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March 17, 2009

Biosimilars, Data Exclusivity, and the Incentives for Innovation: Response to Grabowski

In a recent article, “Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff’s White Paper,” February 2009, Henry Grabowski and Joseph DiMasi strongly criticize my paper “Stimulating Innovation in the Biologics Industry: A Balanced Approach to Marketing Exclusivity, September 2008. I respond here to these authors’ criticism.

As background, let me summarize the points in my paper.

- New and improved medications are critical to Americans’ health and welfare. Today, the most significant, but also most expensive, advances in medications come in *biologics*. Biologics are protein-based, rather than chemical-based, medicines. The new drugs can be of tremendous help in alleviating, if not curing, a wide range of heartbreaking diseases. But their prices are remarkably high, leaving millions of uninsured and underinsured Americans unable to access their use.
- Four bills introduced in the past Congress and likely to be reintroduced in this Congress propose to do for biologic medications what the 1984 landmark Hatch-Waxman bill did for chemical medications, namely promote a thriving industry in generics, which would dramatically lower the prices of these super-expensive, but also highly-effective medicines. Yet three of the four bills contain *exclusivity* provisions that seriously undermine the bills’ own objectives. These provisions constitute uncontested grants of monopoly rights by government fiat – something that runs far afield of traditional U.S. patent policy. Worse still, these grants of exclusivity would substantially extend the duration of monopoly protection of brand biologic medicines and, thereby, materially delay the arrival of low-cost generic alternatives.
- Exclusivity comes in two types – *data exclusivity* and *approval* exclusivity. Data exclusivity refers to a period of time during which a potential generic supplier of a brand drug is prohibited from filing for an ANDA, where the application makes use of/reference to the safety and other relevant data assembled by the innovator in the course of obtaining its own FDA approval. Approval exclusivity is a period of time during which a generic drug supplier can file for FDA approval using the data generated by the innovator, but cannot receive approval.

- Data exclusivity precludes potential generic manufacturers from any physical contact, including visual contact, of the full safety record assembled by the innovator. This data is viewed by the innovator as its property. But it's critical to understand that the proper economic interpretation of ownership rights is of these data is that they are public property. The reason for this interpretation is simple – the public is paying for the innovation, including all knowledge associated with its generation, via the conveyance of monopoly rights to the innovator for an extended, but finite period of time. I.e., the public pays the innovator for its discovery by agreeing to the innovator's time-limited price gauging.
- Conveyances of exclusive marketing rights to brand biologic companies not only exclude competitors from entering the market with low-cost alternatives for extended periods of time. They also exclude other innovators from building, in a timely manner, on the stock of prior knowledge, much of which was accumulated at public expense.
- New medications that alleviate or cure terrible disease are such remarkable gifts that we are all naturally reluctant to do anything that impairs the prospects of their inventors. But the new drugs of today are not those of tomorrow. And today's inventors are generally not tomorrow's. The reason is clear. Today's inventors have strong incentives to milk their discoveries, not make new ones whose arrival on the market would undermine their existing profits.
- Numerous papers in the economics literature on invention and monopoly protection stress that competition, not protection, is the true source of innovation and that over-extending monopoly protection can be counterproductive. It may do little or nothing to incentivize new discovery and simply delay when the next discovery comes on board. Thus, exclusivity provisions rights can lead to less, not more, innovation over time.
- Hatch-Waxman has proved remarkably successful in balancing the interests of brand drug companies and the American public. Give this success and the absence of any material differences between the biologics and chemical medical industries indicative of longer monopoly protection, Congress should consider limiting biologics exclusivity provisions to those contained in Hatch-Waxman.

Summary of my response: Grabowski and DiMasi attack my work and build their case for exceptionally long periods of exclusivity with misleading, disingenuous, and factually incorrect assertions.

On page 3, they claim that “Data exclusivity is ... complementary to patent protection,” when, in fact, it is no different from extra patent protection in terms of its main effect, namely extending the period of state-sanctioned monopoly protection of brand biologics.

On page 3, they claim that “Data exclusivity recognizes the long and costly investment that a firm must undertake ... to demonstrate a product’s safety and efficacy to the FDA.” In fact, no independent panel of economists has conveyed this high purpose on data exclusivity. Data exclusivity was introduced under Hatch-Waxman to provide transition relief to brand companies. As I showed in my paper, data exclusivity under Hatch-Waxman is sufficiently short as to make it essentially irrelevant to the market for new chemical medications. Hence, the proper statement is that data exclusivity was introduced back in 1984 as a grandfather clause -- to appease particular brand companies with existing products, but to have no real impact over time. The provision in Hatch-Waxman that recognizes the time needed to demonstrate safety and obtain FDA approval is *patent restoration*, which restores to a new chemical entity’s patent life half of the time spent in clinical testing and all of the time spent securing FDA approval, up to a maximum of five years. The amount of patent restoration is also subject to a ceiling; total patent life beyond FDA approval cannot exceed 14 years. So there is recognition in Hatch-Waxman of the time needed to prove safety and efficacy, but that recognition comes via patent restoration, which, incidentally, would apply to biologics even under the 2008 Hatch-Schumer Bill, which provided no data or approval exclusivity.

On page 3, the authors claim that “biopharmaceuticals have longer lags between patent filing and market launch compared to other research-intensive industries.” But as Grabowski has, himself, shown, the average development time for new biological entities is only 7.4 months longer than that for new chemical entities.¹ This hardly justifies providing up to 9 years of additional monopoly protection compare with Hatch-Waxman.

On page 3, they claim that “data exclusivity does not provide an innovator with either a monopoly or marketing exclusivity from competitors with therapeutic alternatives,” and that my equation of data exclusivity with monopoly protection and marketing exclusivity is, thus, “conceptually flawed.” This legal parsing intentionally misreads my meaning. I never claimed that data and approval exclusivity would eliminate all competition of all kinds for existing medications and that no new drug innovations would ever arise to compete directly or indirectly with an existing innovation. What I claimed, based on the facts, is that data plus approval exclusivity of up to 14 years could easily extend the duration of monopoly protection for biologics by 30 percent relative to the duration of protection afforded chemical-based

¹ Grabowski, Henry. "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery*. Volume 7, June 2008.

medications and 50 percent relative to the duration of protection afforded all other inventions. In using the term “monopoly protection,” I was clearly referring to preventing competitors from bringing to market a generic alternative to a brand biologic based on knowledge paid for by the public in the form of granting the brand company a temporally monopoly, which permits prices of biologics to vastly exceed their marginal production costs. So data exclusivity certainly does provide monopoly/marketing exclusivity from generic competitors offering bio similar alternatives.

On page 3, they claim that “... data exclusivity does not produce disincentives for innovators to make improvements or advances in their products.” This statement runs directly counter to essentially all the theoretical literature on such incentives, beginning with Kenneth Arrow’s seminal tract on the topic.² The disincentive is clear. Improvements and advances can undermine sales of existing products and since they come at a cost, they may not be undertaken. Competitors don’t have this built-in disincentive to innovate. This is not to imply that innovators have no incentive to innovate or that no one tries to compete around patents. Nor does this imply that monopoly protection is unnecessary and can never be too short. It’s necessary, and it can be far too short. But it can also be far too long, which appears to be the clear outcome of the data and approval biologics exclusivity provisions being advocated by Grabowski and DiMasi.

On page 4, the authors warn that rapid entry of imitators using an abbreviated filing could deter innovation and that such rapid entry results from “... the potential of biosimilar firms to gain most of the associated benefits from the increase in market size without incurring any of the R&D costs for the additional clinical trials.” The language here is as loaded as it is off base. In fact generic companies are not using for free the findings paid for by innovators. They are applying knowledge fully purchased by we the public in the form of letting innovators charge us what often appears to be outrageous prices for extended periods of time. Once the monopoly period has passed, the innovators are no longer the owners of their inventions. At this point, ownership rights revert to the public that paid for the invention and the public is then free to do with its property as it sees fit. And the way it sees fit is to arrange for qualified producers to deliver the discovery’s production in a competitive market, i.e., at marginal cost. Once monopoly protection has expired, all producers, including the innovator, himself, are “imitators” insofar as they are all doing the same thing, namely using knowledge developed years in the past to produce and sell the public’s purchased discovery at least cost.

On page 5 the authors claim that my concerns about evergreening are overstated and that “none of the bills introduced in 2004 provided additional data exclusivity times for minor changes such as new dosage strengths.” I’m glad to hear that the bills contain no explicit authorization of evergreening and that the authors are confident that evergreening would not

² Arrow, Kenneth J., “Economic Welfare and the Allocation of Resources for Invention,” Rand Corporation working paper P-1856-RC, December 15, 1959.

materialize during the many extra years they envision protecting brand biologics. But no one would expect the legislation to endorse evergreening, and I don't take their assurances that it wouldn't happen as reassuring. What we know from the world of chemical medications is that evergreening is a standard business practice of brand companies. This is why googleing everygreening results in 55 pages of entries about the problem. No legislation can foresee what will be determined as "minor changes" by regulators who are being hard pressed by monopolists to treat their product improvements as fundamental and deserving of years more protection.

On page 5 the authors claim that longer monopoly protection won't delay innovators from bringing their products to market because they have plenty of reason to want to bring their products to market early. I agree there are incentives in place for innovators to want to bring their products to market early. But doing so comes at a cost. As soon as you lower the marginal cost of delay, you provide more incentive for delay. This is what the bills with extensive data and approval exclusivity do; they incentivize delay. Indeed, as I showed, the bills reward greater delay with longer exclusivity.

On page 6 the authors claim that I made significant errors on the data exclusivity provisions of certain bills and that I make implausible assumptions about the length of time the FDA will take to approve biogenerics. My "error" identified on page 21 of their paper is that the bills with extensive data exclusivity, permit generic companies to file for FDA approval prior to the elapsing of the data exclusivity period. But being able to file an application, i.e., being able to mail the FDA some paperwork, is not remotely the point. The real issue is whether biogenerics can file effective applications for biosimilars without developing the drug from scratch; i.e., without forcing society to pay twice, thrice, or many more times over to acquire the same knowledge. Data exclusivity has real bite. The authors would not otherwise have written, under the auspices of the brand biologic companies, a 27 page reply to my study. The real bite is that innovator companies are able to prevent biogenerics from viewing tens of thousands of pages of documents, paid for and ultimately owned by the public, that are essential for demonstrating bioequivalence.

Re the implausible assumptions about the length of time needed to achieve FDA approval once the data are made available, let me quote from Robert Shapiro's recent study³:

While small-molecule drugs are generally manufactured in labs using chemical synthesis, the production of most biologics requires cell-culture facilities that can take three to five years to build, using materials 20 to 100 times more expensive than those for facilities used to manufacture molecule based drugs, at a cost of \$200 million or more. These factors also could extend the process of approval for many biogenerics, with one analyst estimating that developing a generic biologic, producing it and gaining FDA approval could take five to eight years: One to two

³ Shapiro, Robert J. "The Potential American Market for Generic Biological Treatments and the Associated Cost Savings." www.insmed.com. February 2008.

years to carry out the cell biology, one year for process analysis, two to four years for new clinical trials and one year for final approval.

Better yet, let me quote from Grabowski's Congressional testimony⁴:

Estimates from generic firms indicate that development times for a follow-on biological are likely to range from five to eight years. This estimate is based on one to two years for cell biology, one year for process analysis, two to four years for clinical trials, and one year for approval. By comparison, generic drugs seldom require more than a few years to do bioequivalence tests and gain regulatory approval.

Next the authors, on page 6, criticize my failure to determine, via economic analysis, the appropriate length of the exclusivity period. This is a valid criticism, but developing such a framework would require going far beyond the partial equilibrium present value calculations presented in Grabowski (2008)⁵ and criticized in Brill (2008)⁶. A general equilibrium analysis would necessarily incorporate the gains to society of innovation and the cost of paying above marginal cost for new discoveries during the period of monopoly protection. It would also incorporate the supply of innovators and innovations and recognize that there is no absolute "break even" length of protection short of which innovation will not occur. Instead, the variables included in Grabowski's present value calculations would endogenously change as a function of changes in government monopoly protection policy. As the many papers in the literature modeling patent protection make clear, there is no agreed-upon framework of analysis. Hence, any theoretically appropriate derivation of the optimal length of protection would necessarily be highly arbitrary and stylized. Consequently, I felt it best to consider the issue of the duration of monopoly protection for biologics by reference to an economically very similar problem, namely the appropriate duration of monopoly protection for chemical medications. The fact that Hatch-Waxman has proved so successful in stimulating innovation in chemical entities while also fostering a highly successful generics industry seems to me quite telling. So does the fact that there are very few differences between biologic and chemical medications suggestive of different lengths of monopoly protection and those that exist suggest strongly that biologics should receive less protection. I refer here primarily to the extra time required for biogenerics to prove safety and efficacy, obtain FDA approval, and bring their products to market.

Having said the above re "break even" analysis, let me point out that Grabowski's break even analysis is conceptually flawed, even from a partial equilibrium perspective. The break even date he generates is the date the project's cumulated cash flows turn positive; it's not the potentially much shorter date for the cessation of monopoly protection that's needed to make the project break even over its entire lifetime. To see this point, take a very simple example in which the inflation rate as well as the interest

⁴ Statement by Henry G. Grabowski, Ph.D., Duke University, House Oversight and Government Reform Committee March 26, 2007; <http://oversight.house.gov/documents/20070416132526.pdf>

⁵ Grabowski, Henry G., "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition," *Nature Reviews Drug Discovery. Advance Online Publication*, 12, May 2008.

⁶ Brill, Alex M., "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," November 2008.

rate (discount rate) are zero and consider a project to develop a new biologic that costs \$50 million per year for 8 years, at which point it becomes FDA approved and earns, absent generic competition, \$40 million per year for the next 20 years. Grabowski would argue that this project's break even date is 10 years after FDA approval because at that point the \$400 million in cumulated revenues equal the \$400 in cumulated costs. But over the life of this product, revenues will outstrip costs by \$400 million. So the term "break even" is terribly misleading.

The real question begging an answer here is what is the earliest date at which generic competition can begin without making the lifetime returns from this project negative. This requires specifying what happens to revenues when generic competitors enter the market. Assume, for example, that generics were able to cut revenues for the innovator in half – to \$15 million per year. In this case, letting generics compete 10 years after FDA years would leave the project generating cost of \$400 million over the first 8 years, revenues of \$400 million over the first ten years after FDA approval, and revenues of \$150 million over the 10 years subsequent to entry by the generics. Now the project nets \$150 million. To get the project to really break even, we need to shorten the length of monopoly protection to 4 years. Now there is \$160 million during the 4 monopoly years plus \$240 million (\$15 million per year times 16 years) for the remaining 20-year life of the drug. So Grabowski's methodology is coming up with 10 years for the break even period in this case, when the correct number is 4 years.

On page 7 the authors cite my failure to acknowledge that biological patents are more easily challenged and invented around. The authors offer no proof to this effect, but their point, on the hypothetical that it is correct, bears little connection to the issue at hand. The issue at hand is how long to protect biologics for which protection is actually effective. Moreover, as the economics literature makes clear, too much protection will invite would-be-competitors to innovate around existing patents. This is particularly the case if innovating around is relatively easy, as the authors allege.

On page 8, the authors claim that data exclusivity provides an insurance policy on the patent system. The insurance is against the risk that the innovation will be innovated around. As I pointed out in my paper, the risk to biologics that is relevant is the riskiness of the biologics industry, not of any single product or firm, whether incorporated or not. And as I showed, biologic pharmaceuticals, based on the standard beta risk measure, is a less risky industry than is chemical pharmaceuticals. Hence, if it is insurance we are trying to provide, it should be provided to chemical compounds, not biologics. But the lesson from chemical compounds is that providing very limited and, ultimately, irrelevant data exclusivity works just fine in motivating more R&D, more patent applications, and more patent grants.

On pages 9 through 11, the authors extol the tremendous advances achieved in biologics. They suggest that I am unaware of these advances even though I cite them repeatedly in my paper starting in the second sentence.

On page 12 the authors claim that data exclusivity does not prevent firms from building on the prior stock of knowledge in a timely manner. I beg to differ. Data exclusivity prevents would-be biogenerics from gaining access for years to thousands of pages of findings concerning testing results, efficacy, manufacturing and safety procedures, etc. Yes, patents are in the public domain. But the data is of very

considerable importance with respect to permitting biogenerics to develop and receive approval of their biosimilar products. But the key issue here is using the initial innovation to produce the next innovation, i.e., to have the baton passed to the next runner in a reasonable amount of time so as not to slow down the race. Company X can read at the patent office about company K's discovery of Y, but if it takes company X 29 years to be able to use discovery Y to produce discovery Z, discovery Z will take a very long time to materialize. And yes, company X can potentially license discovery Y from company K to make discovery Z. But if discovery Z undermines company K's profits on the sale of Y, this license agreement may never arise. There is not, therefore, "a fundamental misunderstanding" on this issue on my part as the authors allege.

On page 14, the authors claim that there is no evidence that revenues are much higher relative to costs in biologics than in pharmaceuticals. Even though the available data make precise revenue and cost comparisons difficult, there is quite striking evidence that biologics are more profitable at the margin than chemical medications. First, biologics sell, on average, at a price that is 22 times higher than the average price per dose of chemicals. Second, biologics is a growth industry and growth industries are those that are most profitable.

On page 16 the authors question my assertion, based on beta findings, that biologics are less risky than chemicals on an industry basis. They claim in response that the cost of capital should be based on a weighted average of the cost of debt and equity finance. This is arguable, but would not, in any case, change the fact that the cost of capital is lower for biologic than for chemical pharmaceuticals. Next they claim that Fama-French models beat CAPM models for making risk adjustments. This is also debatable, but, in any case, the authors provide no comparison based on Fama-French modeling that biologics are more risky than chemicals. Their final point is that many biotech firms are small and aren't traded. This is true of the chemical medication industry as well, but has no direct bearing on overall industry risk.

Between pages 17 and 21 the authors make a number of points that appear to me to have no bearing on my main conclusion that Hatch-Waxman worked exceptionally well for chemical medications and can be expected to do the same for biologic medications.

On page 21 the authors reveal my key "error," which they claim is my failure to realize that biogenerics can do all their filing with the FDA and testing during the period of data exclusivity. But this assertion is simply preposterous given that generic firms would not have access during this period to the thousands of pages of documents which are essential to produce a biosimilar without starting from scratch.

To conclude, I appreciate professors Grabowski's and DiMasi's analysis of my work, but feel it is almost entirely off target.