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Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901

Identifying an appropriate data exclusivity period for biologics is a critical component of any bill establishing an abbreviated regulatory pathway for biosimilar market entry. The data exclusivity period is designed to recognize the long, costly, and risky process involved in gaining FDA approval for an innovative product. Investment in biotechnology research, and the valuable new therapies produced, will be strongly influenced by the establishment of an appropriate data exclusivity period in conjunction with the legislation establishing an accelerated biosimilar FDA approval pathway.

Data exclusivity periods are an important complement to patent protection. They are an "insurance policy", ensuring a market period during which investors have the opportunity to recoup the costs of their investments, even if patents have expired during this lengthy process, or can be circumvented or "invented around". Because data exclusivity periods extend from the date of product approval, and run concurrently with any remaining patent term protections, they

only provide incremental protection when the remaining effective patent length at the time of product launch is shorter than the period of data exclusivity.

In an article recently published in *Nature Reviews Drug Discovery*, (Grabowski, 2008; henceforth referred to as the *Nature* article) I develop a model for identifying the length of time it would take for a representative portfolio of biologics to recover the discounted costs of drug development (the "breakeven" period), including an industry-wide cost of capital.[1] I find that for a typical biologic the breakeven period is 12.9 to 16.2 years. In a recent white paper (available online at http://www.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf), I have modified the *Nature* article breakeven model to consider biosimilar entry, and to incorporate updated analysis on important assumptions in the model.[2] This modified model indicates that limiting the data exclusivity period to less than 12 to 16 years results in the failure of the representative portfolio to break even within an extended period. This result is consistent with a wide range of reasonable assumptions on cost of capital and contribution margins for biotechnology companies.

The Appendix to this letter contains a discussion of the framework of the model developed in the white paper and compares it to the general framework presented by FTC staff in session 2 of the "FTC Roundtable on Follow-on Biologic Drugs: Framework For Competition and Continued Innovation," on November 21, 2008.

My finding that a substantial data exclusivity period is necessary to maintain R&D incentives is in contrast to the seven-year data exclusivity period recommended by others recently,[3] and reflects the correction of problems in the application by others of the *Nature* model to estimate the impact of data exclusivity period limits on the breakeven period, of problems with the selection of non-representative values for key assumptions, and to the sensitivity of results to more reasonable values for key assumptions.

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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] Grabowski, H., Long, G., Mortimer, M. "Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques, "Duke University Department of Economics Working Paper, No. 2008-10, December 2008.
[3] Brill, A., "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," unpublished manuscript, November 2008.

For instance, I find four primary flaws in a recent analysis by Alex Brill:

(1) Brill's calculations include problems in correctly incorporating assumptions made by the Congressional Budget Office in its scoring of follow-on biologics bill S. 1695 into my *Nature* model; correcting these computational problems changes his results as reported and do not support a seven year data exclusivity period.[4]

(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 commonly used industry metrics.

(3) Brill's assumption for the average contribution margin relies on results from six of the most successful biotech firms, fails to consider the high degree of variability in profits even among this small, upwardly biased sample and puts inordinate weights on the two most successful biotech firms.

(4) Brill ignores countervailing assumptions already reflected in the *Nature* article breakeven analysis (such as excluding the lowest quintile of sales from the sample), which have the effect of producing estimated breakeven periods that are shorter than likely actual breakeven periods. Even for larger firms, the risk and investment associated with research and development is large.

As discussed in my *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:

- 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 candidates in discovery and development from a spectrum of small start-up firms to larger established entities. Most of this pipeline

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

emanates from firms without marketed products whose investors are very sensitive to levels of expected future returns and risks.

- The potential to "invent around" patents for biologic products necessitates a strong complementary data exclusivity form of protection.

The potential cost of setting too short a data exclusivity period would be lower investment in R&D, and consequently a lower probability of developing and marketing important new therapies for patients. Given the tremendous potential value of these new therapies, setting a sufficient data exclusivity period to maintain investment incentives should be an important consideration in the evolving legislation to create an abbreviated pathway for biosimilars.

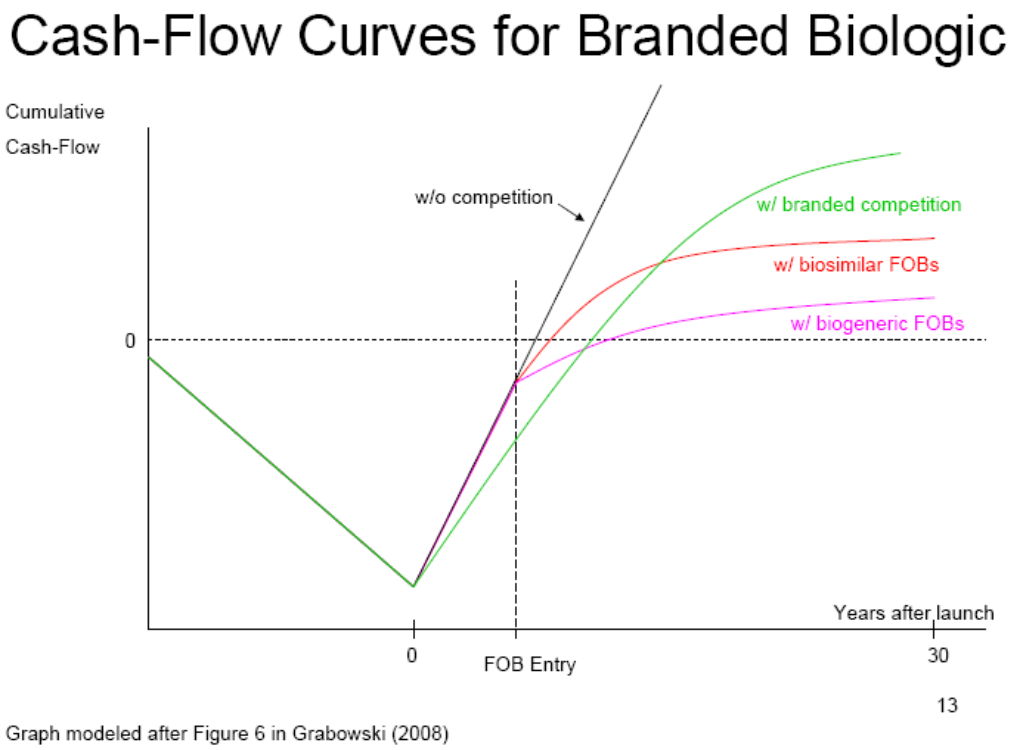
Sincerely,

Henry G. Grabowski
Professor of Economics

Appendix

At the "FTC Roundtable on Follow-on Biologic Drugs: Framework for Competition and Continued Innovation," on November 21, 2008, FTC staff presented a graph meant to generally reflect my Nature article model but allowing for various forms of biosimilar and other competition. Figure 1 below contains the graph the FTC presented:

Figure 1



Graph modeled after Figure 6 in Grabowski (2008)

While the FTC graph follows much of the spirit and form of the Nature model analysis, there are a few distinctions that are important. My Nature article essentially corresponds to the line in Figure 1 that represents "w/ branded competition." Specifically, in the Nature article I assume that, starting ten years following launch of the innovator biologic, revenues will begin to decline due to obsolescence at a rate of 3.5% per year. The introduction of new branded biologics by competitors (branded competition with other "first generation" and "second generation" products) is a likely source of this obsolescence.

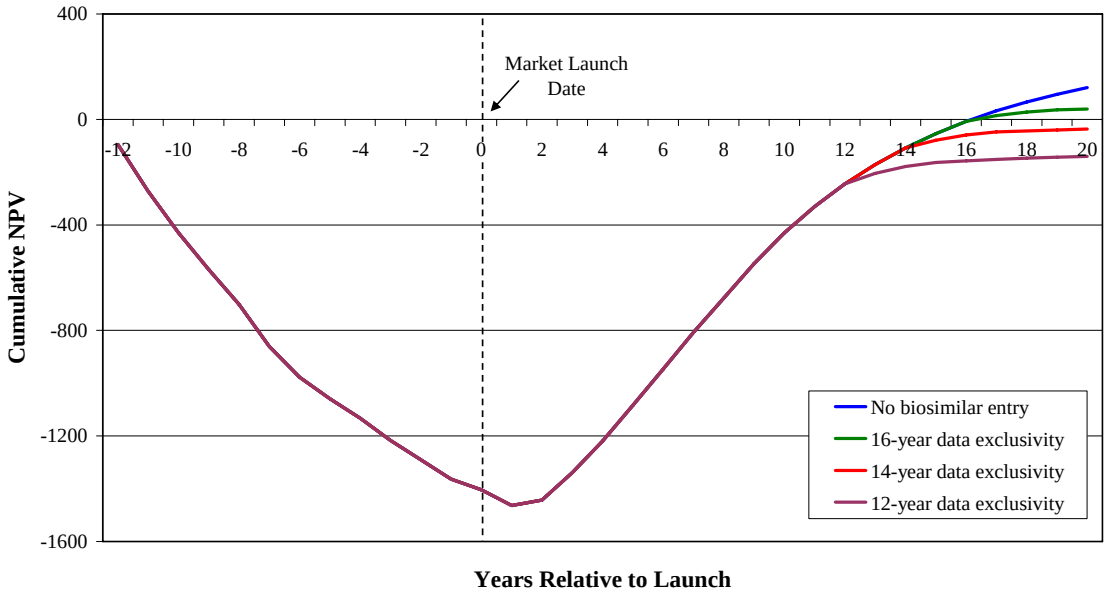
I never envision an outcome corresponding to the line representing "w/o competition" as brand biologics are currently facing, and will continue to face significant competition from other branded biologics, along with other forms of treatment. I also do not model generic competition for biologics, or the line corresponding to "w/biogeneric FOBs" in Figure 1. This is because, in the near-to-medium-term foreseeable future, scientific and other limitations will preclude the FDA from approving FOBs under a classification of "biogeneric" similar to the AB-rated classification of generic small molecule drugs, which may be fully substitutable for reference brand products at the pharmacy level. This is consistent with the remarks of FDA scientific expert Dr. Rachel Behrman at the November 21, 2008 Roundtable discussion and with other senior FDA experts in previous forums. A similar distinction is noted in the current European framework, which refers to "biosimilars" and not to "biogenerics."

In a recent white paper I do modify my Nature article model to consider biosimilar entry, or the line corresponding to "w/biosimilar FOBs" in Figure 1. One correction to the FTC representation in Figure 1 is that both biosimilar and branded competition would occur. That is, at the time of "FOB entry," the line in Figure 1 corresponding to "w/biosimilar FOBs" should meet with the "w/branded competition" line, not the "w/o competition" line. This would result in a substantial shift down in the line representing biosimilar entry in the FTC graph.

Figure 2 below presents a graph from my recent white paper (available online at http://www.econ.duke.edu/Papers/PDF/Data_Exclusivity_Periods_for_Biologics.pdf) depicting cumulative net present value cash flows for a typical biologic under illustrative assumptions for profitability and cost of capital and under alternative data exclusivity periods.

Figure 2

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.

Based on the assumptions relied on for Figure 2, *only a data exclusivity period of 16 years is associated with a breakeven period of less than 50 years following launch*. The white paper presents sensitivity analyses for a wide range of assumptions demonstrating that limiting the data exclusivity period to less than 12 to 16 years results in the failure of the representative portfolio to breakeven within an extended period under reasonable assumptions.