Biosimilars, Data Exclusivity, and the Incentives for Innovation: A Critique of Kotlikoff's White Paper

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Authors:

Henry Grabowski
Professor of Economics and Director of the Program in Pharmaceuticals and Health Economics
Duke University
grabow@econ.duke.edu
Corresponding Author

Joseph DiMasi
Director of Economic Analysis
Tufts Center for the Study of Drug Development
Tufts University
joseph.dimasi@tufts.edu

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I. INTRODUCTION

Congress is expected to consider legislation for an abbreviated pathway for biosimilar versions of branded biologics, (biosimilars are also referred to in the literature as follow-on biologics [FOBs]). In the United States, most biologics are regulated through the Public Health Service Act (PHSA). At present, the PHSA does not have an abbreviated pathway for biosimilars analogous to that which exists for chemical entities through the 1984 *Drug Price Competition and Patent Term Restoration Act* (Hatch-Waxman Act). Under Hatch-Waxman, an abbreviated filing allows a manufacturer to rely in whole or part on the innovator's data on safety and efficacy in order to encourage low cost entry and increase price competition. Generic drugs must meet the same compendial standard as the reference product on strength, quality, purity and identity. The manufacturer must also demonstrate that the generic drug is bioequivalent, that is, that there is no significant difference in the rate and extent of absorption of the active ingredient. As the Food and Drug Administration (FDA) and others have indicated, it is not likely that biosimilars will be able to meet the standard of being identical to the reference brand that is the established standard for chemical entities by Hatch-Waxman [1] (Woodcock, 2007). However, particular entities may be similar enough to receive an abbreviated pathway under the enabling legislation and regulations that would be developed by the FDA for biosimilars.

Five different legislative bills were introduced in the previous Congress that would provide for an abbreviated regulatory approval pathway for biosimilars. While it is unclear whether these same bills will be introduced in 2009, an important dimension of any new

[1] 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."

legislation will be the provisions around a data exclusivity period. The provisions in the bills introduced in the previous Congress varied from establishing zero to fourteen years of data exclusivity. Data exclusivity is an important form of intellectual property protection that is complementary to patent protection. Specifically, data exclusivity is the period of time after FDA approval of the innovator's brand before a biosimilar can enter with an abbreviated filing. Data exclusivity recognizes the long and costly investment that a firm must undertake after patents are filed to demonstrate a product's safety and efficacy to the FDA. This is unique to products that need to obtain pre-market approval from a federal agency. With the lengthy clinical development and regulatory review periods, biopharmaceuticals have longer lags between patent filing and market launch compared to other research-intensive industries.

II. KOTLIKOFF'S REPORT ON DATA EXCLUSIVITY

In a recent report, Professor Larry Kotlikoff (2008) criticizes the data exclusivity provisions in three of the bills considered by Congress in 2008 and argues that they would lead to excessive intellectual property protection. In particular, he argues that data exclusivity periods of twelve to fourteen years would inhibit both innovative performance as well as price competition. From a policy perspective, he advocates a relatively short data exclusivity period like the five-year period in the 1984 Hatch-Waxman Act.

In this paper we analyze Kotlikoff's claims regarding data exclusivity and show that they are subject to a number of problems and conceptual flaws. We highlight here some of the key points of our critique.

a. Throughout his report, Kotlikoff equates data exclusively with monopoly protection and marketing exclusivity. However, data exclusivity does not provide an innovator with either a

monopoly or marketing exclusivity from competitors with therapeutic alternatives. Rather, data exclusivity is a much more limited form of intellectual property protection for innovators. As noted, it is the period of time before FOB firms can enter the market relying on the innovator's data with an abbreviated filing. In the case of human growth hormone, for example, there are currently six different manufacturers with multiple product offerings, and only one became available through an abbreviated filing.[2]

b. Contrary to Kotlikoff's claims, data exclusivity does not produce disincentives for innovators to make improvements or advances in their products. Biologicals are characterized by vigorous competition across innovative firms with respect to the introduction of therapeutic alternatives and advances (Calfee, 2008). An innovative firm cannot simply rely on the status quo in the face of this dynamic competition from other innovative firms. Furthermore, it is the risk of rapid entry from imitators using an abbreviated filing that could deter a firm from making research and development (R&D) investments in new indications post-approval. This 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. New indications are an important source of innovative advances in biologics. Some prominent examples include Intron-A, initially approved for hairy cell leukemia and subsequently for hepatitis C; Enbrel, first approved for rheumatoid arthritis and later for psoriasis; and Avastin,

[2] Given that human growth hormone (hGh), along with a few other initial recombinant products, were approved through a new drug application process by the Bureau of Drugs (rather than as a biological licensing application by the Bureau of Biologics), it was subsequently determined that hGh was eligible for an abbreviated filing through the 505(b)(2) regulatory pathway. This pathway allows the FDA to rely on the published scientific literature or its previous finding for similar products. In June 2006, the FDA approved Sandoz's application for Omnitrope (FDA 2006), its version of hGh. The other hGh products were approved through standard new drug applications rather than abbreviated filings.

initially approved for colorectal cancer and later for non-small cell lung cancer. These and other biologics are currently in clinical development for a large spectrum of new indications that would expand their scope of therapeutic benefits significantly (PhRMA, 2008).

c. Kotlikoff argues that data exclusivity will lead to "evergreening" as innovators stack exclusivity terms by "gaming" the system with minor changes such as the introduction of new dosage strengths. However, none of the bills introduced in 2008 provided additional data exclusivity times for minor changes such as new dosage strengths. Some of the bills explicitly allowed for one to three extra years in data exclusivity for regulatory approval of a new indication where the FDA determines there is a significant clinical benefit. This is a reasonable incentive to encourage further R&D investment on beneficial new uses for patients. Where a new generation of products is involved---that is a new molecule involving a complete Biological Licensing Application (BLA) to the FDA--- the sponsoring company usually will have to perform a full regimen of pre-clinical and clinical tests to gain approval. In that case, data exclusivity for the new molecule can be justified on economic incentive grounds to encourage innovative advances for patients. Furthermore, the pharmacy and therapeutic committees of insurance firms and pharmacy benefit managers will assess the value to patients of these new formulations and indications and this will be reflected in reimbursement decisions. In any case, none of the bills in Congress in 2008 would have led to "evergreening" as characterized by Kotlikoff.

d. Kotlikoff also claims a shorter exclusivity period will incentivize innovative firms to accelerate development schedules and avoid delays in getting product to market. However, this

does not follow because biologic manufacturers already have strong incentives to develop biologics as quickly as possible. This is because delays lower the expected present value of revenues, decrease the likelihood of first mover advantages, and reduce the time before competition develops from other innovative firms pursuing biologics and drugs for the same indications.

e. Kotlikoff has also made some significant errors on the data exclusivity provisions of specific bills that affect his calculations on marketing exclusivity. In addition, he makes implausible assumptions on the time regulatory agencies will take to approve an abbreviated filing for biosimilar drugs (in particular that it will take five years on average to submit abbreviated applications and get them approved by the FDA). As we demonstrate in Section V, his errors on permissible filing times and his implausible assumptions on review times exaggerate the length of the effective marketing exclusivity arising from data exclusivity in the current bills before Congress.

f. While Kotlikoff makes many unsupportable claims about the impact of data exclusivity on innovation incentives, it is striking that he offers no economic analysis to determine the appropriate length of the exclusivity period from a return on R&D investment perspective (see, for example, Grabowski, 2008). Rather, in the absence of any economic analysis, Kotlikoff advocates a five year data exclusivity period for biologics based on a few stylized trends and descriptive statistics. His argument appears to be that five years of data exclusivity has worked well for new chemical entities, and biologics are similar enough to small molecule drugs for Congress to institute the same period for biologics. His approach to the issue, however, is

flawed, both conceptually and empirically, and is not a sound basis for making policy decisions on data exclusivity.

g. In terms of industry and product characteristics, Kotlikoff fails to recognize some of the particular features of biologic drugs that make data exclusivity especially important for R&D incentives. First, from an intellectual property standpoint, biological patents appear to be more easily challenged or invented around than those of chemical entities since biologicals often rely on process and formulation methods. Second, from an R&D investment perspective, biologicals require substantial additional investment in up front process engineering and manufacturing know-how compared to small molecule drugs. Third, from a market structure standpoint, the biologics sector is populated by a wide spectrum of firms including start-ups, emerging development stage companies, and fully integrated firms with marketed products. R&D projects in this sector rely on funding from many sources including venture capital and private equity as well as many partnership deals between companies. This funding is very sensitive to expected risks and returns, including the risks arising from very short data exclusivity periods.

In summary, we believe Kotlikoff's report contains a number of errors and misrepresents the nature of innovative competition in the biopharmaceutical industry. Subsequent sections consider the problems and issues with Kotlikoff's study in more detail. However, none of our criticisms of Kotlikoff's study are intended to question the importance of establishing a new regulatory pathway for biosimilars. This pathway should result in increased price competition and cost savings (Congressional Budget Office, 2008; Ahlstrom et al., 2007). Biosimilar firms are projected to offer lower prices because they will not have to bear the high risk and high R&D costs of innovators or the information expenses necessary to establish a new market.

Nevertheless, it is also important that the strong innovative performance of the biologics industry be nourished and enhanced, given its strong contribution to patient welfare over the past two decades, which include new treatments for a number of rare cancers and other diseases that represent medical breakthroughs. Issues surrounding data exclusivity need to be addressed in an accurate and objective fashion, especially Kotlikoff's far-reaching and incorrect claims that the data exclusivity provisions in most bills before Congress in 2008 would lead to entrenched monopolies and inhibit future innovation in biologics.

III. THE ROLE OF DATA EXCLUSIVITY AND THE NATURE OF COMPETITION AND FUNDING OF BIOLOGICAL R&D

A. Data Exclusivity as a Backup to the Patent System

From the standpoint of innovative firms, data exclusivity protection provides a back-up or insurance policy to the patent system. Why is this necessary? First, it is important to recognize that biosimilars will be comparable but not identical molecules to the innovator's product. Hence, these products may be able to avoid infringing the innovator's core patents (for example, by using different processes and formulations), while at the same time being able to gain regulatory approval on an abbreviated pathway for a small fraction of the innovator's investment (Manheim, Granaham, and Dow, 2006).

In the case of new chemical entities, generic firms have developed a business model revolving around early patent challenges in order to gain first mover advantages *vis a vis* other generic competitors. Under Hatch-Waxman provisions, an abbreviated new drug application accompanied by a patent challenge (a so-called paragraph IV certification) can be filed one year

prior to the expiration of the five-year data exclusivity period. The amount of these ANDAs with patent challenges has escalated dramatically since the inception of Hatch-Waxman in 1984—from two percent of all ANDAs in 1984 -1989 to twelve percent from 1990 to 1997 to twenty percent from 1998 to 2000 (Berndt et al., 2007). Moreover, there is a strong trend to undertake these challenges early in the product life cycle of successful innovative products, well before potential recoupment and return on an R&D investment portfolio can occur. Given the lengthy and costly R&D period for new drugs and biologics, it takes a correspondingly lengthy period for innovative firms to recover their R&D costs and earn a risk adjusted return on this investment.[3]

Legislation facilitating circumvention of the innovator's patent, combined with quick and easy entry through an abbreviated filing has the potential to significantly curtail innovation incentives in the biologics sector. Uncertainty about recoupment periods and the ability to earn a risk adjusted return on particular new product candidates will result in fewer of these candidates being taken forward into development. Data exclusivity provisions in the bills critiqued by Kotlikoff were designed to reduce uncertainty and provide some stability and predictability against early patent disruption. They also provide an important incentive for products that spend long times in basic research or clinical development after their core patents are filed. Without adequate data exclusivity many such products would be destined to remain on the shelf because they have little or no effective patent time remaining at the time of launch. Data exclusivity also encourages continued R&D by innovators for new indications. This is an important pathway in biologics for enhancing patient health and welfare.

[3] Historical analysis of the cost and returns on R&D for pharmaceuticals for various time cohorts indicates payback for the representative new drug takes 14 to 16 years (Grabowski, Vernon and DiMasi, 2002; CBO, 1998). Analysis of this issue for biologics indicates similar payback periods (Grabowski, 2008; Grabowski, Long, and Mortimer, 2008).

B. Innovative Competition in Biologics is Dynamic in Nature

Kotlikoff repeatedly characterizes innovators in the biopharmaceutical industry as "winner take all" monopolists, enjoying the fruits of monopoly profits or rents with a reluctance to innovate lest they cannibalize these monopoly profits. This characterization of industry behavior, however, does not fit the dynamic competition between innovators that has been documented by many researchers. He acknowledges that R&D competition in biologics has provided several valuable new therapies across various therapeutic classes, including many cancers, multiple sclerosis, rheumatoid arthritis, asthma, and Alzheimer's disease. He does not recognize, however, that it is the vigorous competition in R&D investment by innovative firms that has led to the development of many therapeutic options and provided valuable improvements in these classes. This industry is an embodiment of Schumpeter's dynamic competition. There is currently a rich pipeline of product candidates in clinical testing. This is reflected by the fact that there are more than 600 biotechnology drugs currently under development in various therapeutic areas including 250 biotechnology drugs alone under development for cancer (PhRMA, 2008).

For example, a recent review of medical research and clinical studies for new treatments of multiple sclerosis found a large number of new biologics under study. These include several monoclonal antibodies as well as some oral agents that have advanced to the later stages of development. The authors of this review conclude, "It has also become apparent that traditional views of multiple sclerosis simply as a $DC4^+$ T-cell mediated disease of the central nervous system are incomplete. The pathogenic role of other immune components such as the innate immune system, regulatory T cells, T helper 17 cells and B cells is reaching centre stage,

opening up exciting avenues and novel potential targets to affect the natural course of multiple sclerosis" (Lopez-Diego and Weiner, 2008).

In a recent paper, Grabowski and Wang (2006) found that new biological entities had a significantly higher likelihood of being a first-in-class or novel introduction compared to new drug introductions. New biological introductions have been particularly focused on oncology and immunologic areas in recent years. Substantial improvements in survival, morbidity, and patients' quality of life have been documented in diseases previously resistant to successful treatment, including cancers such as aggressive HER-2 positive breast cancer (Smith et al., 2007) and gastrointestinal stromal tumor, or GIST (ASCOG, 2004), as well as in preventing the disease progression, functional decline, joint destruction and disability associated with rheumatoid arthritis (Weaver, 2004).

In a recent paper, Calfee and DuPre (2006) have pointed out some important features of competition involving new biological entities. These include new indications associated with the same or related biological pathways, but often linked to very diverse health problems and disease states. For example, two of the leading rheumatoid arthritis drugs also have approved indications for psoriasis (Enbrel) and Crohn's disease (Remicade). At the current time, Avastin is being studied worldwide in more than 450 clinical trials and in more than 30 different tumor types (Genentech, 2009).

Calfee and DuPre (2006) also point out that multiple therapeutic interventions are possible in the biological cascade of proteins that often influence the same ultimate target (e.g., a particular receptor or dysfunctional enzyme). For example, there are many targeted drugs currently in Phase II or III for breast cancer targeting the HER-2 receptor, and related proteins downstream from HER-2. Similar competition is occurring in the INF inhibitors for rheumatoid

arthritis and the angiogenesis inhibiting drugs for cancer, and some competitive drug candidates have already been approved (Million, 2008).

In his paper, Kotlikoff claims that data exclusivity will keep innovative firms from building on the prior stock of prior knowledge. This appears to be a fundamental misunderstanding of the limited role of data exclusivity. The patent system requires disclosure of an invention as a quid pro quo for receiving a patent. The FDA requires key information about a product's safety and efficacy be disclosed in the approval product label. The vigorous competition around common biological pathways discussed above illustrates that innovative firms do build extensively on the prior stock of knowledge in their R&D efforts. Data exclusivity will do nothing to inhibit this from continuing to occur in the future.

C. Funding of Biological R&D Depends on Internal and External Sources

In the case of biopharmaceuticals, early stage development is frequently done in firms supported by venture capital (VC) funds. VC-backed firms constitute 40% of the employment in biotechnology (Burns, Housman and Robinson, 2009). VC firms specialize in high risk-high return ventures. Risk capital is supplied in exchange for equity positions at high implicit costs of capital. Intellectual property is a key dimension of the decision to invest in early stake life science companies. Even after a biopharmaceutical firm goes public, it typically will need to raise additional funds to finance clinical trial activity. This generally occurs through secondary financing in the public market and partnerships with larger firms. In this latter regard, a rich market exchange for new technologies has emerged in the life sciences area over the past two decades (Danzon, Nicholson and Pereira, 2005; Robbins-Roth, 2000).

Success in the biopharmaceutical area is ultimately predicated on the fact that when firms develop novel and useful therapies for diseases with unmet needs, they will be able to earn significant profits over a full product life cycle. If these profits are endangered by uncertainty about the prospect of early entry by biosimilars through patent challenges and abbreviated filings, it will lead to a shift in financing away from biopharmaceutical firms. Early stage research is likely to be the most adversely affected. VC firms are agnostic about the choice of industries in which they invest. They can shift to information technology companies or even a new fast food chain if there is heightened uncertainty about returns from biopharmaceutical firms.

Development portfolios across the full spectrum of biopharmaceutical firms will be affected by the risks of easier and faster imitation if there are abbreviated fillings with limited data exclusivity. Higher adjusted returns will be necessary to compensate for increased risks yielding fewer leads that meet the standard for established as well as early-stage companies. Such a prospect is a particularly unfavorable outcome for firms and industries whose products contribute to important long term advancements in public health.

IV. IS HATCH-WAXMAN A GOOD MODEL FOR BIOLOGICS?

Kotlikoff bases his policy conclusions about data exclusivity for FOBs on a comparison of estimates of R&D costs, development times, and the cost of capital for firms that develop small molecules and those that develop biologics (in the case of the cost of capital, he compares biologic firms to firms in other industries as well). His basic argument is that these metrics are similar for small molecules and biologics and the innovative experience with small molecules has been satisfactory, and so therefore the protections that have been developed primarily for

small molecules in the Hatch-Waxman Act should be adequate for FOBs. He also argues that the Hatch-Waxman Act stimulated innovation. These claims, and the discussions around them in the report, are not supported by the empirical evidence, and cannot be used to justify the policy prescription that he advocates.

A. Comparisons Between Biologics and Pharmaceuticals

Kotlikoff's report does not provide a rate of return analysis for new biologics. First, while he compares R&D costs and development times for chemical drugs and biologics based on estimates in the published literature, he does not account for the substantially higher process engineering and production costs faced by manufacturers of biologics.[4] While biologics generally involve more complex molecules produced from large-scale cultures of living mammalian, microbial, or yeast cells, manufacturing process issues in R&D typically are more straightforward for drugs based on chemical synthesis. Likewise, the costs of constructing a new manufacturing facility or retrofitting an existing plant for such large-scale commercial production are substantially greater in the case of biologics (Grabowski, Cockburn and Long, 2006; Molowa, 2001).

Second, while Kotlikoff repeatedly makes mention of high unit prices for some biologics, he does not offer any evidence on volumes. Therefore, he cannot make revenue or profit comparisons between chemical drugs and biologics. There is no evidence for his assertion that

[4] As noted by Kotlikoff, DiMasi and Grabowski (2007) have found the average cost of developing a new biologic to be $1.24 billion. As part of that analysis, they found that biologics have higher discovery and pre-clinical expenditures than new chemical entities. As discussed, early stage R&D is frequently conducted in venture backed firms and these outlays are highly sensitive to increased risks on the likelihood of returns.

revenues are much higher relative to R&D expenditures and capital investment outlays in biologics than pharmaceuticals (Grabowski, Vernon and DiMasi, 2002; Grabowski, 2008).

Third, Kotlikoff compares the cost of capital for biotechnology firms to that for pharmaceutical firms and firms in other industries. He finds that the cost of capital is higher for pharmaceutical firms and for firms in a wide range of other industries than it is for biotechnology firms. The measure that he uses is the equity cost of capital, based on the capital asset pricing model (CAPM). However, it is the weighted average cost of capital that matters (weighted for both debt and equity financing). Publicly traded biotechnology and pharmaceutical firms are primarily equity financed, while firms in other industries have substantial debt financing. Tax-adjusted debt costs of capital are typically much lower than equity costs of capital. Thus, the weighted average costs of capital for firms in non-drug industries should be much lower relative to those for firms in the biotechnology industry than is the case when only equity costs of capital are compared (Myers and Shyum-Sunder, 1996).

Furthermore, with respect to cost of capital estimates, Golec and Vernon (2009) point out that the Fama and French three factor models are considered superior to CAPM in industries like biotechnology. In particular, three factor models capture additional elements of systematic risk--namely size related and book to market risk—that are not included in CAPM. Using this approach, Golec and Vernon find substantially higher cost of capital for biotechnology firms than using a CAPM approach. Their analysis is consistent with estimates using this methodology in Ibbotson's Cost of Capital 2008 yearbook, a widely accepted industry source for publically traded firms.

Another key point with respect to the cost of capital is the fact that many biotechnology firms are not publicly traded, do not have marketed products, and have investment portfolios that

are concentrated in early stage discovery and development. Such firms can be expected to have high costs of capital, even relative to pharmaceutical firms and large integrated biotechnology firms. For example, 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%.[5] There is also evidence that many small biotechnology firms that rely heavily on VC for financing are facing increasing difficulties obtaining this financing in the face of the current credit crunch (Boyle, 2008).

In summary, Kotlikoff's analysis of the cost of capital and R&D costs and revenues in biologics and pharmaceuticals is incomplete, and exhibits a number of flaws from both a conceptual and empirical perspective.

B. Pharmaceutical Industry Performance Under Hatch-Waxman

Kotlikoff also argues that the Hatch-Waxman Act, which substantially lowered the cost of imitation, served as a substantial spur to innovation for chemical drugs. As support for that claim, Kotlikoff presents a bar graph that gives the total number of new molecular entity (NME) approvals granted by the FDA for the periods 1974-1983 (pre-Hatch-Waxman Act), 1984-1993 (immediately post-Hatch-Waxman Act), and 1994-2007 (more recent post-Waxman-Hatch Act). Kotlikoff maintains that, relative to the pre-Hatch-Waxman period, the number of new drug approvals increased by one-third for the immediate post-Hatch-Waxman period and doubled for

[5] Grossman also estimates a nominal cost of capital for biotechnology firms with at least one biologic approved of 18.17%. Assuming a 3% annual inflation rate, his estimates would correspond to real costs of capital of 23.69% for firms with development candidates only, and 15.24% for firms with one or more products.

the more recent post-Hatch-Waxman Act period.[6] However, there are two major problems with this analysis.

The first two periods that Kotlikoff considers are ten years in length, but the most recent period covers 14 years. If we, more appropriately, consider the average annual number of approvals, the values are 19.2 for 1974-1983, 24.1 for 1984-1993, and 27.1 for 1994-2007. The average annual approval rate for 1994-2007 is therefore only modestly higher relative to the 1984-1993 period, and much less higher relative to the pre-Hatch-Waxman period than Kotlikoff indicated.

The second problem is that the number of NME approvals spiked in 1996 and for the next several years. This is shown in Exhibit 1. Much, if not all, of that increase was arguably a statistical artifact produced when the FDA eliminated a substantial backlog of new drug applications in the initial years following the effective implementation of the prescription drug user fee program (which was enacted in 1992 and resulted in a substantial increase in the number of medical reviewers at the FDA). Kotlikoff's over-aggregation of the data misses the decline in NME output that has occurred in recent years. If we examine the five most recent years (2003-2007), instead of the last 14 years, we find that average annual approval rate is 20.8, which is lower than the rate for 1984-1993 and only marginally different from the pre-Hatch-Waxman period (1974-1983).

Even if the number of NME approvals had increased substantially over the entire post-Hatch-Waxman Act period, this would hardly constitute proof that the Hatch-Waxman Act

[6] Judging by the heights of the bars, however, the numbers in the figure appear to be wrong The figure indicates that the number of NME approvals are approximately 150 for 1974-1983, 200 for 1984-1993, and between 300 and 350 for 1994-2007. The correct values are 192, 241, and 379, respectively. Using the correct number of NME approvals, the relative increases in the totals for the two later periods relative to the 1974-1983 period are nonetheless approximately as indicated in the report.

increased innovation rates. A number of factors not considered by Kotlikoff affect the pace of innovation in pharmaceuticals – scientific opportunities, regulatory developments, increased incomes and demand, reimbursement changes, and so forth. For example, there have been substantial advances in basic biomedical research during the post-Hatch-Waxman Act period, thereby increasing the scientific opportunities for the development of new therapies. In addition, prescription drug insurance became much more widespread in the United States during the 1990s and the 2000's. Consequently, the demand for prescription drugs increased. Stylized trends in industry statistics can not be determinative of the specific or marginal impact of the five year data exclusivity rule on industry incentives. Furthermore, as discussed in the next section, most health care experts expect the future will be characterized by extensive cost containment and other demand side limiting trends and factors.

C. The Analysis of Hatch-Waxman Act by the Congressional Budget Office

The Kotlikoff report also makes mention of a Congressional Budget Office (CBO) report on the effects of the Hatch-Waxman Act on pharmaceutical firm profitability (CBO, 1998). One important finding of that report, not cited by Kotlikoff, is that the typical market exclusivity period (the time from brand approval to first generic entry) in the pre- and post-Hatch-Waxman periods, was approximately 14 years in length.[7] Furthermore, their rate of return analysis found that a time period of 14 years or more was necessary for the representative new drug to achieve breakeven status and earn a return commensurate with its risk adjusted cost of capital. While data exclusivity has not been the main constraint on market exclusivity periods for small molecule

[7] Grabowski and Kyle (2007) have examined this issue for a more recent sample of products experiencing initial generic competition. They found the annual marketing exclusivity period for new molecular entities was in the rage of 12 to 15 years, with products with larger sales at the time of patent expiration having lower average marketing exclusivity periods.

drugs (although in recent years it has become increasingly important due to the increase in paragraph IV challenges), it is expected to be more determinative for many biologics for reasons related to the specific characteristics of biologics and biosimilars discussed in Section III.

The CBO report also found that the Hatch-Waxman Act was associated with a 12 percent decline in the average expected average returns for pharmaceutical R&D. Since this study was completed more than a decade ago, a number of the key inputs to that analysis have changed significantly. In particular, R&D costs for a new entity are significantly higher, the average time to generic entry has been shortening for largest selling products, and the attrition rate for branded products in terms of lost sales to generic entrants is much faster than in the mid-1990s.[8]

Aitken, Berndt, and Cutler (2008) in a recent paper point out that the growth in real prescription drug expenditures in the United States has declined rapidly since 2003. In particular, they grew by only 1.6% in 2007, the slowest growth rate since the mid-1970s. They attribute this, in significant part, to more patent expirations, faster generic penetration rates, and a reduced annual number of new molecular introductions.

Looking forward, even with the potential for policy changes that would permit the currently uninsured to be covered by prescription drug insurance, the scope for increased demand seems more limited than it was for the recent past, while the potential for more extensive and effective cost containment efforts seems likely. In addition, as noted above, the trend in recent years has been for patent challenges to become much more frequent. Thus, the economic prospects for new drug and biologics development is likely to be more constrained in the future

[8] One of the contributing factors to these trends is the growing number of patent challenges discussed earlier. Grabowski and Kyle (2007) found that patent challenges have had a statistically significant negative effect on market exclusivity times (the time from brand approval to first generic entry).

than they were for the period analyzed by the CBO, thereby reducing the incentives for development for a given amount and scope of intellectual property protection.

Finally, it is important to recognize that past new biologics development was undertaken with no abbreviated regulatory approval pathway for biosimilars in place, and only a prospect that one would be developed at some uncertain point in the future. It is difficult to know what probabilities developers attached to the likelihood that their investigational molecules would be subject to any particular biosimilar provision at some particular future date. Nevertheless, introducing a specific biosimilar pathway now with a limited amount of data exclusivity would represent a drastic change from prior regimes and would not be a favorable development for future innovation prospects.

V. DATA EXCLUSIVITY PROVISIONS AND LEGISLATION PROPOSALS

A. Kotlikoff's Analysis Contains Implausible Assumptions and Errors

Kotlikoff has produced a table on how the bills in Congress in 2008 would affect marketing exclusivity (defined as the time from FDA approval of the innovator to expiration of both patent and data exclusivities). This is Table 2 in his paper which is reproduced here in Exhibit 2.[9] In this table he claims the Inslee bill and Eshoo-Barton bill would lead to a floor of seventeen years of marketing exclusivity from all sources, with the Kennedy Biologics bill producing twelve to fourteen years, and the Waxman biologics bill and Hatch-Waxman Act yielding between five and fourteen years of marketing exclusivity.

[9] Table 1 in his report shows marketing exclusivity measured from the time of patent filing. However, since much of this time is lost through the long development and regulatory review time, effective marketing exclusivity is appropriately measured from the time of marketing approval (Table 2 rather than Table 1 of his analysis).

The first column of Kotlikoff's Table 2 displays an array of different values for the Years Between Patent Application and FDA Approval of the Drug. This lag between patent filing and FDA approval determines the amount of effective patent time remaining (before any patent term restoration under Hatch-Waxman). In particular, the elapsed time is subtracted from the twenty-year nominal life. To this amount, Kotlikoff adds three years of patent restoration time from the Hatch-Waxman Act. This is based on the average extension observed for all new molecules. This portion of the Hatch-Waxman Act applies to biologics as well as new chemical entities. New molecules would also be subject to a fourteen-year constraint on the effective patent time extended under the Hatch-Waxman Act (only one patent on a drug product may be extended).

To take account of the effect of data exclusivity, Kotlikoff assumes that it will take five years to do the testing and gain approval for a new molecule. He assumes this five-year period starts at the beginning of the filing period for biosimilars in these bills. This is a highly implausible assumption. There is no provision in the Hatch-Waxman or these pending bills that would prevent firms from doing all the necessary testing on biosimilars prior to the beginning of the filing period. Indeed, firms would have strong incentives to do so to get as early a launch as possible to have more time on the market, and also to gain important first mover advantages. Currently the review time for new biological licensing applications is just over one year. There is no reason to expect it will be longer for abbreviated applications, after an initial transition period. Under the assumption that the FDA will approve these applications within two years, while keeping all Kotlikoff's other problematic assumptions, the maximum protection for any of these bills is fourteen years.[10]

[10] This would also be the case for the Gregg bill, not analyzed by Kotlikoff, since it allows filing after 12 years and data exclusivity for 14 years.

Kotlikoff's Table 2 is also based on an incorrect interpretation of the data exclusivity provision in the case of the Eshoo-Barton and Inslee bills. This biases upward his values on marketing exclusivity, even if one retains the highly implausible assumption of a five year period for the typical biological to gain approval. In particular, he asserts that filing for a biosimilar cannot take place under these two bills until 12 years have elapsed from the date of first FDA approval for the innovator's product. In fact, based on the legislative bills from the last Congress, filing could occur after four years in the Eshoo bill and after two years in the Inslee bill. Marketing approval could then have occurred after 12 years in the Eshoo bill and 14 years in the Inslee bill. New values are presented as an amended Table 2A after correcting Kotlikoff's errors on filing times. As shown, the Eshoo bill had values that were identical to the Kennedy bill – marketing exclusivity arising from data exclusivity are limited to 12 years while the Inslee bill would be limited to 14 years. This is compared to the 17 years claimed in his report.[11]

B. Incremental Effects of Data Exclusivity

It is useful to point out that if the lag between patent application and FDA approval of the innovator's drug is in the six to eight year range, all the bills provide fourteen years of IP protection, and it all comes from patents and patent restoration (Kotlikoff's analysis does not take into account any risks associated with patent challenges or the ability of biosimilar products to more easily circumvent the innovator's patents). As the time between patent filing and FDA brand approval increases beyond eight years in Table 2A, data exclusivity provides some marginal or incremental protection relative to the Waxman biologics bill (which has no data

[11] As noted, these bills also provide for incremental extensions in data exclusivity of one to two years (three years in the case of Gregg's bill) for new indications deemed to have significant clinical benefit by the FDA.

exclusivity) and also compared to the Hatch-Waxman Act (with its minimal five years exclusivity).

For an innovative product for which twelve years have elapsed between patent application and FDA approval, data exclusivity provides one extra year in the Kennedy and Eshoo-Barton bills and three extra years in the Inslee bill.[12] But total time is still constrained to be in the range of 12 to 14 years. This is consistent with historical market exclusivity times for pharmaceuticals (Grabowski and Kyle, 2007). It is also consistent with payback periods necessary to earn a risk-adjusted return on R&D investment for biologics (Grabowski, 2008).

Table 2A highlights an important feature of data exclusivity as a backup to the patent system. In particular, it's only when there are very lengthy time delays from patent application to FDA approval that data exclusivity leads to incremental increases relative to the exclusivity times from patents. However, these are precisely the circumstances when one wants data exclusivity to back-stop the patent system. Long delays between patent filing and FDA approval will generally be caused by above-average periods for the clinical development process (patents are typically filed shortly before clinical development begins). This is characteristic of innovative and risky R&D projects that can lead to important advances. Regulatory holds and delays can also contribute to a lengthy period between patent filing and FDA approval and result in a shortening of effective patent life (while the Hatch-Waxman Act can be used to restore the portion of a patent term lost during regulatory review, the act has a limit on the total amount of time that can be restored).

When a lengthy development and regulatory review period causes patent time to elapse before launch, marketing exclusivity shrinks to five to seven years under Hatch-Waxman and

[12] The Gregg bill would also lead to three extra years assuming that the time from filing to FDA approval takes up to two years rather than the five years assumed by Kotlikoff.

Waxman biologics bills introduced in 2008. No one who has studied the innovative process in biopharmaceuticals believes this is sufficient time for a representative product from an innovative portfolio of biologics to earn a satisfactory return on capital.[13] Such low exclusivity periods can result in many products being shelved prior to the pivotal and very expensive later stage testing. This will especially be true for biological products where large numbers of firms have no cash flow from existing products and must raise funds from external sources at elevated costs of capital.

Kotlikoff claims that the Hatch-Waxman Act and Waxman biologics bill are preferable to the other potential legislative proposals because they would result in less protection for longer development periods, and therefore provide greater incentives to speed development. However, such a conclusion is not warranted because biopharmaceutical firms would still have considerable incentive to develop biologics as quickly as possible even with longer data exclusivity periods. Every year of development delay means lower revenues on a present discounted value basis from the firm's perspective at the beginning of development, a lower likelihood of gaining first mover advantages, and greater competition from different drugs and biologics that treat the same conditions during the biologic's period of market exclusivity.

VI. SUMMARY AND CONCLUSIONS

In this paper we have addressed and critiqued many of the claims made by Professor Kotlikoff with respect to the data exclusivity provisions of several bills that were before

[13] Alex Brill (2008) has attempted to show that data exclusivity of seven years is compatible with breakeven economic returns for the representative new biologic, based on historical data on R&D costs and returns. However, his analysis is based on implausible assumptions regarding the appropriate cost of capital and margins for biologics and other conceptual problems. In this regard, see the discussion of Brill's analysis in Grabowski, Long, and Mortimer (2008).

Congress in 2008 and which we expect will be included in legislative proposals introduced and considered in 2009. Kotlikoff's paper has a number of misconceptions and errors. He has not provided any economic basis for his policy recommendation of a five year data exclusivity beyond a few stylized facts that are not determinative. The bills that he critiques were in fact quite consistent with the principle that new entities should be allowed sufficient exclusivity time to earn a risk-adjusted return on their lengthy and costly R&D environment. Contrary to his contentions, these data exclusivity periods do not result in disincentives for continued innovation by first-to-market innovators, or lead to "evergreening" of exclusivity periods through minor changes in an innovator's product. Data exclusivity runs concurrently with the length of patent protection remaining after FDA approval. It provides an important insurance policy for promising innovative activities in cases where patent protection is uncertain, is narrow in scope, or has largely expired due to lengthy development and review periods.

Kotlikoff also misrepresents the nature of competition in biologics, repeatedly characterizing new product introductions as leading to entrenched monopolies, while ignoring the robust dynamic competition that has resulted in many therapeutic advances for life-threatening and disabling diseases. While the creation of an abbreviated regulatory approval pathway for biosimilars is desirable, it is important that it not deter progress in biological innovation. The congressional bills he criticizes sought to provide an appropriate balance between the twin objectives of obtaining cost savings and ensuring incentives for continued medical breakthroughs. As the new Congress considers legislative proposals in 2009, it is important to continue to seek that balance since this legislation is expected to have far reaching implications for future advancements in public health.

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Exhibit 1

Annual Number of NME Approvals

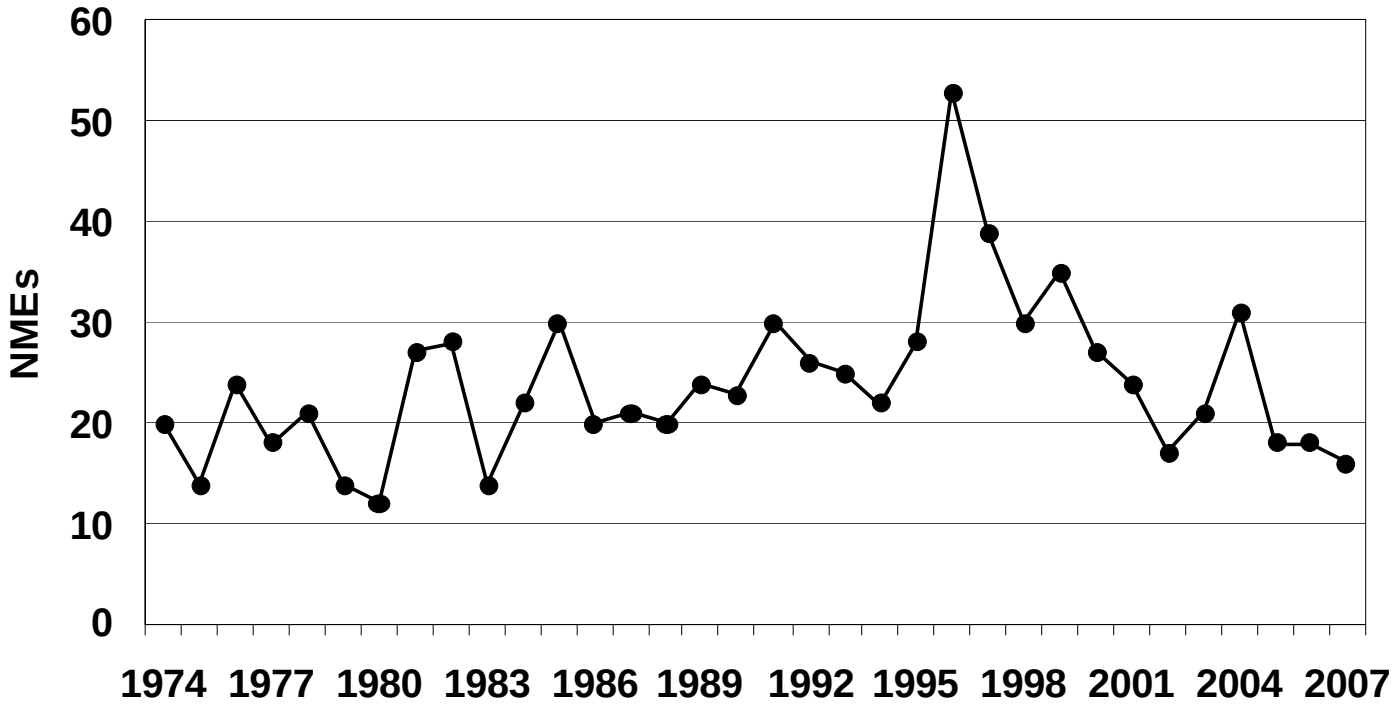

Exhibit 2

Table 2 from Kotlikoff

Table 2: Years of Marketing Exclusivity from Date of Patent Application

Years Between Patent Application and FDA Approval of Brand Drug	Hatch-Waxman Chemical Drugs	Waxman Biologics Bill (H.R. 1038)	Kennedy Biologics Bill (S. 1695)	Eshoo-Barton Bill (H.R. 5629)	Inslee Biologics Bill (H.R. 1956)
6	14	14	14	17	17
8	14	14	14	17	17
12	11	11	12	17	17
16	7	7	12	17	17
20	5	5	12	17	17
Table assumes no evergreening, incorporates exclusivities, assumes five years for testing and approval of biosimilars commencing at ANDA filing, and assumes a three-year patent restoration period.					

Table 2A
Amended Kotlikoff Table 2 corrected for errors

Table 2: Years of Marketing Exclusivity from Date of Patent Application

Years Between Patent Application and FDA Approval of Brand Drug	Hatch-Waxman Chemical Drugs	Waxman Biologics Bill (H.R. 1038)	Kennedy Biologics Bill (S. 1695)	Eshoo-Barton Bill (H.R. 5629)	Inslee Biologics Bill (H.R. 1956)
6	14	14	14	14	14
8	14	14	14	14	14
12	11	11	12	12	14
16	7	7	12	12	14
20	5	5	12	12	14
Assumptions: Same as Kotlikoff Table 2 except errors with respect to the allowed filing times in the data exclusivity provisions of Eshoo-Barton and Inslee bills are corrected in this table.					