and plausible estimates, the model indicates that the number of years before break-even is reached is near nine. Second, we explain that this "break-even" point is beyond the optimal number of years of data exclusivity given the fact that economic profits of the innovator drug are expected to continue following the end of data exclusivity. Assuming that prices and market shares decline according to the assumptions laid out by the Congressional Budget Office (CBO 2008), we find that seven years of data exclusivity would result in a break-even point of 10 years, beyond that point the portfolio continues to earn profits in excess of the required rate of return.

Grabowski (2008) and the variations to that model presented here are stylized approximations of the market for biologics. Important other factors, including other patent protection issues and the aforementioned evergreening issue, not modeled here will affect incentives to innovate and affect the ability of biogeneric competition to improve access to drugs. Nevertheless, a critical factor in any legislation creating a pathway for follow-on biologics will be the duration granted for data exclusivity. Results presented here indicate that seven years is a reasonable duration to balance incentives for innovators with the market benefits of competition.

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