Data Exclusivity Periods for Biologics:

Updating Prior Analyses and Responding to Critiques

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I. SUMMARY

Recent discussion, including at the November 21, 2008 Federal Trade Commission Roundtable on Follow-on Biologic Drugs, has addressed the question of the appropriate duration of data exclusivity (also called data protection) for innovative biologics. This paper proposes that the breakeven financial analysis outlined in an earlier paper is an appropriate framework for the assessment of different data exclusivity periods being proposed in the context of an abbreviated regulatory approval pathway for biosimilars.[1] Among the key parameters in this model are: the cost of capital;[2] expected margins produced by marketed biotech products (contribution margin);[3] and other financial parameters such as required pre-marketing and post-marketing R&D investments. Applying this model led to the conclusion that a representative portfolio of biologics would "break even" or just cover its costs of development, manufacturing and sales, together with the industry's cost of capital, in 12.9 to 16.2 years, thereby providing support for a substantial data exclusivity period.

A recent critique, which adopts the same model and framework for its assessment of the appropriate duration of data exclusivity periods, suggests that alternative values for the cost of capital and contribution margin parameters are more appropriate and that, applying them

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[1] Grabowski, H., "Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition," *Nature Reviews Drug Discovery*, 7, 479 – 488 (2008).

[2] The cost of capital is the annual rate of return that an investor would require on average in order to make a given investment. In the case of biologics, this accounts for the risks associated with potential failure to develop or market the biologic candidate product successfully.

[3] The contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative expenses. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items.

supports a lower breakeven period, and therefore, a lower data exclusivity period.[4] It also considers the effects on breakeven periods of different assumptions for innovator product share and price impacts resulting from biosimilar entry. This paper corrects computational problems and inconsistencies in Brill's critique of the breakeven period. Furthermore, it disputes his claim that a 10% cost of capital and an average 60% contribution margin assumption are reasonable and appropriate baseline valves, and performs a number of sensitivity analyses using a range of input values. Together, these analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions.

The remainder of this paper is organized as follows:

- **Section II** discusses the importance of data exclusivity to biologics, including why patents alone may be insufficient to provide protection for biologics;
- **Section III** summarizes why the portfolio cash flow approach adopted in this paper is an appropriate framework for analysis of the impact of data exclusivity limits on investment and competition in the biotech industry;
- **Section IV** summarizes the key points in a recent critique of the previous "breakeven" analysis published in *Nature Reviews Drug Discovery* (hereafter referred to as the *Nature* model) and identifies four problems and implausible assumptions in this critique;
- **Sections V and VI** refute key assumptions from this critique, including the a cost of capital that is too low (Section V) and contribution margins that are too high (Section VI);
- **Section VII** notes that the critique fails to take into account other countervailing assumptions in the prior *Nature* analysis that tend to understate expected breakeven periods;
- **Section VIII** extends the previous *Nature* analysis to incorporate other impacts associated with biosimilar entry, and summarizes the results of sensitivity analyses on the extended model;
- **Section IX** summarizes the overall results of the additional analysis in this paper; and
- A brief **Appendix** addresses the critique's computational inconsistencies

[4] Brill, A., "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," unpublished manuscript, November 2008.

II. THE IMPORTANCE OF DATA EXCLUSIVITY TO BIOLOGICS

Data exclusivity is the period of time between FDA approval and the point at which an abbreviated filing for a biosimilar relying in whole or in part on the innovator's data on safety and efficacy can receive final approval. Data exclusivity is designed to preserve innovation incentives, and recognize the long, costly, and risky process necessary for the innovator to gain FDA approval. Data exclusivity is a critical issue for the future of biologics, with different provisions for data exclusivity in recent legislative proposals ranging from zero to 14 years. All bills other than H.R. 1038, sponsored by Representative Henry Waxman of California, proposed combined periods of at least 12 years.[5, 6]

Data exclusivity periods are essential to compensate for some important shortcomings in patent protection for biologics. Data exclusivity extends from the date of product approval, and this protection period runs concurrently with any remaining patent term protection for the biologic. That is to say, data exclusivity provides additional protection to the innovator when the remaining patent length is shorter than the data exclusivity period at the time of approval (which can occur due to lengthy preclinical and clinical research required to obtain FDA approval), or to

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[5] Although H.R. 1038 contains no data exclusivity period at all, its absence did not necessarily indicate opposition to a provision, according to coverage at the time, but rather a desire to hold off on backing a specific figure until more was learned about what an appropriate period should be. See summary in *Inside Health Policy,* "Boston University Study Criticizes Exclusivity Measures in Biogenerics Bills," September 30, 2008. Access October 29, 2008 at www.insidehealthpolicy.com/secure/health_docnum.asp?f=health_2001.ask&docnum=9302008_boston&DOCID=9302008_boston.

[6] Recent legislative proposals for establishing an abbreviated pathway for biosimilar entry consider both permissible filing dates and overall market protection periods. For example, the bill S.1695, sponsored by Senator Kennedy, allows for four years before an abbreviated filing can occur, during which the FDA cannot rely on innovator's data on safety and efficacy to review an abbreviated biosimilar application, followed by an additional eight years during which FDA review of the application can take place but the application cannot be approved, for a total of 12 years of data exclusivity.

the extent that the patent is circumvented by a biosimilar prior to its expiry. Patent protection alone may be insufficient for biologics in the context of biosimilars for two primary reasons:

(1) The standard for FDA approval of biosimilars is likely to be based on *similarity* rather than *sameness*, allowing for greater differences between the biosimilar and the reference product than are allowed between an AB-rated generic small-molecule drug and its reference product. As a result, development of a biosimilar may allow for greater deviations from the reference product and greater opportunity to deviate slightly from the patented technology, thereby sidestepping patent infringement while still benefiting from an abbreviated FDA application process. In 2007 remarks before the Committee on Oversight and Government Reform, Dr. Janet Woodcock of FDA noted, "Because of the variability and complexity of protein molecules, current limitations of analytical methods, and the difficulties in manufacturing a consistent product, it is unlikely that, for most proteins, a manufacturer of a follow-on protein product could demonstrate that its product is identical to an already approved product."[7]

(2) Patents for biologics, unlike for small-molecule drugs, do not typically protect the entire molecule or class of related molecular structures. Biologics are much more complex than small-molecule drugs, and the patents protecting biologics tend to focus on certain aspects of the protein or ways of producing the protein rather than on protecting the entire molecule.[8]

Data exclusivity provides investors with an "insurance policy" against the potential failings of patent protection for biologics. Recent evidence suggests that the effective marketing

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[7] Woodcock, J. "Follow-on Protein Products" Statement before the Committee on Oversight and Government Reform, U.S. House of Representatives, 26 March 2007, FDA web site (online), http://www.fda.gov/ols/2007/rotein32607.html, (2007).

[8] Manheim, H., Granaham, P., and Dow, K., "Follow-on Biologics: Ensuring Continued Innovation in the Biotechnology Industry," Health Affairs, 25:394-404 (2006).

exclusivity period for small-molecule drugs (the time between launch and first generic entry) is approximately 12 years on average.[9] Data exclusivity for small-molecule drugs is generally not the constraint on generic entry (although in recent years, it has become increasingly important for small molecules due to the rise of Paragraph IV challenges under the Hatch-Waxman Act), whereas it is expected to be more determinative for biologics due to the nature of their patent protection.[10]

III. A PORTFOLIO DISCOUNTED CASH FLOW APPROACH IS AN APPROPRIATE FRAMEWORK FOR ANALYSIS OF THE IMPACT OF DATA EXCLUSIVITY LIMITS ON INVESTMENT AND COMPETITION IN THE BIOTECH INDUSTRY

In evaluating the impact of data exclusivity periods of different durations on the incentives for innovation, an appropriate perspective to adopt is that of a potential investor who weighs alternative investments, together with their expected risks, costs and returns. Venture capital and private equity are the primary sources of early stage investment in biotech start-ups, which account for many new pipeline biologics. Venture capital-backed firms constitute 40 percent of employment in biotechnology.[11] Such investors account for the low probabilities of success of any individual opportunity by investing in a long-term portfolio of opportunities, most of which ultimately will not succeed, but one or two of which may earn significant returns years later. Larger established firms, as well as venture investors, need to take a portfolio approach,

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[9] Grabowski, H. and Kyle, M., "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics*, 28: 491-502 (2007). For drugs with first-generic entry in 2005, the average market exclusivity period (MEP; the time between product launch and first-generic entry) was 11.5 years (drugs with sales greater than $100 million) to 13.0 years (all drugs).

[10] Grabowski, H. "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents, and Political Pressures, *PharmacoEconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24.

[11] Lawton R. Burns, Michael G. Housman, and Charles A. Robinson, "Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital," *Health Affairs* 28, no. 1 (2009): w76-w86.

given the low probability of success for new biological candidates, and the skewed distribution of sales revenues for approved marketed candidates. Venture capital firms use discount rates that vary by stage of investment, and account for a decreasing level of risk as products approach launch and commercialization. An empirical analysis of this issue found that discount rates vary from 70% down to 25%, depending on stage of finance (start-ups to IPOs).[12] Similarly, established biotech or pharmaceutical firms apply a portfolio approach to their selection of which candidate molecules to advance in development and to the valuation of licensing and acquisition opportunities, using a risk-adjusted cost of capital, as discussed below.

This approach was outlined in an article recently published in *Nature Reviews Drug Discovery* (Grabowski, 2008; henceforth referred to as the *Nature* article). In a recent unpublished white paper, Alex Brill utilizes the same framework to comment on the optimal data exclusivity period. Brill accepts the basic premise of the *Nature* article, namely that data exclusivity times should be guided by the time necessary for a representative new biological entity to just cover its expected R&D, sales and marketing investments, together with the industry-wide cost of capital. This is defined as the "breakeven lifetime" in the parlance of economics and financial studies.

Brill also accepts the appropriateness of a portfolio approach to evaluating R&D investment decisions, like the one performed in the analysis in the *Nature* article. Accordingly,

[12] Sahlman,W.A., "The Structure and Governance of Venture-Capital Organizations," *Journal of Financial Economics*, 27(1990) pp. 473-521, Table 6 at p. 511.

he also focuses on the returns for a representative biological product from a portfolio based on the historical distribution of R&D costs and revenues.[13]

IV. BRILL'S ANALYSIS

As discussed, the analysis presented in the 2008 *Nature* article results in breakeven returns for the representative biologic between 12.9 years and 16.2 years. This is depicted in Exhibit 1, which is Figure 7 from the *Nature* article. This diagram shows the cumulative net present values over a 30-year period from the beginning of the R&D investment period through market launch and over the product life cycle. As shown in this diagram, it takes 12.9 years after launch, at a discount value of 11.5%, for the cumulative net present value (NPV) to become positive in terms of value from cash flow, and 16.2 years for breakeven at a discount value of 12.5%. Alternatively stated, it takes 12.9 to 16.2 years for the firm to earn a rate of return which is just equal to its risk-based cost of capital.

A. DESCRIPTION OF BRILL'S ANALYSIS

In his white paper, Brill makes three changes from the analysis presented in the *Nature* article that affect the breakeven point calculation:

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[13] In particular, his basic inputs include average R&D investment from DiMasi and Grabowski, 2007 (DiMasi, J., and Grabowski, H., "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics*, Vol. 28, Issue 4-5, pp. 469-479), sales revenue distribution for biologics based on Grabowski, 2003 (Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries," *Science and Cents*, edited by John Duca, Federal Reserve Bank of Dallas, 2003, pp. 87-104), and post approval R&D costs and product launch expenditures based on Grabowski, Vernon and DiMasi, 2002 (Grabowski, H., Vernon, J., DiMasi, J., "Returns on Research and Development for 1990s new Drug Introductions," *Pharmacoeconomics*, Vol. 20, Supplement 3, 2002, pp. 11-29).

(1) First, he assumes that the innovator's product will retain a significant share of its pre-entry sales after the market entry of biosimilars, and bases his estimates in this regard on recent assumptions from the Congressional Budget Office (CBO).[14]

(2) Second, he utilizes a 10% baseline real cost of capital for the representative biotechnology firm, compared to the 11.5% to 12.5% range utilized in the *Nature* article.

(3) Third, he utilizes a 60% contribution margin for the representative biologic product, compared to a 50% baseline value in the *Nature* article.

The *Nature* article estimates a breakeven lifetime of between 12.9 and 16.2 years for the representative biological product. With the above changes in assumptions, Brill claims that relatively short exclusivity periods would still be compatible with significant innovation incentives. In particular, he claims that a seven-year data exclusivity period with subsequent biosimilar entry would still allow firms to break even in just over ten years.

However, Brill's analysis is subject to computational problems and inconsistencies, as well as implausible assumptions. When these are corrected and accounted for, his implication that short data exclusivity periods, coupled with rapid biosimilar entry, still provide strong innovation incentives is not valid. In this paper, we perform alternative sensitivity analyses on particular inputs and assumptions, and confirm the importance of a substantial data exclusivity period for biologics.

[14] Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.

B. CRITIQUE OF BRILL'S ANALYSIS

Exhibit 2 is taken from Brill's white paper (it is Figure 3 in his paper and appears with results uncorrected). This exhibit uses the same framework as Exhibit 1, but reflects the changes Brill implemented to incorporate biosimilar entry (including his calculation errors and implausible assumptions). In particular, for the specific case presented in this exhibit, there is a hypothesized data exclusivity period of seven years, after which biosimilars are assumed to enter. Brill relies on a discussion of shares and prices from the CBO bill-scoring document to make assumptions on innovator share and price erosion following biosimilar entry. Brill assumes that, on average, biosimilars will capture a 10% share of the market in the first year of entry, growing to a steady state of 35% within 4 years. He further assumes that price (sales-weighted) would decline by 20% in the first year, and reach a steady state of a 40% price discount by the fourth year. The analysis is also performed under Brill's assumption of a 10% cost of capital and a 60% contribution margin. As shown by the dotted line in this diagram, Brill finds the firm can still break even in year 10, and earn increasingly positive cash flow values after that point.

The four problems and implausible assumptions in Brill's analysis are:

(1) ***Brill's calculations include a significant computational problem and inconsistency in incorporating assumptions made by the CBO in its scoring of follow-on biologics bill S. 1695 into the Nature model; correcting these problems does not yield his results as reported and does not support a seven year data exclusivity period.*** Since the publication of the *Nature* article, the CBO has published a bill-scoring estimate that includes some discussion of potential market shares and price discounts with biosimilar entry. Brill references the CBO discussion in his assumptions of biosimilar shares and price discounts, which

are used to evaluate whether particular data exclusivity periods are compatible with eventual breakeven returns. In doing so, however, the treatment of price discounts and margin changes in Brill's analysis are inconsistently incorporated into the investment returns model in the *Nature* article. This in turn results in a significant underestimation of breakeven times.

(2) ***Brill's assumption on the cost of capital is not reasonable and is at odds with most current best thinking on the subject and with other commonly used industry metrics***. Indeed, the most sophisticated analysis in the current literature, together with accepted published industry metrics, suggests real costs of capital for biotech firms are well above the 11.5% to 12.5% assumed in the *Nature* article. (Golec and Vernon, 2007; Ibbotston Annual Cost of Capital Yearbook, 2008)[15] Brill also fails to acknowledge the large subsample of private and public biotech firms without marketed products that need to rely on venture funding and financial instruments at very high costs of capital.

(3) ***Brill's assumption for the average contribution margin relies on results from six of the most profitable biotech firms, and fails to consider the high degree of variability in profits even among this small, upwardly biased sample. His approach also puts inordinate weights on two of the most successful biotech firms[16].*** As a result of these sample selection issues, his 60% margin can be viewed as being an extreme value, or upper bound, rather than being a plausible baseline value.

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[15] Golec, J., and Vernon, J., "Financial Risk in the Biotechnology Industry," *Journal of Applied Economics and Health Policy*, forthcoming; also NBER Working Paper # 13604, November 2007. Ibbotson, *Cost of Capital Yearbook*, Morningstar, 2008.

[16] Together, Amgen and Genentech alone receive 67 percent of the overall weights in Brill's calculation of the average.

(4) ***Brill ignores countervailing assumptions already reflected in the Nature article breakeven analysis, which have the effect of producing estimated breakeven periods that are shorter than likely actual breakeven periods***. For example, the representative portfolio modeled reflects the mean values observed for only the top four ranked quintiles of the sales distribution of established biotechnology drugs, with the bottom quintile excluded. Excluding all biologics in the lowest tail of the distribution biases breakeven periods downward. In addition, the *Nature* model assumes that firms can use existing plant assets to produce the biologics in the modeled portfolio at commercial scale and that capital costs are captured fully by depreciation charges subsumed in the contribution margin. This approach also biases breakeven periods downward, as some new plant construction or retrofitting would be required. The cost of a new multi-product manufacturing plant for large-scale commercial production is substantial. It has been estimated elsewhere that a new manufacturing plant can take three to five years to construction and can cost $250 million or more.[17] Even retrofitting existing plant assets can cost between $50 and $100 million. Finally, the *Nature* model assumes a 3.5% reduction in branded biologic share each year, beginning in the 10th year to account for therapy obsolescence. Vigorous dynamic competition in the therapeutic areas with high unmet need (such as rheumatoid arthritis, oncology and other areas) typically served by biologics, and the high numbers of pipeline products in these areas suggest actual rates of share attrition may be higher in the coming years.

[17] Molowa, D.T. The State of Biologics Manufacturing. J.P. Morgan Securities, Equity Research Healthcare Note. 16 February 2001.

C. CORRECTING LOGICAL INCONSISTENCIES IN BRILL'S ANALYSIS

Brill's first point concerning innovator sales after biosimilar entry can be viewed as a logical extension or sensitivity analysis to the breakeven analysis. In the *Nature* article, various qualifying points that had countervailing effects on the breakeven lifetime were presented.[18] One such qualifying point was that, for the foreseeable future, innovative firms may retain significant shares of the market after the entry of biosimilars. This is in contrast to the current experiences of small-molecule drugs, where as behavior under Hatch-Waxman has evolved over the years, high sales products now often lose 90 percent of the market to generics within just a few months (Grabowski, 2004; Silver, 2008).[19] Over time, the markets for biosimilars may evolve to more closely resemble the now intensely competitive ones for generic chemical entities (Grabowski, Cockburn and Long, 2006).[20] In the meantime, however, current biologics may be able to earn potentially significant revenues after biosimilar entry, prolonging the innovative product's life beyond the expiration of data exclusivity periods. Therefore the impact of innovator sales and price erosion on the breakeven calculation needs to be further investigated.

Brill's analysis of these issues, however, has inconsistently implemented how the price erosion assumption will affect the model results presented in the *Nature* article. In calculating changes in contribution margins, Brill assumes that the innovator will discount the price of the brand biologic in response to biosimilar entry, by the same amount as the sales weighted price of

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[18] Most of the other qualifying points in Grabowski (2008) operate in an opposing manner as discussed below, and these points were ignored by Brill.

[19] Grabowski, H., "Are the Economics of Pharmaceutical R&D Changing? Productivity, Patents and Political Pressures," *Pharmcoeconomics*, Vol. 22, Suppl. 2, 2004, pp. 15-24. Silver, R., "A Wall Street Perspective on Generics," 2007 GPhA Annual Meeting, March 1-3, 2007, available at http://www.gphaonline.org/AM/CM/ContentDisplay.cfm?ContentFileID=593.

[20] Grabowski, H., Cockburn, I., Long, G., "The Market for Follow-On Biologics: How Will it Evolve?," *Health Affairs*, 25, no. 5 (2006), pp. 1291-1301.

the biosimilar entrants. However, he fails to correspondingly reduce the level of assumed brand biologic sales in his modification to the model by the same price discount. This inconsistent computational approach means that he multiplies margins that take the price erosion assumptions into account by revenues that do not.[21]

As discussed in the sensitivity analysis later in this paper, Brill's interpretation of the CBO assumptions on the brand's price response is open to question. The CBO report states that biosimilar entry will constrain innovator prices, but does not specify by how much it will do so.[22] Hence, this is a subject for further sensitivity analysis that we undertake in Section VIII. In this section, however, we examine the effects of the logical inconsistency in Brill's analysis, given his interpretation that the innovator price will be the same as the sales weighted average of the biosimilars. Further details and an illustrative example of this computational problem are presented in the Appendix.

Correcting Brill's computational problems and inconsistencies has a substantial impact on his findings. Applying his overstated baseline profit margin assumption of 60% and understated baseline cost of capital assumption of 10% to the corrected model, and maintaining his assumption of a seven-year exclusivity period results in a breakeven period of over 13 years, not the just over 10 years that he reports. Furthermore, he erroneously states that even with a cost of capital of 11.5% and a seven-year exclusivity period (and his other assumptions

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[21] These issues are discussed more specifically in the Appendix to this paper. In the updated *Nature* model calculations presented in this paper, we assume that costs are reduced proportionately with reductions in output.

[22] In a telephone conversation on December 22nd, CBO confirmed that the appropriate interpretation of the assumption in their report that the availability of biosimilars will constrain brand-name prices is that brand-name prices will be lower than they would otherwise be without any biosimilar entry. However, the CBO has not released any quantitative assumptions in this regard and are still analyzing the issue in light of new information.

unchanged), a breakeven period (of unspecified magnitude) results. In fact, when his calculation error is corrected, there is no breakeven period in the first 50 years when applying an 11.5% cost of capital assumption and a seven-year breakeven period.[23]

D. SENSITIVITY OF BRILL'S RESULTS

After correcting for calculation problems and inconsistencies, Brill's findings are extremely sensitive to small changes in his assumptions. Exhibit 3 uses the same framework as Exhibit 2, but corrects for Brill's calculation error. Using reasonable assumptions, a seven-year exclusivity period is insufficient:

- Keeping all of his assumptions unchanged but reducing the margin assumption from 60% to 55% results in ***no breakeven period within the first 50 years***.
- Similarly, increasing just his cost of capital assumption from 10% to 11.5% (and keeping his margin assumption at 60%), again results in ***no breakeven period within the first 50 years***.

Even if Brill's margin and cost of capital assumptions were reasonable, which they are not, such high sensitivity in findings to small changes in those assumptions would be of significant concern.

It is also important to keep in mind that while biosimilar penetration rates and/or brand price discounts may be modest in the near term (as reflected in estimates for existing products by

[23] Whether or not a breakeven period exists beyond 50 years following launch of the brand was not investigated, as it is unlikely that investors will consider projects with such a lengthy term to break even regardless of the discount rate.

the CBO or others), they could very well exceed those assumed by Brill in the longer run.[24] Data exclusivity provisions are focused on innovation incentives for the long-term. Many of these molecules will not reach the market for a decade or more, and biosimilar entry will be even further removed in time from market launch. Over time, attrition rates may increase for biologics as the FDA develops a larger experience base, and private and public reimbursement systems evolve for biosimilars.

Even if one accepts Brill's cost of capital and contribution margin assumptions, increasingly aggressive biosimilar entry following the expiration of data exclusivity periods would result in longer breakeven periods over time or no breakeven period at all over a reasonable timeframe.

V. 10 PERCENT COST OF CAPITAL IS NOT CREDIBLE FOR BIOTECH FIRMS

The *Nature* article's estimates of the real cost of capital, 11.5% and 12.5%, are substantially below reliable broad industry estimates of the cost of capital for biotech R&D investments. These original estimates were based on a small group of biotech firms that had multiple FDA-approved biologics and a history of positive operating profits over the past decade, and understate cost of capital for the industry more broadly, which includes smaller biotech firms with few or no biologics on the market. As noted in the *Nature* article, for these reasons, the values used for the real cost of capital are conservative, meaning they are below those faced by most firms. In addition, recent best academic literature estimates the real cost of capital for

[24] The CBO's estimate focuses on a 10-year timeframe beginning with the present when the initial implementation of a regulatory pathway for biosimilars would be developed and implemented and the first biosimilars would enter the market.

biotechnology firms to be no lower than 13.25%, and in some cases much higher when the focus is small to mid-size biotechnology firms:

- Golec and Vernon (2007) estimate costs of capital for the biotechnology industry generally, relying on a three-factor Fama French model (as opposed to a CAPM model), which is the generally accepted, appropriate methodology for estimating cost of capital.[25] Golec and Vernon (2007) estimate a nominal cost of capital of 16.75% for biotech R&D investment, and Vernon recently noted that this corresponds to a real cost of capital of 13.25%, significantly higher than the 11.5% and 12.5% figures used in the *Nature* models.[26]
- Ibbotson's Cost of Capital 2008 Yearbook, a widely accepted general industry source for cost of capital estimates, reports a similar nominal three-factor Fama-French estimate of 17.49% for the median publicly-traded company within the biotechnology SIC code (2836). Assuming a 3% annual inflation rate, this figure would correspond to a 14.07% real cost of capital.

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[25] Fama-French three factor return models are considered to be far superior for estimating cost of capital in industries such as biotechnology. As noted in Golec and Vernon (2007), the finance literature has established that "[s]ingle factor models such as the Capital Asset Pricing Model (CAPM) do not capture all of the types of systematic risk that influence firm cost of capital. In particular, the CAPM does not reflect the empirical evidence that supports both a size-related and a book-to-market related systematic risk factor."

[26] As estimated by Vernon in comments filed with the FTC during its comment period. This is consistent with Myers and Shyum-Sunder, 1996 (Myers, S., and Shyum-Sunder, L., "Measuring Pharmaceutical industry risk and the cost-of-capital," In: RB Helms, editor, *Competitive Strategies in the Pharmaceutical Industry*, Washington, DC, AEI Press (1996), pp. 208-237), who estimate a 14% real cost of capital for seven medium-sized publicly traded biotech and pharmaceutical firms for 1989. Brill cites this paper, but neglects to mention the 14% estimate in the paper or their corresponding analysis of "small" firms (including Biogen, Cetus and Genentech, along with other firms like Scherer and Mylan, with lower average betas than the true biotechs); the small firm sample had real equity costs of capital of 16.1% (p. 228), and higher if one just used biotech firms.

- Grossman (2003) estimates the cost of capital for smaller biotechnology firms and finds that biotechnology firms without a marketed product but with one or more biologic candidates in Phase II or III trials have an average nominal cost of capital of 27.4%.[27] He also estimates a nominal cost of capital for biotechnology firms with at least one biologic approved of 18.17%.[28] Again assuming a 3% annual inflation rate, these figures would correspond to real costs of capital of 23.69% and 15.24%, respectively.

Consistent with these findings, many small biotechnology firms rely heavily on venture capital for financing, which typically implies very high cost of capital requirements, and biotechnology firms are facing increasing difficulties obtaining this financing in the face of the current credit crunch.[29] Table 1 summarizes biotechnology industry cost of capital figures from a wide range of sources.

Brill relies on a real cost of capital of 10%, which is far lower than estimates typically reported in the academic or trade literature for the biotechnology industry. His results are also highly sensitive to increases in this estimate.[30] Brill claims to substantiate his 10% cost of

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[27] Grossmann, M., *Entrepreneurship in Biotechnology*, Physica-Verlag New York, 2003.

[28] Myers and Howe (1997) similarly find that smaller biotech firms had much higher betas (measures of risk) than larger biotech companies, which would result in substantially higher cost of capital for smaller firms. They estimate an average beta in 1992 of 1.38 for "mature" biotech firms, 2.38 for biotech firms with drug candidates in advanced stages of clinical testing, and 2.17 for biotech firms without drug candidates in advanced stages of clinical testing.

[29] See for example, Boyle, C., "Credit Crunch Threatens Investment in Medicines," TimesOnline, October 27, 2008.

[30] Brill's claim in footnote 9 of his paper that breakeven still occurs with a cost of capital of 11.5% and a 7 year data exclusivity period is not accurate (even if one relies on his assumed 60% profit margin). Prior to correcting for errors in Brill's calculations, his model yields a 17 year breakeven period with a cost of capital of 11.5% rather than 10%; after correcting the calculations in his model but keeping all inputs other than cost of capital unchanged there is no breakeven in the first 50 years.

capital assumptions by citing the paper, DiMasi and Grabowski (2007), along with Myers and Shyam-Sunder (1995), and by citing a website maintained by Damodaran:

- Brill's interpretation of DiMasi and Grabowski,(2007) as being consistent with a 10% cost of capital is not correct. The 10% estimate is the lowest of several estimates found (other estimates included 12 and 12.5%) and reflects a period of low risk-free rates and risk premiums. Investors will consider *long-term* investment conditions, however, and the lower observed short-term period of risk-free rates and risk premiums are unlikely to be a reliable guide as to long-term future rates and premiums. Furthermore, the estimate is based on relatively large, publicly traded biotech and pharmaceutical companies and does not reflect the cost of capital of small or mid-sized biotechs.
- In discussing DiMasi and Grabowski (2007), Brill also cites Myers and Shyam-Sunder (1995), but ignores their 1989 analysis of "small" firms that finds a real equity cost of capital of 16.1%, or even higher if one examines just biotech firms. Their "small" firm sample actually includes several well-established companies that are now leaders in the biotech field.[31]
- Using data on a website maintained by Damodaran, Kotlikoff (2008) finds the real cost of capital as of January 2008 to be 12.7% for biologic firms. To calculate this cost of capital he uses a risk-free rate based on U.S. Treasury inflation protected securities ("TIPS") of 2%. Brill relies on the same data but estimates a real cost of capital of 10.25%, apparently suggesting that Kotlikoff's estimates are overstated. To arrive at a lower cost of capital than Kotlikoff, it is likely the case that Brill is assuming a lower

[31] Such as Biogen and Genentech, along with other firms like Scherer and Mylan with lower average betas than the true biotechnology firms.

risk-free rate and a lower equity premium. In fact, Brill's risk-free rate would need to approach zero to account for the difference between his and Kotlikoff's cost of capital estimates, as the other input data currently available from Damodaran's website appear to be unchanged from those relied on by Kotlikoff.[32] Biotech firms and early stage investors cannot and do not change their R&D investment decisions based on monthly changes in U.S. Treasury rates, however, as would be suggested by Brill's analysis of the Damodaran data. In comparison, the 13.25% real cost of capital estimate found by Golec and Vernon (2007) reflects a superior approach that is longer-term in focus and less susceptible to such volatility.

Relying on cost of capital inputs that do not accurately reflect the actual biotech industry cost of capital to determine an exclusivity period risks adverse effects on financing. This would severely restrict investment in the development of new therapies and have a potentially strong negative effect on competition. As discussed earlier, the costs of capital for firms without marketed products exceed the industry average substantially and would be particularly adversely affected.

[32] The sample of companies that Damodaran relies on for the biotechnology industry includes a number of firms that are not true biotechs for the purposes of this paper, including: Luminex, a bioassay testing firm; Martex Biosciences, which markets supplements; Ista, primarily focused on small molecule opthamalic products; and Mamatech, which develops breast tumor detection products.

VI. CONTRIBUTION MARGINS OF 60 PERCENT ARE TOO HIGH AND REFLECT THE EXPERIENCE OF ONLY A FEW OF THE LARGEST AND MOST SUCCESSFUL FIRMS

The *Nature* article simulations rely on a 50% contribution margin,[33] which is based on the contribution margins realized by the eight largest biotech firms with multiple products on the market. However, few biotech companies are actually profitable, and the universe of biotech firms is populated with development-stage companies whose principal assets are their human capital and intellectual property. These companies would be expected to experience lower contribution margins than a firm with an established line of approved products as represented by the sample that reflects even a 50% margin.

Brill argues for a much higher contribution margin of 60%, which is not reflective of the expected profit potential for most biotechnology products. He bases this estimate on a market-capitalization-weighted average of large and very successful companies, which has the effect of biasing his figure upward and is not representative of the sector.

Brill's use of market-capitalization weighting means that his average margin primarily reflects just two biotech firms with large market capitalizations relative to the other firms in his sample. Even among Brill's six highly successful companies, many of them earn margins well below his 60% average, and there is considerable variation in margins from 43.4% to 63.7%.

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[33] As noted earlier, the contribution margin is a measure of how much a company earns in sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative (SG&A) expenses. It is expressed as a ratio of sales, less cost of goods sold and less SG&A, to sales. Contribution margin is not equivalent to profit margin, which also subtracts the costs of R&D, and interest, taxes and all other expense items. All calculations of the contribution margin in this paper were based on publicly available sources.

Furthermore, three of the six firms identified by Brill earn margins of 50% or less over the 2001 to 2007 time period that he examines.

Two of the largest biotechnology not identified in Brill's sample that qualify for inclusion and were independent firms during the time period examined earned average margins of 36% and 35%, respectively, during the 2001 to 2007 period, substantially lower than Brill's 60% margin assumption.[34] Including these two additional firms, the range in margins over the time period would be 33.6% to 63.7% with five of the eight biotechnology firms reviewed earning margins of 50% or less.

Not only do a number of highly successful biotech companies fail to earn contributions margins consistent with his 60% assumption, but contribution margins for medium and smaller biotechnology companies would also be far lower than 60%.

Relying on Brill's overly optimistic contribution margin assumption to determine appropriate exclusivity periods for biologics would result in estimated breakeven periods that are too low. If these figures are used to determine data exclusivity period limits, it would have the effect of making investment in some potentially important innovative biotech products too unattractive to warrant the cost and risk of investment..

VII. BRILL HAS IGNORED OTHER COUNTERVAILING ASSUMPTIONS IN THE PRIOR *NATURE* ANALYSIS

The *Nature* analysis imposes a number of countervailing assumptions that are likely to overstate expected revenues and understate expected costs, resulting in breakeven periods that err on the side of being shorter than what would actually be experienced in the biotechnology

[34] These firms are MedImmune and Chiron.

industry. Brill fails to note any of these countervailing assumptions in his critique, or the fact that reasonable alternative assumptions result in longer breakeven periods, and potentially no breakeven point using his cost of capital, contribution margin, and seven-year data exclusivity assumptions. These countervailing assumptions include:

(1) ***The lowest quintile of sales is excluded when estimating the expected average revenue stream.*** Excluding the lowest quintile results in estimates that potentially overstate expected revenues, and understate expected breakeven periods.

(2) ***A very low rate of product obsolescence from new biologics is assumed.*** Specifically, the *Nature* model assumes no product obsolescence in the first 10 years following release, and only a 3.5% annual reduction in sales after 10 years. The recent surge in the biologic product pipeline and R&D growth for biologics suggests that a faster rate of new product introduction, and therefore a higher rate of obsolescence (shorter product life cycles) may apply than that assumed in the *Nature* model. Currently, over 600 biologics are in development.[35] This low rate of product obsolescence further serves to potentially overstate the expected revenue stream from successful biologics. Including the effect of more robust brand-to-brand competition would produce longer required breakeven periods.

(3) ***Finally, the Nature model assumes that firms are able to utilize existing plants with no retrofitting costs.*** The *Nature* model assumes that product validation costs are the only costs required to produce successful biologic products. In actuality, many firms may face

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[35] The Pharmaceutical research and Manufacturers of America (PhRMA). Medicines in Development – Biotechnology 2008. PhRMA web site (online), http://www.phrma.org/images/110308%20biotech%202008.pdf (2008).

substantial upfront capital investment costs. The model may therefore understate expected costs of bringing a biologic product to market and, thus, understate expected breakeven periods.[36]

VIII. SOME FURTHER EXTENSIONS AND SENSITIVITY ANALYSIS OF THE *NATURE* MODEL

Data exclusivity periods should be established that are robust to alternative reasonable assumptions for contribution margin, cost of capital, biosimilar share, and brand price discounts in response to biosimilar entry. Brill relies on the following assumptions:

- Contribution margin of 60%
- Biotech cost of capital of 10%
- Biosimilar shares increasing from 10% in the first year to 35% by the fourth year of biosimilar entry
- Brand price discounts increasing from 20% in the first year to 40% by the fourth year of biosimilar entry.

This section presents the results of sensitivity analyses on a range of potential values for each of these key assumptions.

A. SENSITIVITY ANALYSES ON COST OF CAPITAL AND MARGIN ASSUMPTIONS

Table 2 presents the results of sensitivity analyses on breakeven period findings for different cost of capital and contribution margins, and also includes Brill's cost of capital and

[36] 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.

data exclusivity assumption for comparison. The breakeven periods are reported for data exclusivity periods of 7 years, 10 years, 12 years, 14 years, and 16 years. The results reflect the same biosimilar share and brand price erosion assumptions that Brill uses (i.e., a biosimilar share of 10% in the first year of biosimilar entry, increasing to 35% by year 4, and a 20% brand price discount in the first year of biosimilar entry increasing to 40% by year 4, reflecting a branded competition model). Results indicate that a data exclusivity period of 12 to 16 years is required for breakeven periods of less than 50 years, under reasonable assumptions.

The cost of capital and margin assumptions applied in the sensitivity analyses include:

- The best current estimate now available of the cost of capital for the biotechnology industry is 13.25%, as supported by Golec and Vernon (2007). Breakeven periods are estimated under cost of capital assumptions including the 11.5% and 12.5% assumptions from the *Nature* article, Golec and Vernon's finding of 13.25%, and a real cost of capital estimate of 14.1% based on Ibbotson's median three-factor Fama-French measure. As stated, the 11.5% and 12.5% assumptions are lower than the best current estimates for cost of capital in the biotechnology industry, and therefore would have the effect of understating breakeven periods.
- A contribution margin of 50% is reasonable based on large successful biotechnology companies. Half of the companies in the sample of very successful biotechnology companies used by Brill earn contribution margins of 50% or less. Furthermore, small biotechnology companies typically have margins that are substantially lower. As a result, 50% likely overstates the margin that would be earned by an average biotechnology company. The sensitivity of findings is tested by applying average contribution margins of 60%, 55%, 50%, 45%, and 40%.

The cost of capital and contribution margin sensitivities are reported relying on the same biosimilar share and brand price erosion assumptions that Brill implements (his interpretation of the CBO's assumptions in its cost estimate of S. 1695). In addition, sensitivities with respect to alternative biosimilar share and brand price discount assumptions are also calculated in the next section.

In general, results confirm the importance of a substantial data exclusivity period to R&D returns. Notably, with an exclusivity period of 7 years, the *only* combination of assumptions that yields a breakeven point of less than 50 years is the one used by Brill (i.e., a cost of capital of 10% and a contribution margin of 50% or lower). Even with a 12-year exclusivity period, reasonable breakeven periods are possible only under the more extreme assumptions (e.g., if the best current estimate of the cost of capital of 13.25% is assumed, breakeven is achieved only when the contribution margin assumption is 60%, and breakeven is achieved at 17 years).

Exhibits 4(a), 4(b) and 4(c) present the results for cumulative net present value over time for selected data exclusivity periods, assuming costs of capital of 11.5%, 12.5% and 13.25%, respectively, and a 50% average contribution margin. Exhibit 4(a) shows that the cumulative net present value of returns to the innovator approaches a value just above zero when a cost of capital of 11.5% is assumed and a 12-year exclusivity period is applied. The innovator fails to break even if a cost of capital of 12.5% is assumed under either a 12-or 14-year data exclusivity period (Exhibit 4(b)), and if a 13.25% cost of capital is assumed, the innovator does not break even with a 12-, 14-or even a 16-year data exclusivity period (Exhibit 4(c)).

Exhibits 5(a), 5(b) and 5(c) present the same sensitivities as in Exhibit 4 but assume a 55% average contribution margin. With the higher assumed contribution margin, the innovator would be able to break even with a 12 year data exclusivity period but only if the cost of capital

is 11.5% or 12.5% (Exhibits 5(a) and (b)). In this regard, breakeven is achieved for the combination of a 12.5% cost of capital and 12 year data exclusivity period in approximately 17 years (Exhibit 5(b)). Assuming instead the preferred Golec Vernon-derived 13.25% cost of capital, the innovator breaks even only with a 16-year data exclusivity period, but fails to do so with shorter exclusivity periods of 12 and 14 years (Exhibit 5(c)).

B. SENSITIVITY ANALYSES TO ALTERNATIVE BIOSIMILAR SHARE AND BRAND PRICE EROSION ASSUMPTIONS

1. Biosimilar Share and Brand Price Erosion Assumptions

In this section, we report alternative assumptions on biosimilar share and brand price erosion reported in the literature. We calculate the impact of some alternative assumptions on breakeven results in a series of sensitivity analyses.[37] Before presenting these calculations, as background, it is useful to review the CBO report assumptions, together with other studies that have considered the competitive effects of biosimilar entry.

Table 3 shows the peak market penetration and biosimilar price discount estimates from four recent studies. Each of these studies is focused on established biologic products that could experience biosimilar competition over the next several years. Most studies generally acknowledge that biosimilar penetration rates are expected to increase as markets evolve from a regulatory, scientific, and reimbursement perspective. Hence, these estimates tend to underestimate penetration rates for the products which are now in discovery and development. Peak biosimilar penetration rates reflected in various recent studies range from 35 to 60%, with

[37] All of the assumptions in the sensitivity analyses are guided by the existing literature, economic theory, and the judgements of the authors.

the CBO estimate being the most moderate. Some of these figures reflect biosimilar penetration rates only among the largest selling products, however, while the CBO estimate is described as a sales-weighted average. All of the studies are based on comparators that may be imperfect predictors of the future biosimilar market.

Table 3 also displays the corresponding assumptions on biosimilar price discounts relative to the pre-biosimilar entry price of branded products. In this case, the CBO estimate is generally consistent with other sources at least in terms of initial year price discounts. All of the studies shown expect discount rates to reach at least 25 percent over time, especially for larger-selling products where more entrants are expected.

In terms of the branded products' competitive response to biosimilar entry, only one of the sources in Table 3, Avalere, provides an initial estimate of expected branded product's price impacts. [38] In general the Avalere study predicts that the reference brand will decrease prices in response to biosimilar entry.[39] Economic theory suggests that a competitive price response on the part of the innovator is expected, where there is a small number of entrants in these markets.[40]

Given these considerations and possibilities, further sensitivity analyses appear warranted on biosimilar share and the brand's price response.

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[38] Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics, White Paper, Avalere Health, April, 2007 < http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf >, accessed December 20, 2008.

[39] Avalere has indicated they are refining their estimates on branded share and price impacts as new information becomes available.

[40] Grabowski, H., Ridley, D., and Schulman, K., "Entry and Competition in Generic Biologics," *Managerial and Decision Economics*, 2007, 28(4-5), pp. 439-451.

2. Results of Sensitivity Analyses

Table 4 presents the breakeven period findings for alternative assumptions on biosimilar share and brand price erosion. Specifically, we test the following brand share and price erosion assumptions:

- ***Biosimilar share*** is assumed to be 10% in the first year of entry regardless of scenario, but we test alternative steady-state biosimilar shares in year 4 of 25%, 35%, 45%, and 55%. The 35% assumption is consistent with Brill's assumptions; other values are associated with other recent estimates shown in Table 3.
- ***Brand price erosion*** is assumed under three scenarios: to be 0% in all years (i.e., no increase or decrease in real brand prices from the point of biosimilar entry); to be a 10% brand price decrease in year 1, increasing to a steady-state decrease of 25% by year 4; or to be a 20% decrease in year 1, increasing to a steady-state decrease of 40% in year 4, relative to real prices at the point of biosimilar entry.[41] The scenario that assumes brand price erosion increasing from 20% to 40% in the first four years is consistent with Brill's assumptions.

As shown in Table 4, a 10 year data exclusivity period is consistent with breakeven only in the extreme case where both the cost of capital and margin assumptions fall beyond the best baseline estimates.

All of the above described sensitivity analyses reflect a cost of capital of 13.25% and a contribution margin of 50%. The breakeven periods are reported for data exclusivity periods of

[41] Since over time nominal prices for biologics are expected to be adjusted for inflation and other factors, reductions have been reflected on a real, or inflation-adjusted, basis in the *Nature* model. Assuming no real price changes implies nominal price will increase only with inflation.

7 years, 10 years, 12 years, 14 years, and 16 years. As in the earlier sensitivity analyses, the results for these brand share and price erosion sensitivity analyses suggest that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period of time, under reasonable assumptions.

As a further sensitivity analysis, Table 5 presents results for similar calculations as those presented in Table 4, but assuming a lower cost of capital of 12.5% and a higher contribution margin of 55%. The results in Table 5 are likely to understate breakeven periods as the cost of capital is lower than the best estimate for biotechnology investments and the contribution margin is higher than for many biotechnology companies. Nevertheless, data exclusivity periods of less than 12 to 16 years are still associated with long, or no, breakeven period. For data exclusivity periods of 7 years, breakeven periods of less than 50 years only occur with no brand price discounts and limited biosimilar shares. For data exclusivity periods of 10 years, breakeven periods of less than 20 years only occur with no brand price discounts; and breakeven periods of less than 50 years occur with moderate brand price discounts (10% to 25%) and limited biosimilar shares.

The analysis presented by Brill and the sensitivity analyses that are presented in this paper are based on worldwide revenues, and it should be noted that these worldwide revenues will be affected by variation in data or market exclusivity periods worldwide. In a review of top selling biologic drugs, the U.S. market is by far the most significant, varying substantially depending on where the drug is in its life cycle.[42] As a result, because volume is a key driver,

[42] According to a December 12, 2008 telephone call with a Sanford C. Bernstein & Co. analyst, in 2008, U.S. sales as a percentage of world-wide sales for all tracked biologic products are expected to average

U.S. data exclusivity periods are likely to have the most significant impact on biologic revenues and investor decisions.

IX. SUMMARY AND CONCLUSIONS

Identifying an appropriate data exclusivity period for biologics is an important component of any bill meant to establish an abbreviated regulatory pathway for biosimilar entry. The data exclusivity period is an essential component in allowing investors to earn a market return on biotechnology investments. As a result, continued investment in biotechnology research, and the valuable new products that such investment will produce, is dependent upon the establishment of an appropriate data exclusivity period in conjunction with any legislation establishing an abbreviated biosimilar regulatory approval pathway.

Appropriately modifying the Nature article breakeven model to consider the effects of biosimilar entry on market shares and prices indicates that limiting the data exclusivity period to less than 12 to 16 years results in failure of the representative portfolio of biologics to break even within an extended period, under reasonable assumptions. An adequate exclusivity period is necessary to maintain incentives to invest in the development of innovative new biologic products.

This finding is in stark contrast to the seven-year data exclusivity period suggested by Brill and others, and reflects the correction of errors in Brill's application of the model and the sensitivity of Brill's results to small changes in the key assumptions.

66%. Danzon and Furukawa (2006) previously report that U.S. biologics spending represented 63% of the ten countries examined in 2005.

As discussed in the earlier *Nature* article, analyses of breakeven lifetimes, based on historical cost and revenue data, are only one guidepost for selecting appropriate data exclusivity periods. The future environment for biologic innovation may differ from the past in many important ways – including the cost of development, prices and sales revenue, and the intensity of competition from branded therapeutic alternatives and from biosimilars. Nevertheless, a substantial data exclusivity period also appears to be consistent with a few core principles and facts that were outlined in that article and the introduction to this paper:

- Biologic introductions have been among the most novel therapies directed at life threatening and disabling diseases and offer hope for many important unmet medical needs for thousands of patients.
- There is currently a rich pipeline of product candidates in discovery and development from a spectrum of small start-up firms to larger established entities. Most of this pipeline emanates from firms without marketed products whose investors are very sensitive to expected future returns and risks, as many product candidates never make it to market, and there is no guarantee that those that do will be successful. Even for larger firms, the risk and investment associated with biologics research and development is large.
- The nature of patent protection for biologic products necessitates a strong complementary data exclusivity form of protection.

Given the tremendous potential benefits to patient from new biologics, setting a sufficient data exclusivity period to maintain investment incentives under a range of reasonable assumptions about expected returns should be an important consideration.

Appendix – A Note on Brill's Computational Inconsistencies

The sales and price erosion assumptions that Brill relies upon require three modifications to the model presented in the *Nature* article based on the time of biosimilar entry:

(1) Brand biologic revenues must be reduced based on the assumed brand price discount in response to biosimilar entry, and according to the time path of assumed price discounting. This adjustment reflects the fact that even if the same number of units of the brand product are sold, those sales generate less revenue due to the price discount.

(2) The assumed profit margin earned by the brand biologic must be adjusted to reflect the fact that brand price discount results in a smaller margin. Moreover, in computing margins one also expects costs to decline given changes in output and sales. It is reasonable to assume that production and other costs will decline in proportion to output reductions.

(3) Brand biologic revenues must be reduced by the assumed share of sales that the biosimilar is assumed to capture, and according to the time path of assumed biosimilar penetration. This adjustment reflects the fact that fewer units of the brand may be sold following biosimilar entry. Similarly, non-R&D production costs must be adjusted proportionately.

Brill makes the second and third of these modifications, but fails to implement the first. As a result, he overstates the level of brand biologic revenues following biosimilar entry that would be implied by his assumptions.

As an example for purposes of illustration, assume the following set of facts, and perform the associated calculations:

- Assume brand revenues in absence of biosimilar entry are $1,000.
- Further assume that with biosimilar entry, the biosimilar captures 35% of unit sales and the brand reduces its price by 40%.
- Brand revenues for determining cash flow in the presence of biosimilar entry are then $390, calculated as: $1,000 x (1 – 35%) x (1 – 40%) = $390, to which one would then apply the appropriate profit margin. Assuming that after taking account of the price changes, the appropriate margin in this illustrative example of 50% , the total margin contribution would be $195.

Brill's calculation error would instead yield the incorrect figure of $650 in brand revenues, calculated as $1,000 x (1 – 35%), and $325 in total margin contribution, again assuming a 50% margin.[43]

[43] The margin is assumed to not be affected by the share penetration of the biosimilar; that is, the share of unit sales captured by the biosimilar is assumed to reduce costs and revenues proportionally. Conversely, the brand price decline is assumed to reduce revenues but not costs, resulting in a lower margin.

Table 1

Cost of Capital Estimates for the Biotechnology Industry

Source	Sector/Group	Model	Cost of Capital	
			Nominal	Real
Golec & Vernon (2007)	Biotech industry-wide	Fama-French	16.75%	13.25%
Ibbotson [1]	Median	Fama-French	17.49%	14.07%
Grossman (2003) [2]	Large drug companies	CAPM	15.70%	12.33%
	Biotech with ≥1 drug approved	CAPM	18.70%	15.24%
	Biotech drugs in phase II or III trials	CAPM	27.40%	23.69%
	Medium-sized publicly traded	CAPM	19%	14%
Myers and Shyam-Sunder (1995)	Small firms	CAPM		16%
Grabowski (2008) [3]	Biotech industry-wide	CAPM		11.5%-12.5%

Notes:

Highlighted cells indicate calculated estimates of real cost of capital based on reported nominal values and assuming a 3% annual inflation rate.

[1] The reported number is for the WACC; Ibbotson includes 73 firms in SIC 2836.

[2] Grossman (2003) relies on a nominal risk free rate of 6.8% and a risk premium of 8.6%.

[3] Grabowski (2008) estimates are based on DiMasi and Grabowski (2007).

Table 2
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Seven-and Ten-Year Data Exclusivity Periods

7-Year Data Exclusivity Period:

Cost of Capital \ Contribution Margin	60%	55%	50%	45%	40%
10%	13.5	>50	>50	>50	>50
11.5%	>50	>50	>50	>50	>50
12.5%	>50	>50	>50	>50	>50
13.25%	>50	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

10-Year Data Exclusivity Period:

Cost of Capital \ Contribution Margin	60%	55%	50%	45%	40%
11.5%	10.6	14.5	>50	>50	>50
12.5%	17.4	>50	>50	>50	>50
13.25%	>50	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

Sources:

[1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.

[2] Real costs of capital:

11.5% and 12.5% - Grabowski (2008)

13.25% - Golec and Vernon (2007) and Vernon (2008)

14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.

[2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 2 (Continued)
Breakeven Periods in Years

Alternative Cost of Capital and Contributions Margin Assumptions
Twelve-, Fourteen-, and Sixteen-Year Data Exclusivity Periods

12-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	14.2	>50	>50
12.5%	11.9	17.3	>50	>50	>50
13.25%	17.1	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

14-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	12.9	>50	>50
12.5%	11.9	13.5	>50	>50	>50
13.25%	13.6	>50	>50	>50	>50
14.1%	>50	>50	>50	>50	>50

16-Year Data Exclusivity Period:

Cost of Capital	Contribution Margin 60%	55%	50%	45%	40%
11.5%	10.4	11.4	12.9	15.4	>50
12.5%	11.9	13.5	16.3	>50	>50
13.25%	13.6	16.4	>50	>50	>50
14.1%	18.9	>50	>50	>50	>50

Sources:

[1] Calculations based on the *Nature* model and Brill's interpretation of CBO assumptions for market share and price decline.

[2] Real costs of capital:

11.5% and 12.5% - Grabowski (2008)

13.25% - Golec and Vernon (2007) and Vernon (2008)

14.1% - Ibbotson median Fama-French WACC for SIC 2836, assuming 3% inflation.

Notes:

[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.

[2] Cells highlighted in pink reflect no breakeven within a 50 year period.

Table 3

Biosimilar Assumptions
In Several Recent Studies

Source [1]	Peak Biosimilar Penetration Rate	Basis	Biosimilar Price Discount (Relative to Pre-Entry Brand Price)
CBO (2008)	10% (year 1) to 35% (year 4)	Similar market situations	20% (year 1) to 40% (year 4)
Grabowski, et. al. (2007)	10 - 45%	Higher estimates correspond to complex small molecules	10% - 30% (year 1)
Express Scripts (2007)	49%	Therapeutic alternatives	25% (year 1)
Avalere Health (2007) [2]	60%[2]	Average small molecule generic drug penetration rates	20% (year 1) to 51% (year 3)

Notes:

1. Congressional Budget Office, Cost Estimate: S.1695 Biologics Price Competition and Innovation Act of 2007, June 25, 2008.
   Grabowski, H.,Cockburn, I., Long, G. and Mortimer, R. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," Duke University, Department of Economics Working Paper, August, 2007.
   Miller, S., and Houts, J., "Potential Savings of Biogenerics in the United States," whitepaper, Express Scripts, February 2007.
   Ahlstrom, A., et al., "Modeling Federal Cost Savings from Follow-On Biologics," whitepaper, Avalere Health, April, 2007.
2. This estimate is for largest selling products. Avalere Health is conducting further analysis.

Table 4
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
13.25% Cost of Capital and 50% Contribution Margin

Biosimilar Share (year 4 and beyond)	Brand Price Discount (Year 1 to Year 4 and beyond)		
	No Price Decline	10% year 1 to 25% year 4+	20% year 1 to 40% year 4+
7-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
10-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
12-Year Data Exclusivity Period:			
25%	>50	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
14-Year Data Exclusivity Period:			
25%	30.3	>50	>50
35%	>50	>50	>50
45%	>50	>50	>50
55%	>50	>50	>50
16-Year Data Exclusivity Period:			
25%	25.9	>50	>50
35%	28.7	>50	>50
45%	37.7	>50	>50
55%	>50	>50	>50

Sources:
[1] Calculations based on the *Nature* model.
[2] Real costs of capital 13.25% - Golec and Vernon (2007) and Vernon (2008)

Notes:
[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
[2] Cells highlighted in pink reflect no breakeven within a 50 year period.
[3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Table 5
Breakeven Periods in Years

Sensitivity of Findings to Price and Share Assumptions
12.5% Cost of Capital and 55% Contribution Margin

Biosimilar Share (year 4 and beyond)	Brand Price Discount (Year 1 to Year 4 and beyond)		
	No Price Decline	**10% year 1 to 25% year 4+**	**20% year 1 to 40% year 4+**
7-Year Data Exclusivity Period:			
25%	16.9	>50	>50
35%	19.6	>50	>50
45%	27.2	>50	>50
55%	>50	>50	>50
10-Year Data Exclusivity Period:			
25%	14.5	20.7	>50
35%	14.9	24.2	>50
45%	15.5	42.7	>50
55%	16.4	>50	>50
12-Year Data Exclusivity Period:			
25%	13.7	14.4	16.7
35%	13.7	14.5	17.3
45%	13.7	14.5	18.1
55%	13.8	14.6	19.4
14-Year Data Exclusivity Period:			
25%	13.5	13.5	13.5
35%	13.5	13.5	13.5
45%	13.5	13.5	13.5
55%	13.5	13.5	13.5
16-Year Data Exclusivity Period:			
25%	13.5	13.5	13.5
35%	13.5	13.5	13.5
45%	13.5	13.5	13.5
55%	13.5	13.5	13.5

Sources:
[1] Calculations based on the *Nature* model.
[2] Real costs of capital 12.5% - Grabowski (2008)

Notes:
[1] Cells highlighted in yellow reflect a breakeven period of under 50 years.
[2] Cells highlighted in pink reflect no breakeven within a 50 year period.
[3] Biosimilar share is assumed to be 10% in year 1 for all scenarios.

Exhibit 1

Cumulative Net Present Value of Cash Flows for Representative Biotech Drug

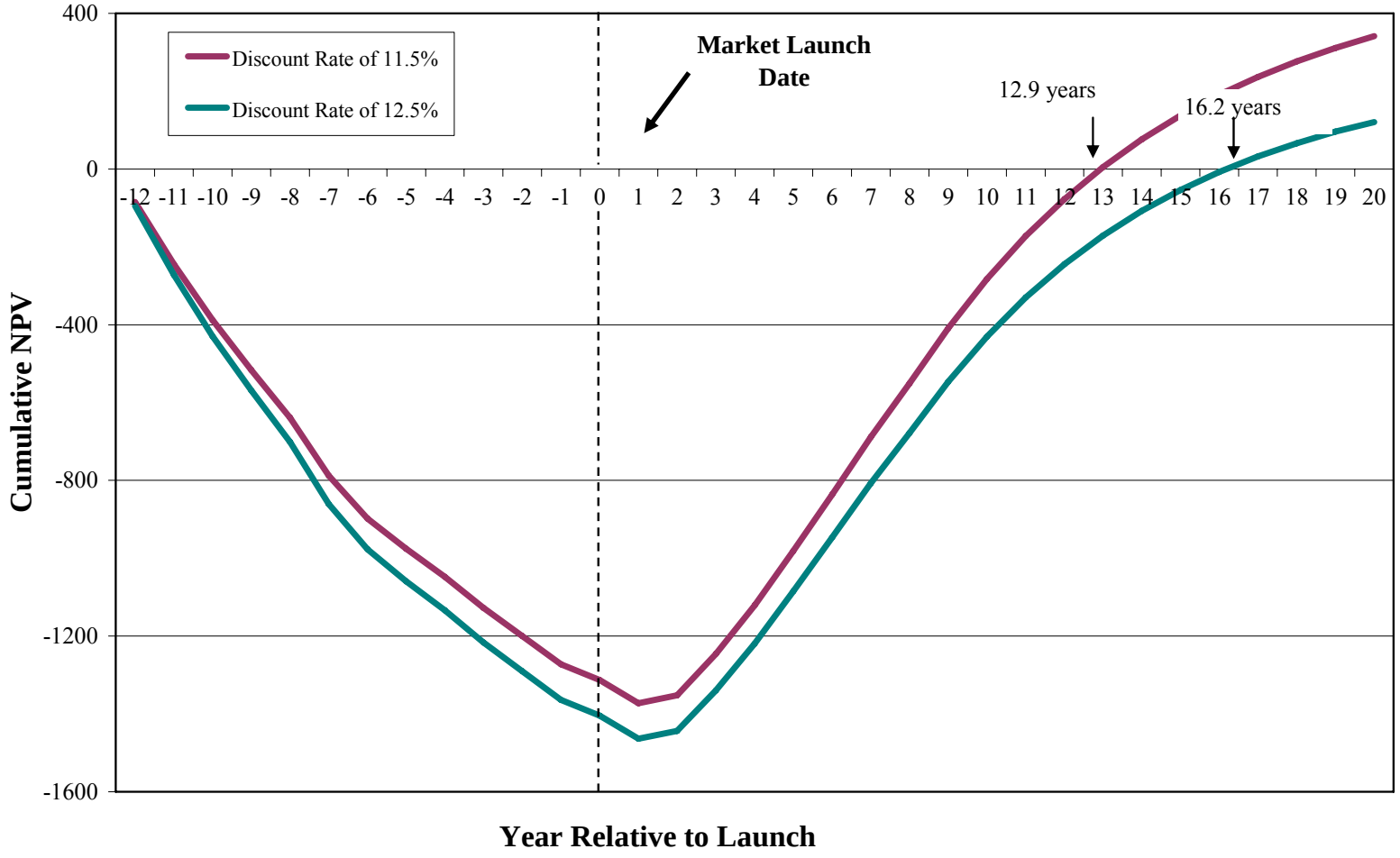
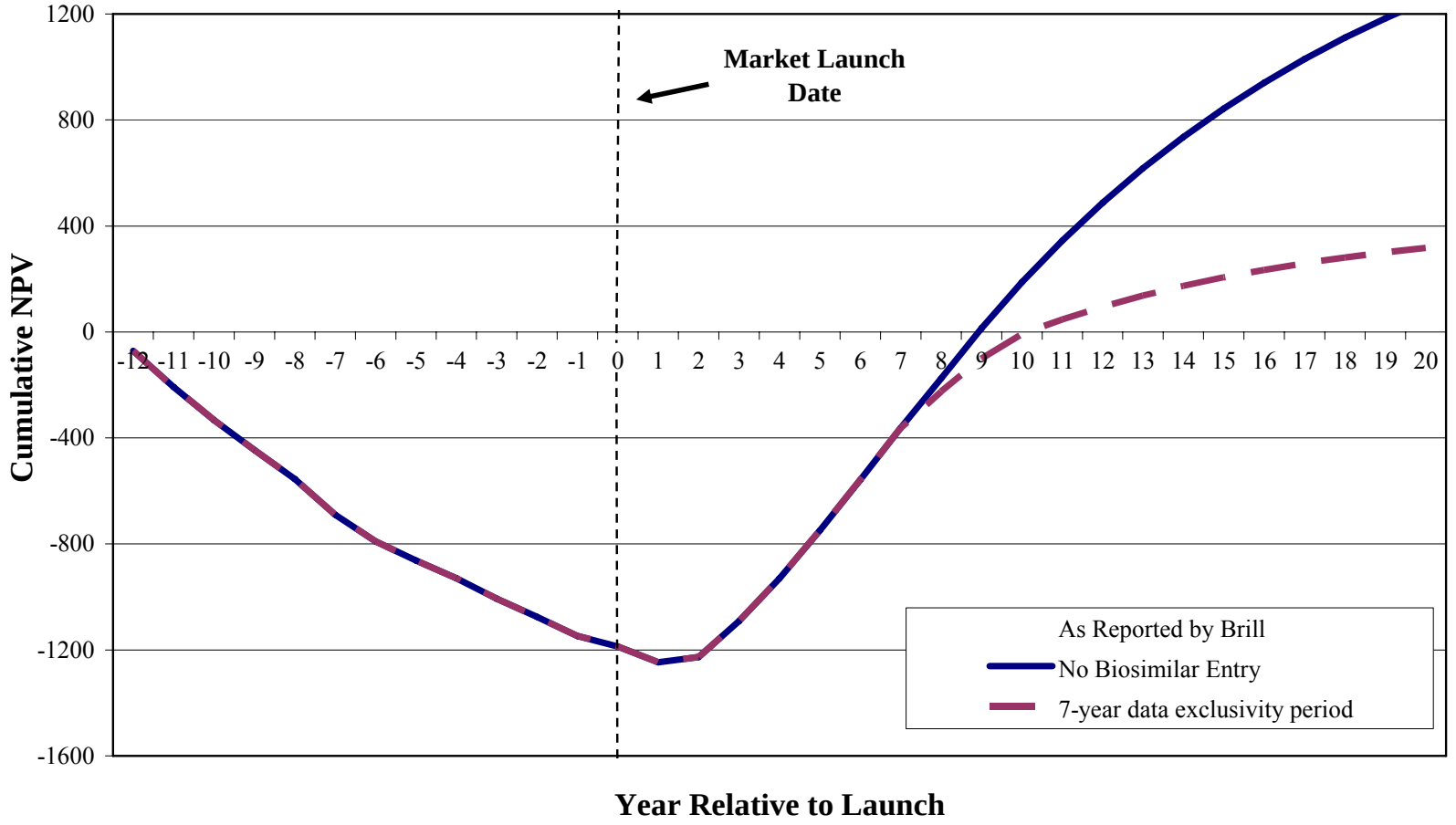


Exhibit 2

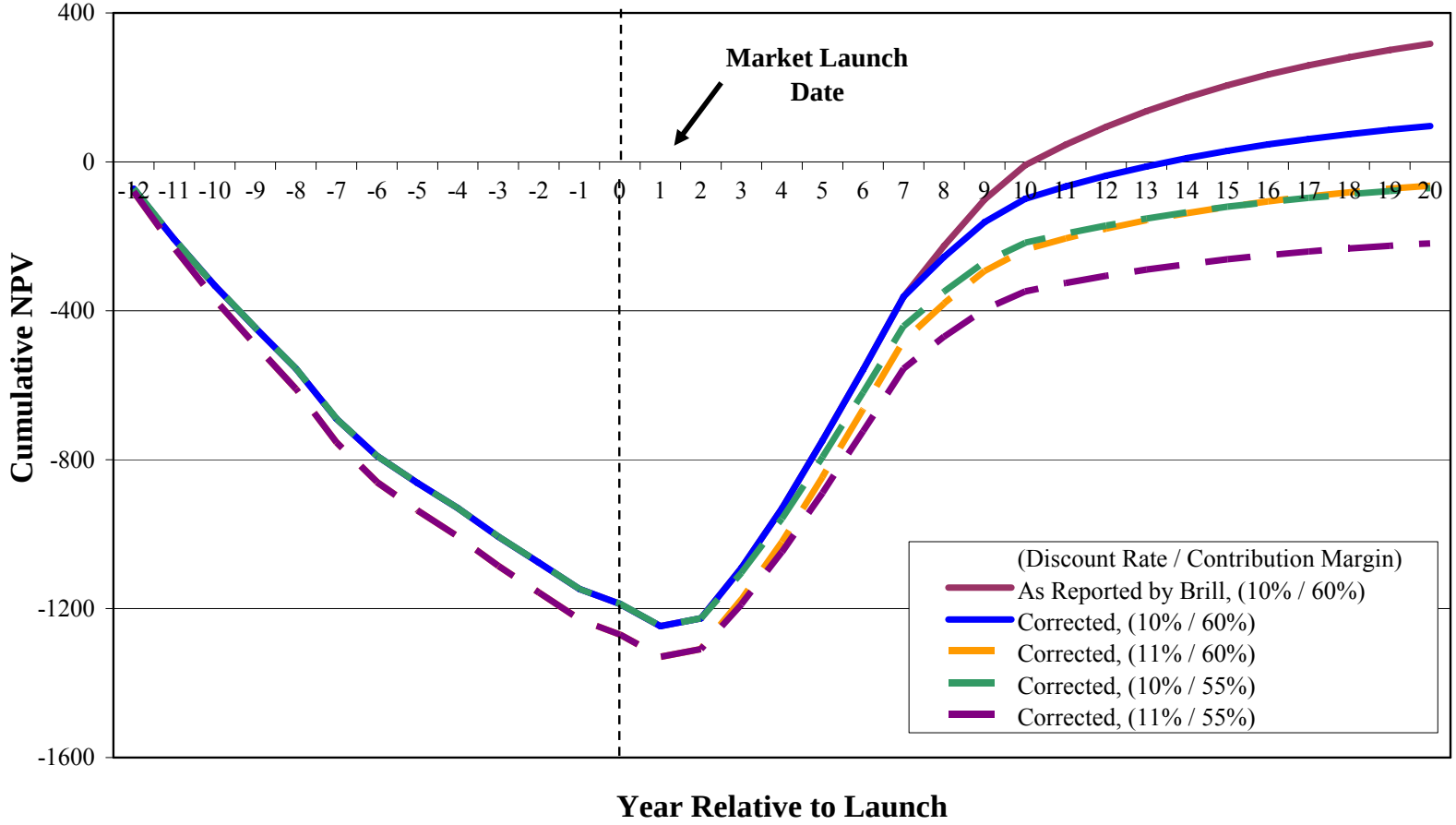
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions.

Exhibit 3

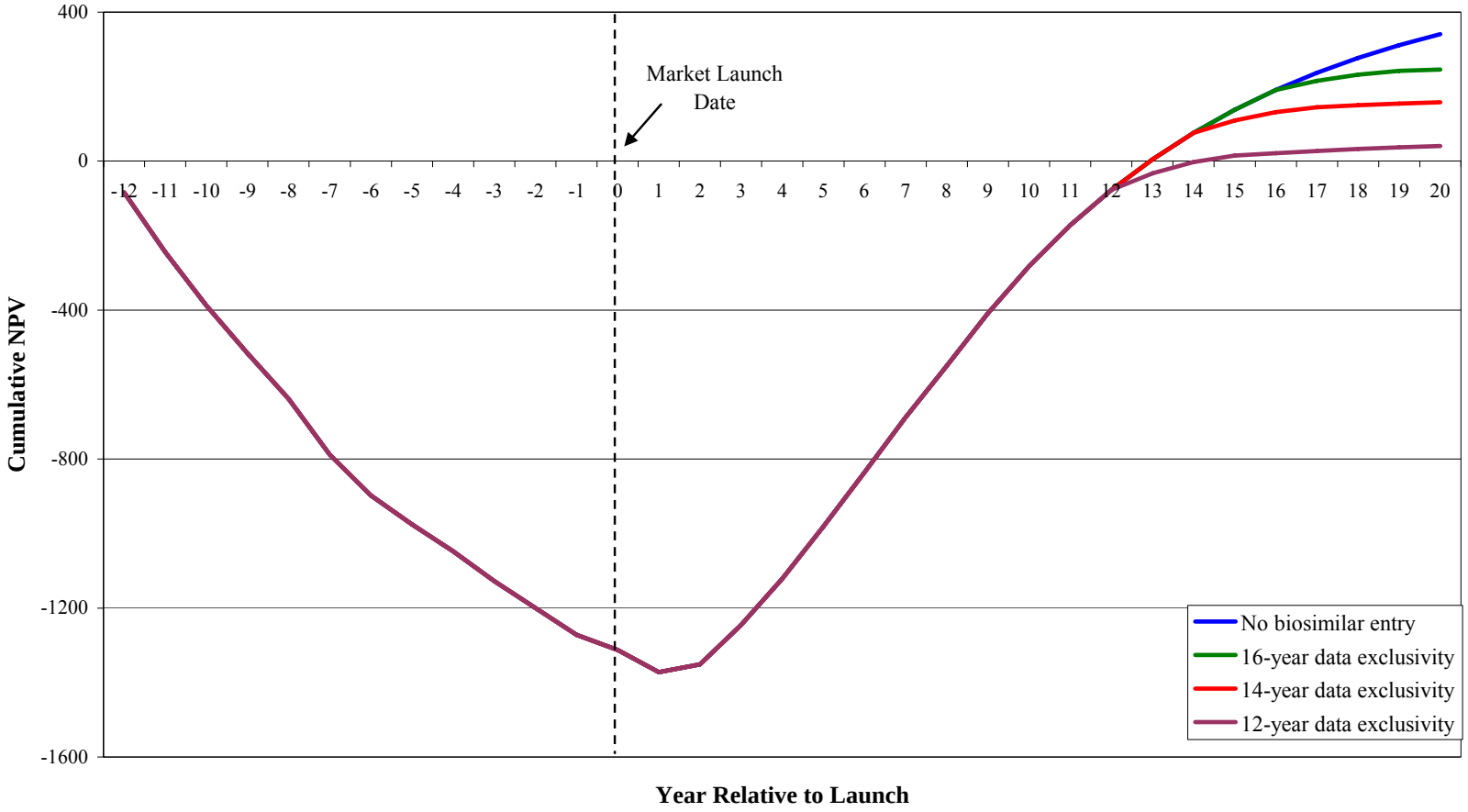
Cumulative Net Present Value of Cash Flows for Representative Biotech Drug
Brill Representation



Note: All scenarios maintain Brill's assumption of a 7-year data exclusivity period and biosimilar share and innovator price discounts, based on his interpretation of CBO share and price assumptions. The innovator does not breakeven within 50 years with either an 11% discount rate, a 55% long-run contribution margin, or both.

Exhibit 4(a)

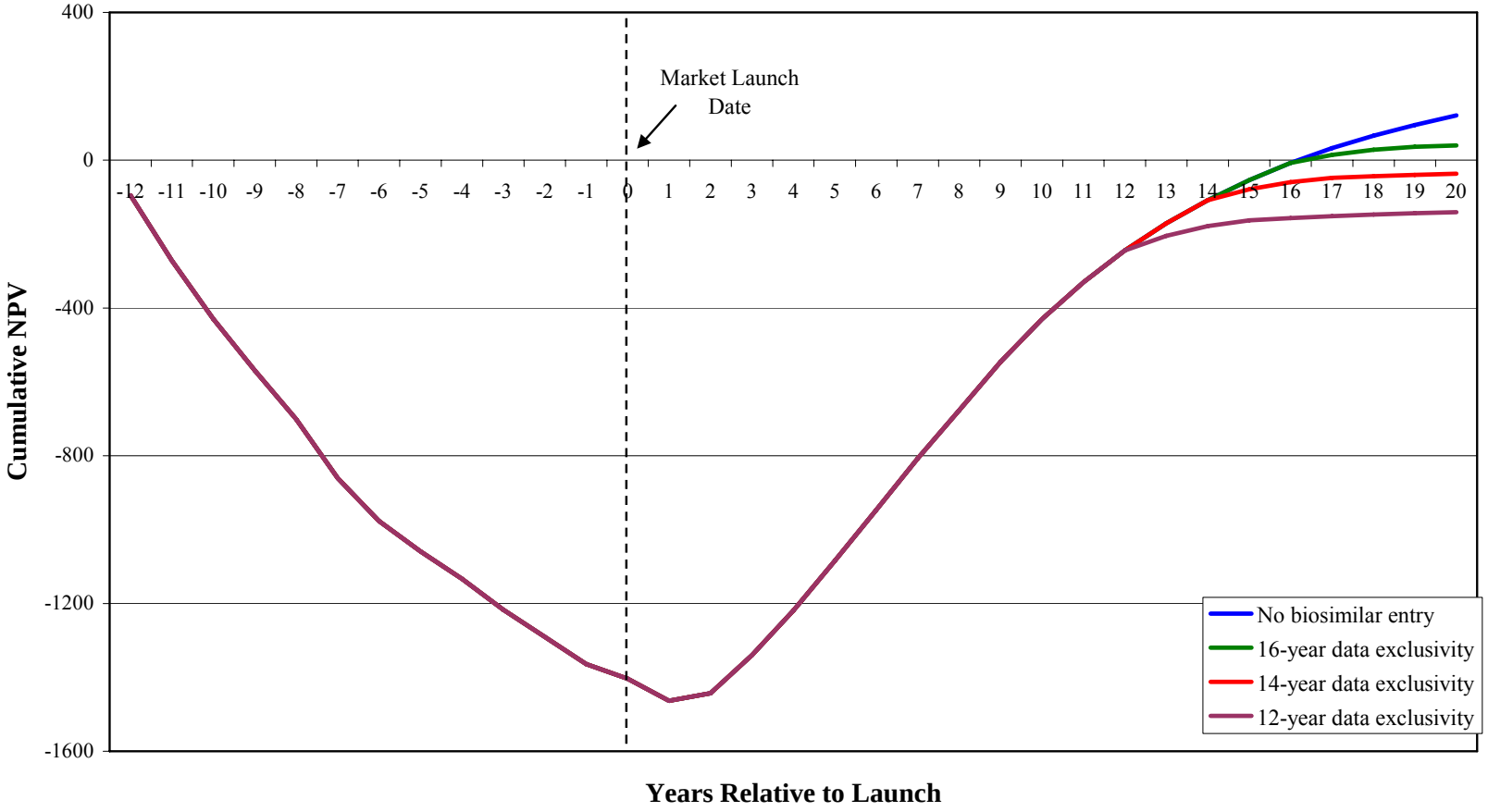
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 11.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 4(b)

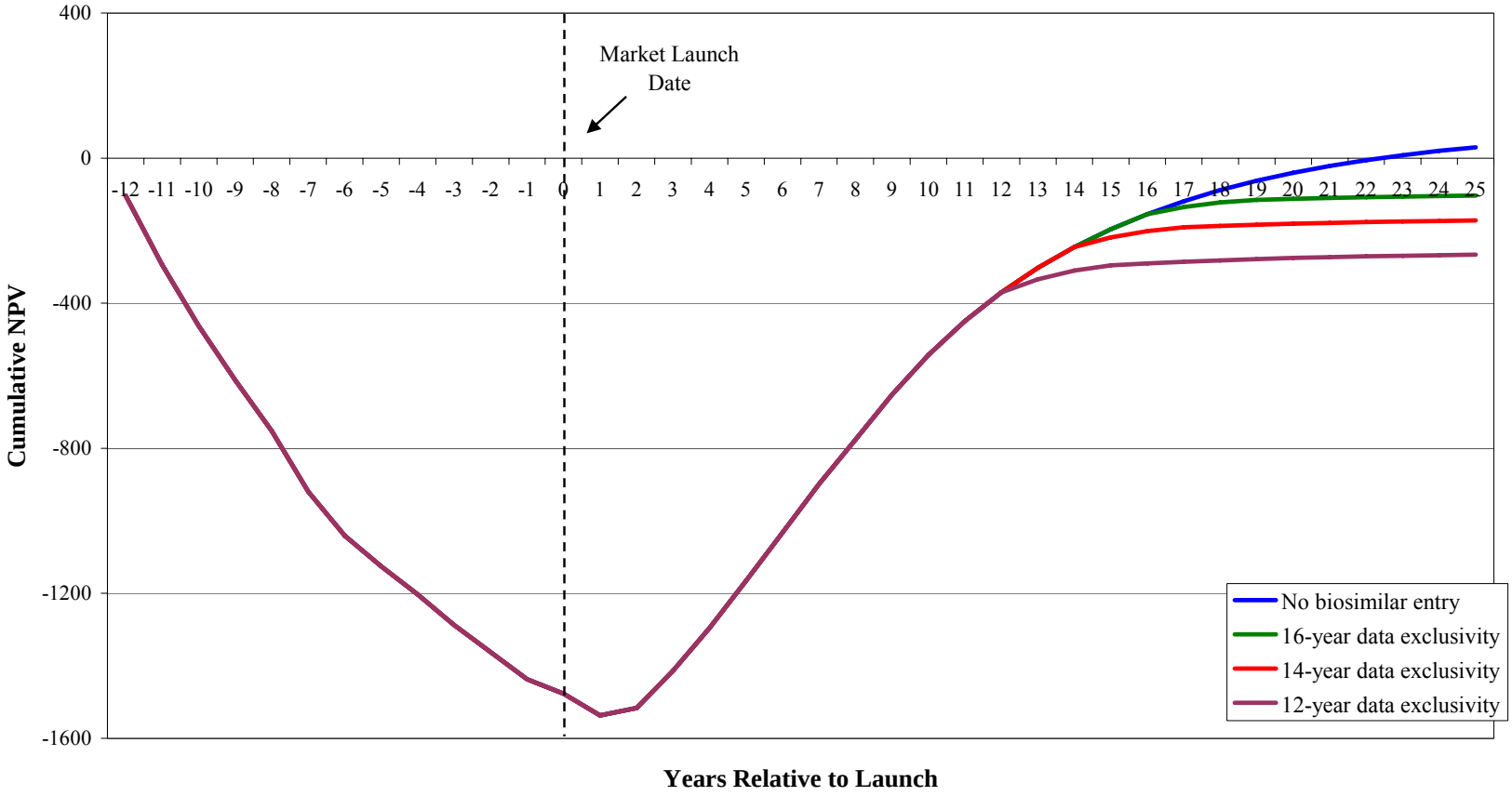
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 12.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 4(c)

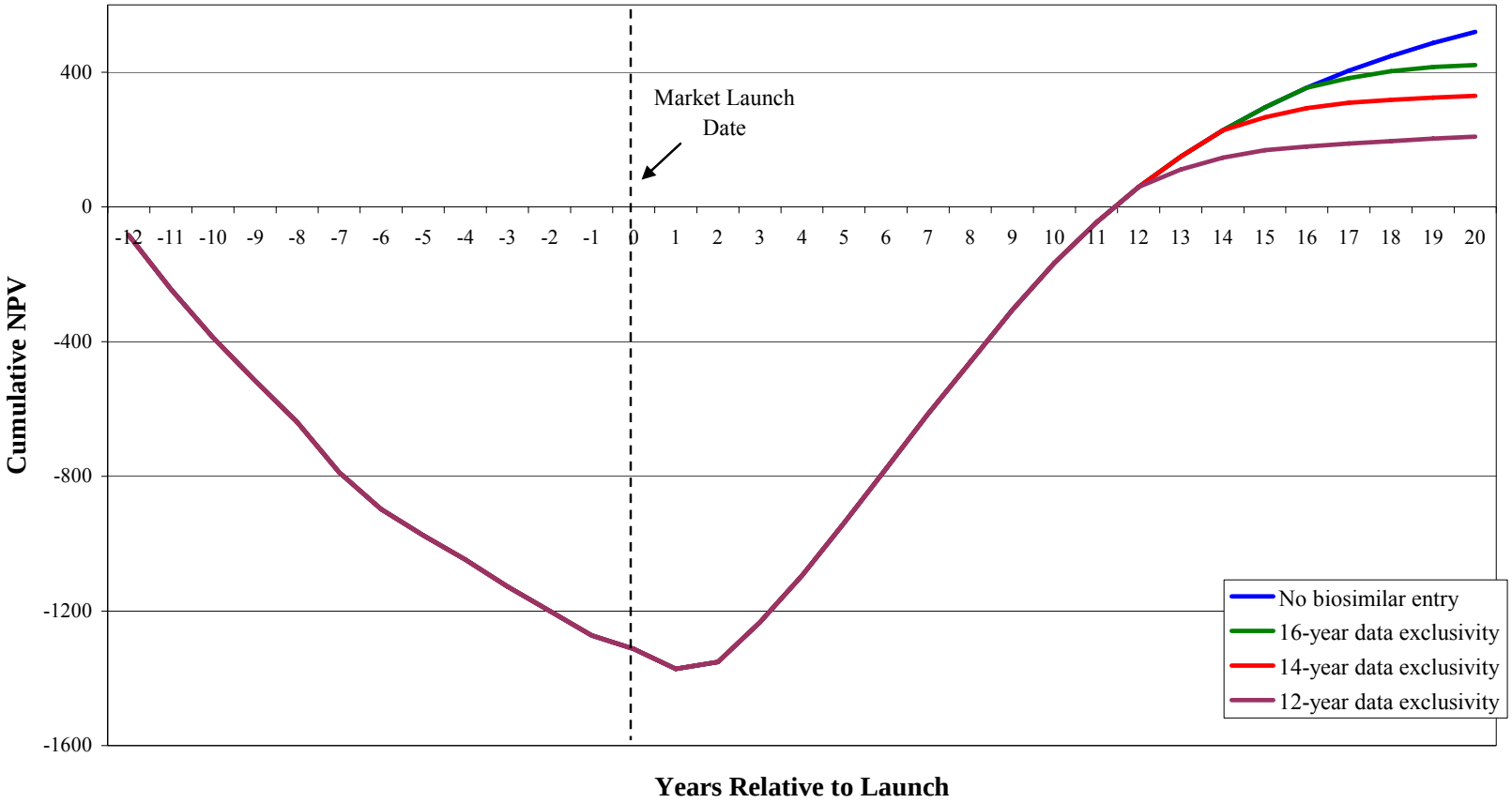
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (50% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(a)

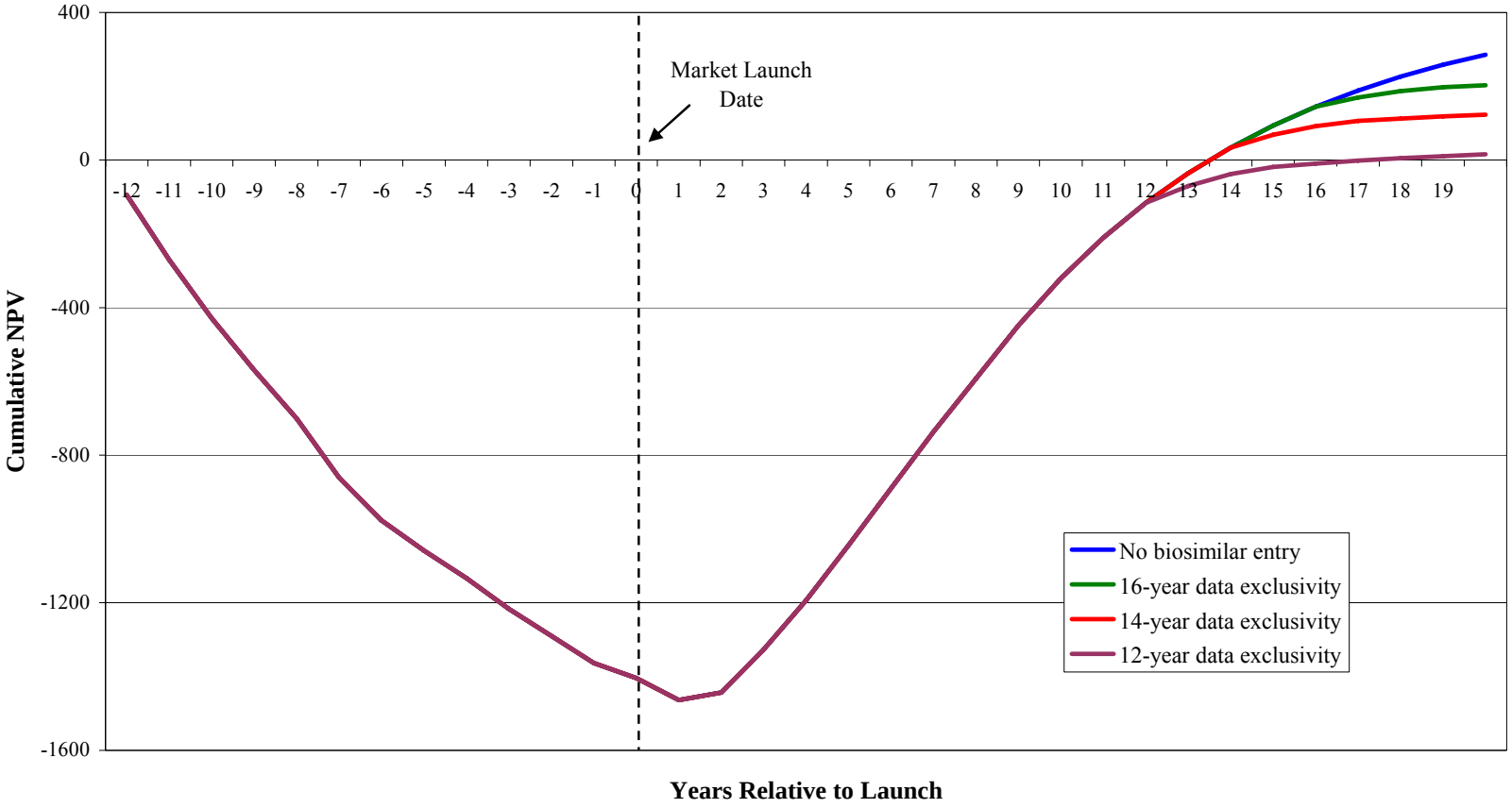
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 11.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(b)

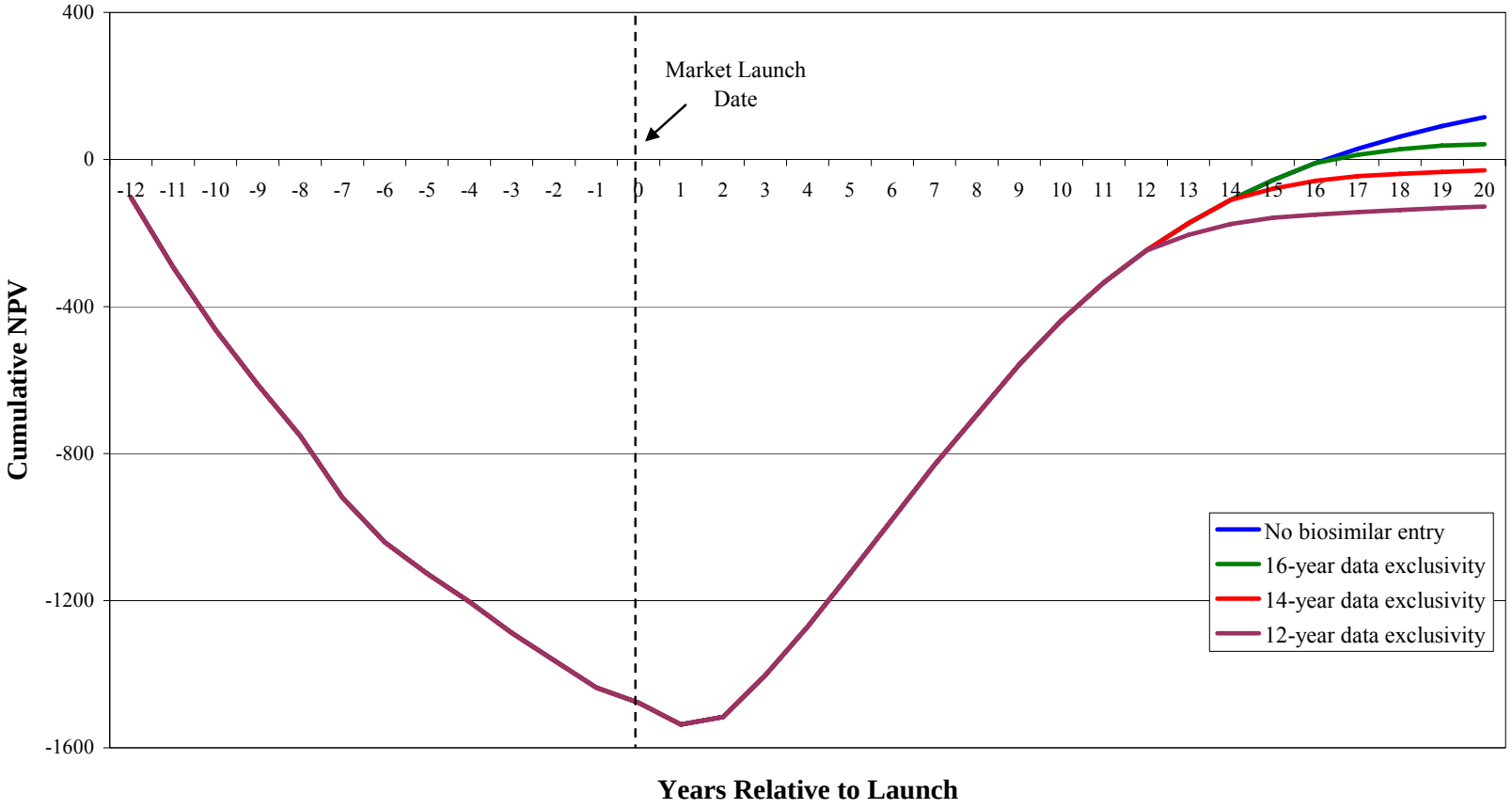
Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 12.5% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.

Exhibit 5(c)

Sensitivity Analysis of Cumulative NPV of Cash Flows for Representative Biotech Drug (55% Average Contribution Margin, 13.25% Cost of Capital)



Note: Biosimilar is assumed to capture 10% share in first year, increasing to 35% by year 4. Innovator price is assumed to decline 20% in first year of biosimilar entry, and 40% by year 4. Assumptions reflect Brill's interpretation of CBO assumptions.