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Re: Emerging Health Care Issues – Follow-on Biologic Drug Competition
Comment on Final Report (Originally Identified as Project No. P083901)

As Congress pursues landmark legislation to establish an abbreviated regulatory pathway for biosimilars, identifying an appropriate data protection period for biologics is a critical consideration. An appropriate balance must be created between the objectives of obtaining short-term cost savings from the current generation of marketed biologics and ensuring long-term incentives for continued medical breakthroughs from future generations of biologics. This legislation will have far-reaching implications for future advancements in public health. It is important that an abbreviated regulatory pathway for biosimilars not deter progress in biologic innovation benefiting future generations of patients.

The data protection period is designed to recognize the long, costly, and risky process involved in gaining FDA approval for an innovative product and serves as an “insurance policy,” providing a guarantee of market exclusivity under only two circumstances:

- When development was particularly long, resulting in little remaining patent life by the time the product reaches the market; and

- When biosimilar manufacturers are able to “work around” the innovator’s patents and patents will therefore not protect innovators’ investments.

Given the structure of the biotech industry, and the investment process for biotechnology research, the continued introduction of valuable new therapies will be strongly influenced by the establishment of an appropriate data protection period in conjunction with the legislation establishing an accelerated biosimilar FDA approval pathway.

In contrast to the bills currently under consideration by Congress, all of which provide data protection periods ranging from 5 to 12 years, the report recently released by the Federal Trade Commission (FTC) adopts the extreme position that no data protection period is necessary, except in rare cases when patent protection is totally absent. This policy, if adopted, would represent a radical departure and “rollback” from current policy in place in the United States under Hatch-Waxman, and for all other developed countries, where both small and large molecules have significant data protection periods (e.g, 10-11 years in the EU). The FTC recommendation that data protection be denied to innovators altogether, except in extreme circumstances of no patent protection, would lead to serious adverse implications for biological innovation. These points are summarized in the comments attached to this letter.

The FTC’s recommendations necessarily would lead to a very “uneven playing field” in the competition between innovators and imitators. Biosimilar entry could occur shortly after a new product is introduced under an abbreviated filing at a small fraction of the innovator’s R&D costs. Faced with such a radical change in incentives, biotechs may elect more often to invest in lower-risk biosimilar manufacturing opportunities, rather than pursuing innovative pioneer positions. The net result would be a shift from an aggressively innovative industry to an imitative one.

In contrast to the FTC’s position, my own peer reviewed research work (referred to in the report as the *Nature* model), indicates that a substantial data protection period is necessary to ensure continued innovation incentives. By contrast, the FTC report argues that this type of modeling, which incorporates the best available information on key parameters and is built on a long line of peer-reviewed research, provides no insights for public policy. While reasonable disagreements can occur on the appropriate assumptions for any model, the FTC’s position is not instructive and offers no alternative model. Furthermore, its position is at odds with many

reports emanating from public bodies like the Congressional Budget Office and the Office of Technology Assessment which have utilized my research work on R&D costs and returns to assess public policy issues relating to innovation initiatives. Indeed, the development of this model's application to policy issues was initially supported by grants from the National Science Foundation and the FTC's own Bureau of Consumer Protection.

I am attaching a detailed response to the FTC report's critique (presented in Appendix A of the report) to provide additional input to the Commission, correct mischaracterizations and errors, and promote continued constructive dialogue as debate on this critical policy question continues. I understand the FTC indicated at the recent House Subcommittee Hearing on Follow-on Biologic Drug Competition that it plans to continue to study the issue and respond to the Subcommittee's questions. In doing so, it may wish to consider the attached materials.

Given the tremendous potential value of future new therapies, and the far-reaching nature of legislation in this area for the biotech industry and patients and consumers, 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. The FTC in the past has undertaken many carefully crafted economic analyses of pharmaceutical industry competition, but in this case it has failed to provide a useful objective analysis that would assist Congress as it creates an abbreviated pathway for biologics.

Sincerely,

Henry G. Grabowski
Professor of Economics

Ensuring Competition and Investment in the Next Generation of Biologics
An Economic Response to the FTC's Report on Follow-on Biologic Drug Competition

Congress is considering legislation to establish an abbreviated regulatory pathway for biosimilars, with the aim of appropriately balancing short-term cost savings from additional price competition with long-term incentives for continued innovation and the development of future generations of novel biologic therapies.¹

One of the most contentious remaining issues in the debate is the optimal data protection period (also called the data exclusivity period) for new, innovative biologics.

The optimal data protection period is critical to a healthy and competitive U.S. biotech industry and will "set the rules" of the industry for many years to come -- there are some 600 biologics in development today, which will be affected by the investment and innovation incentives reflected in any legislation.

The FTC report fails to consider key characteristics and future dynamics of the biotechnology industry when arguing for no or a very limited data protection period, which it justifies based on a hypothesized short-run biosimilar market scenario.

Data protection provisions in current legislation will impact investment incentives beginning immediately and continuing many years into the future, and the impact of potential biosimilar competition should correspondingly be based on competitive effects over a comparable long-term time frame.

Recognizing the need to balance cost savings and incentives for innovation, the bills currently under consideration by Congress all provide data protection periods ranging from 5 to 12 years.

The FTC recommends an extreme position at odds with current policy

The report by the Federal Trade Commission (FTC), however, adopts an extreme position, indicating it does not believe any data protection period is generally necessary, except in rare cases when no patent protection is available

This policy, if adopted, would represent a radical departure and "rollback" from current policy, where data protection for innovative small molecule drugs under Hatch-Waxman provides important protections for innovators and includes:

- a base data protection period of 5 years for new chemical entities. (The FTC report implies that this provision is unusual, but it applies to all new chemical entities, or NCEs, not previously approved. It is a fundamental element of the existing system of development incentives for new drugs in the United States and all other developed countries)²;
- an additional 6 months if pediatric studies are undertaken

¹ The term "biosimilar" -- rather than "biogeneric" -- reflects the fact that FDA scientific experts have consistently concluded that, given the inherent complexity and variability in biologic production, the current state of science does not permit findings of interchangeability between an innovator's branded biologic and a similar product produced by another manufacturer, using a different cell line, production facility and methods.

² The Hatch-Waxman Act allows for a safe harbor in which generic firms can perform testing prior to patent expiration; this so called research exemption does not extend to other patented products.

- a 2.5 year (30 month) period during which patent challenges may be resolved – in recent years, drugs (on a sales-weighted basis) facing first generic entry have faced a roughly 90% probability of a “Paragraph IV” patent challenge.³
- a 3 year period for new clinical investigations for a new indication or new formulation (applicable only to the new indication or formulation)

While the Hatch-Waxman Act provides for 7.5 years of data protection (8 years with pediatric exclusivity), there are many factors which support a longer data protection period as legislators craft an abbreviated pathway for biologics (discussed below). It is also important to recognize that most developed countries, including the European Union, have increased data protection periods for biologics and small molecules in recent years to levels significantly greater than those allowed under the Hatch-Waxman Act.

The FTC’s conclusion that no data protection is necessary for biologics rests on several problematic arguments

The FTC’s conclusion rests on the following assertions:

- Direct competition between brand biologics and biosimilars is predictable and will be very limited (both initially and over time);
- Competition between brand biologics and biosimilars will mimic today’s brand-brand competition in form and intensity;
- The brand will retain a dominant share of the molecule’s sales (70% - 90%) because of first mover advantages, even in the case of large selling biologics with several expected entrants;
- Current patent protection and “market-based pricing” (i.e., current levels of actual net pricing realization) are sufficient to protect innovative incentives in the face of brand-biosimilar competition;
- There are no other relevant differences between biologic and small molecule drugs which need to be considered.

If any of these assumptions proves not to be accurate, the basis of the FTC’s conclusions is called into question and innovation incentives may be significantly compromised by very limited or non-existent data protection periods.

The FTC’s assumptions regarding the short-term and long-term biosimilar market may already be flawed and will certainly be so over time

The market effects of biosimilar entry in the U.S. will vary by market, in terms of the initial impacts of biosimilars, the number of initial biosimilar entrants and how quickly additional biosimilar manufacturers enter the market, how quickly price declines occur, and how quickly and to what extent branded biologic market shares erode.

³ Authors’ calculations, forthcoming updated research on market exclusivity periods for U.S. pharmaceuticals. In addition, Hatch-Waxman provided for a seven year period of exclusivity if the drug was an “orphan,” treating fewer than 200,000 patients.

The FTC claims that, current patent protection and “market-based pricing” alone (with the *elimination* of data protection periods) will be sufficient given the characteristics of brand-biosimilar competition to maintain current biotech investment incentives.

In particular, the FTC claims there will be significant and enduring “first mover” advantages:

- The FTC assumption that brands are likely to retain 70-90% of their pre-biosimilar entry share for a considerable period of time is unsupported empirically;
- However, the FTC report does not provide any information regarding its assumed rate of erosion in brand share over time;
- Similarly, the FTC assumes that price discounts for biosimilars are 10-30%, in comparison with the corresponding branded biologic, and that the pioneer branded product will “respond aggressively and offer competitive discounts.”
- The report does not spell out what this translates into in terms of net price response by branded pioneers;
- The combination of these two effects would result in a biosimilar revenues (all other factors equal) of 49%-81% of the revenues prior to biosimilar entry

Recent evidence with EPO biosimilar entry in Germany suggests that the FTC report assumptions on biosimilar share and price may already be outdated. Contrary to the FTC’s statements, over 50% of the branded epoetin alpha market had transitioned to corresponding biosimilars by the end of December 2008.⁴

The FTC also cites Omnitrope experience in the United States with limited share uptake as justification for an inherent significant and enduring first-mover advantage, but does not note two factors to which its poor commercial performance is generally attributed – the lack of a state-of-the-art, competitive delivery device and the lack of adequate and effective marketing investments.⁵

The FTC neglects critical differences between brand-brand competition and brand-biosimilar competition

The cost of development, clinical trials and launch will be higher than for generic drugs, but much lower than for branded biologics.

- An abbreviated approval process for biosimilars necessarily will be associated with reduced market entry costs as compared with those branded pioneers face, and higher levels of resulting share and price competition.

Current brand-brand competition is premised on demonstrating differentiation from other products, rather than sameness – and current biologic brand-brand competition is typically more focused on feature-based competition in under-satisfied markets.

⁴ Hospira Responses to FTC Questions on Biosimilars, May 19, 2009, accessed at <http://www.ftc.gov/os/comments/healthcarecompissues/090519hospirasupplementonbiosimilars.pdf>. Author’s calculations of biosimilar drugs referencing Erypo as a share of those drugs plus Erypo totals 54% on a standard unit basis as of December 2008.

⁵ Presentation at the National Health Forum, Washington DC June 11, 2009 by Dr. Steven Miller, Vice President, Research of Express Scripts.

The FTC fails to acknowledge the effects of current and expected future developments in the market for biologics and biosimilars

The FTC report suggests existing brand-brand competition will be an enduring model for the impact of FOB-brand, but this fails to consider the potential impact of technological advances, payer response, market acceptance and regulatory changes over an extended period.

- Just as in the case of Hatch-Waxman and generic drugs, there will be a significant “learning effect” by public and private payers, physicians and patients, resulting in increasing adoption of biosimilars.
- Technological improvements and greater review experience at the FDA may greatly reduce the costs of biosimilar entry in the future and result in substantially greater levels of biosimilar share and price impacts than hypothesized in the FDA report.
- Many payers have begun to apply access and utilization controls to branded biologics, even in the absence of biosimilars facilitating greater price-based comparisons. Rather than replicating the current level of payer controls for biologics (as suggested by the FTC report), this trend towards stronger payer management will greatly accelerate with the availability of biosimilars. The FTC report does not account for the impact of large and influential payers (both government and private insurers) on biosimilar pricing and shares. Payers are likely to have a central role in shaping the competitive impact of biosimilar. (See for instance the recently released MedPAC report suggesting ways in which the Medicare program could achieve savings from the existence of biosimilars).⁶

The data protection period is a critical element in the economics of drug development and investment incentives for biotech innovation

The FTC report mischaracterizes the nature of the data protection period and its importance to the economics of pharmaceutical development. It implies that data protection is equivalent to monopoly protection. 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.

Data protection only provides additional market exclusivity (defined as the period of time when the innovative product does not face a biosimilar in the market) under two circumstances:

- When development was particularly long, resulting in little remaining patent life by the time the product reaches the market; and,
- When biosimilar manufacturers are able to “work around” the innovator’s patents and patents will therefore not protect innovators’ investments.

Data protection is particularly important to biologics because patents may provide less clear, predictable intellectual property protection for biologics than for small molecule drugs; data protection periods serve as important “insurance policies” in those cases where patent protection is limited.

⁶ “Report to the Congress: Improving Incentives in the Medicare Program,” MedPAC, June 2009.

Contrary to FTC claims, data protection does not cause innovators to defer improvements and advances in leading biologic products

Data protection does not produce disincentives for innovators to make important improvements or advances in their products. Biologicals are characterized by vigorous competition across innovative firms with respect to the introduction of therapeutic alternatives and advances⁷.

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):

- There are many targeted drugs currently in Phase II or III trials for breast cancer targeting the HER-2 receptor, and related proteins downstream from HER-2.
- Similar competition occurs in the TNF-inhibitors for rheumatoid arthritis and the angiogenesis-inhibiting drugs for cancer.

Because the level of unmet medical need is so high in these categories, there is vigorous competition by multiple manufacturers to achieve greater levels of clinical effectiveness. Products which are able to do so, by interrupting the disease process at a different point in the biologic cascade of events influencing the same ultimate target, can capture rapid changes in share of new patient prescribing behavior. An innovative firm cannot simply rely on the status quo in the face of this dynamic competition from other innovative firms.

Because biologics target specific underlying biological mechanisms, which themselves require significant continuing ongoing research to fully understand, the state of scientific understanding and research may still be relatively immature at the time of launch. Post-approval research programs may yield many clinically significant improvements, particularly in the form of additional approved indications, which were not established at the time of launch:

- Herceptin, originally approved for metastatic breast cancer, was later approved for adjuvant use in early-stage cancer and may prove to be even more valuable there;
- Avastin was approved originally for colorectal cancer, and subsequently for lung cancer and breast cancer;
- Rituxan was originally approved for non-Hodgkin lymphoma and later approved for rheumatoid arthritis;
- Others of the approved therapies for rheumatoid arthritis later proved effective against other auto-immune conditions, from Crohn's disease to psoriasis.

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 economic benefits from important new indications without incurring any of the R&D costs for the additional clinical trials.

⁷ See Calfee JE. 2008. "When Patents Are Not Enough: Data Exclusivity for Follow-on Biologics." *AEI Health Policy Outlook* No. 10, December, for discussion of the dynamics of biologic competition and many of the examples cited here.

Without an appropriate balance between continued incentives for innovation and price competition-based consumer benefits, there is a risk that vigorous biosimilar entry (with rapid share erosion to significantly lower-priced biosimilars) will be achieved, while investment in future biologic therapies may “wither on the vine.”

For adequate investment incentives to exist, investors require:

- an adequate level of investment certainty (“clear rules of the game”); and
- an expectation that resulting profits will be sufficient to overcome risk-adjusted costs of entry.

The FTC acknowledges that a data protection period is warranted to the degree that patents offer *no* market protection for innovators, but it fails to offer any specific recommendation here or to acknowledge other relevant cases where patents may be limited in time or uncertain in nature. While in many instances (depending on the duration selected) data protection may not guarantee a period of market exclusivity any longer than that provided by patents, it provides investors with greater certainty (because it does not depend on the outcome of costly litigation) and therefore provides investors with a clearer expectation of the likely market revenues available to fund risky investments. Without data protection periods and in the presence of biosimilars, when patent protection is uncertain, investors will require a greater “risk premium” to justify investment in already risky biotech development.

Data protection provisions 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 protection 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 protection also encourages continued R&D by innovators for new indications. This is an important pathway in biologics for enhancing patient health and welfare.

Early stage biotech investment today is driven by hundreds of start-ups funded by venture capital and private equity. These investment decisions are very sensitive to changes in risk and return, including those due to a regulatory framework that would result in inability to recoup risky investments.

Biotech development is a highly risky, uncertain process:

- Most projects fail in development and never result in any marketed products or revenues.
- Many other projects receive FDA approval but achieve only limited market success and revenues.
- The biotech industry achieved aggregate profitability for the first time only in 2009.⁸

The biotech “investment ecosystem” today is driven by hundreds of start-ups funded by venture capital and private equity.

- It has been estimated that venture-backed firms represent 40% of biotech employment.
- Most ventures are early stage (fewer than 10% have a product on the market), small (65% have fewer than 50 employees), and never turn a profit.^{9, 10}

⁸.”Biotech 2009: Life Sciences: Navigating the Sea Change,” Burrill & Company (2009).

- Venture capital and private equity are critical in providing risk capital to hundreds of small biotech entrepreneurs to fund uncertain projects leading to future generations of improved therapies for patients – to fund expected losses on many projects, they set high hurdle rates on investments (5x to 10x return on capital for successes).
- *The few successes must pay for the many failures.*

Venture and private equity funding is very sensitive to changes in risk and return, including changes associated with a regulatory framework that would result in inability to recoup risky investments.

- Without the prospects of these returns, risky investments would not be made in the next generation of biologics.
- Changes in the expectations investors have with regard to risk and return will have profound effects on the number and type of biotech start-ups funded, and therefore ultimately on patients and the new therapies that will be developed to help them.
- The firms most vulnerable to these negative impacts are early stage, small biotechnology companies, due to their high costs of capital.

There will be unintended consequences of a data protection period that is too short

- Products with limited remaining patent protection at launch, regardless of clinical value and importance to patients, will not be developed and “no go” decisions will be made earlier not to advance these products.
- To the degree that the regulatory framework adopted results in more litigation over patents early in the life cycle, it will have disproportionate effects on smaller, early stage firms.
- Faced with changes in relative incentives, including very limited or no data protection periods, vulnerable patents or unknown levels of patent protection, and market signals with regard to increases in payer price and utilization control, biotechs may elect more often to invest in lower-risk biosimilar manufacturing opportunities, rather than pursuing innovative pioneer positions, resulting in a shift from an aggressively innovative industry to an imitative one.
- As noted by the American Enterprise Institute in a comment to the FTC round table: “A signal consideration is that if Congress errs by establishing too short a period for data exclusivity, the R&D it suppresses will never be observed, nor will the products that the missing R&D would have created.”¹¹

⁹ BIO 2006 survey of emerging company membership.

¹⁰ Burns, L, Housman, M. and Robinson, C., “Market Entry and Exit by Biotech and Device Companies Funded by Venture Capital,” *Health Affairs*, 28, no. 1 (2009).

¹¹ American Enterprise Institute Comment (12/10/08), p.6.

When Congress considers the most appropriate duration for the data protection period for biologics, there are relevant benchmarks as well as recommendations from respected public bodies that are contrary to the FTC's conclusions

- The net result of the current exclusivity protections for small-molecule drug, together with the current levels of patent protection actually realized for individual drugs (which the FTC suggests are sufficient to spur innovation) is an average market exclusivity period of approximately 12 years (i.e., the period of time that an average small molecule drug faces between launch and market entry of the first generic). This figure has declined slightly since 2000.
- In the European Union, both small-molecule drugs and biologics now receive 10 years of protection plus an additional one year for a new indication.¹² The level of data protection was increased from 6-8 years previously held in several member countries.
- Previously, the National Academies of Sciences and Engineering has analyzed the relevant issues and called for a data protection period in the U.S. at least equal to the E.U period of 10-11 years for small-molecule drugs, and also called for additional research into whether this period is adequate given the complexity and length of drug development:
 - “The current system has been successful in stimulating the creation of new molecules, but the limitations of the patent system sometimes result in denying patients the best that the pharmaceuticals industry could offer. The limitations are due largely to the time constraints under which the patent system operates. Patents generally must be filed as quickly as possible after an invention occurs, and the ticking clock creates a tension with other aspects of drug development.”¹³

Understanding the potential impact of regulatory provisions, including data protection periods, on long-term innovation incentives is critical to designing an optimal framework for biosimilar entry

- In a peer-reviewed article in the scientific journal *Nature Reviews: Drug Discovery*, and expanded upon in an academic white paper, I propose a model for analyzing the economic factors affecting long-term investment incentives for innovative biologics, (called the “*Nature* model” in the FTC report).^{14, 15}
- The model adopts an investor’s perspective, and therefore uses a “break-even” approach, calculating the period of time necessary for a representative portfolio of biologic investments

¹² The “8 + 2 + 1” system provides eight years of data exclusivity before an abbreviated application can be filed, followed by two years during which competitors may file biosimilar applications but cannot enter the market. An additional one year may be granted if a new indication is discovered during the first eight-years.

¹³ Committee on Science, Engineering and Public Policy, National Academy of sciences, National Academy of Engineering, Institute of Medicine, “Rising Above the Gathering Storm: Energizing and Employment America for a Brighter Economic future,” (2007).

¹⁴ Grabowski, H., “Follow-on Biologics: Data Exclusivity and the Balance between Innovation and Competition,” *Nature Reviews Drug Discovery*, 7, 479-488 (2008); for extension of these modeled results to incorporate the effects of data protection limitations on average break-even periods, see also Grabowski, H., Long, G. and Mortimer, R., “Data Exclusivity Periods for Biologics: Updating Prior Analyses and Responding to Critiques,” (2008) Working Paper No.2008-10, available at http://www.econ.duke.edu/working_papers.

¹⁵ The FTC report erroneously claims that this model was developed by “pioneer manufacturers”; this is incorrect. Rather, it is an incremental refinement of previous published research by me and other researchers.

to just cover its discounted costs – without this prospect, risky investments would not be made in the next generation of biologics.

- The *Nature* model integrates, and builds upon, the existing body of peer-reviewed academic research over the past decade that analyzes the factors impacting biologic R&D costs, sales, investment and competition.
 - In every case where they are available from the peer-reviewed literature, it incorporates well-established values for key assumptions (e.g., transition probabilities by phase for R&D projects, R&D costs by phase, cost of capital, revenues, and the sales life cycle);¹⁶
 - For other key assumptions without well-established values in the peer-reviewed literature (e.g., contribution margin), the model is transparent in identifying the values used and the rationale for their selection;
 - It adopts a “sensitivity analysis” approach, laying out a range of plausible assumptions and their associated results -- given the many uncertainties, this approach is the most appropriate.¹⁷
- Under a plausible set of assumptions and in the absence of biosimilar entry, I find that a representative portfolio of biologics takes 12 to 16 years to just cover the discounted costs of development. These results are robust to the assumed entry of biosimilars and a limited data protection period of 5 to 7 years – incorporating these assumptions, the representative portfolio does not break even in a reasonable timeframe (i.e., less than 30 to 50 years).

The FTC report mistakenly criticizes and misconstrues my independent model of economic factors affecting investors’ decisions and the development of innovative biologics. Despite their criticisms, the FTC offers no alternative to my peer-reviewed model

- The FTC report mistakenly claims that the fact that model results are sensitive to changes in critical assumptions such as the cost of capital and annual contribution margins earned by manufacturers demonstrates weakness in the approach.
 - On the contrary, *any* valid model of long-lived investments would highlight the compounding effects of these variables – to show otherwise would be fundamentally incorrect.
 - For instance, consider a saver who invests \$100 today in her 401k account. With an annual return of 10%, her initial investment is worth \$1,083 after 25 years. If that annual return rises by “only” one percentage point, to 11%, the same \$100 grow to \$1,359. Just

¹⁶ See, for instance DiMasi, J.A. & Grabowski, H.G., “The cost of biopharmaceutical R&D: is biotech different?” *Managerial and Decision Economics* 28, 469-479 (2007); 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; Grabowski, H.G., “Patents and New Product Development in the Pharmaceuticals and Biotechnology Industries,” *Science and Cents*, edited by John Duca, Federal Reserve Bank of Dallas, 87-104 (2003); Grabowski, H.G. Vernon, J.M. & DiMasi, J.A., “Returns on research and development for 1990s new drug introductions,” *PharmacoEconomics* 20 (Suppl. 3), 11-29 (2002); Grossmann, M., *Entrepreneurship in Biotechnology*, Physica-Verlag New York, (2003); 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, 208-237 (1996).

¹⁷ In contrast, the FTC report analysis seems to adopt a single point estimate of short-run expected price discount, share and other effects in order to justify its conclusions. Given the long-run and uncertain nature of biosimilar entry, this is an inappropriate approach.

one percentage point difference in the discount rate is associated with more than a 20% difference in the end result. All long-lived investment decisions exhibit this phenomenon.

- Other FTC criticisms do not reflect established industry characteristics – in critiquing the model, the FTC report mischaracterizes both the nature of the industry and the calculations performed.
- Given the potentially far-reaching effects of policies affecting R&D investment, Congress should proceed carefully.
- Sensitivity in the *Nature* model results to alternative cost of capital assumptions indicates that limited data protection periods will disproportionately negatively impact small, early stage biotechnology companies, and therefore competition.
 - Small, typically early stage biotechnology companies experience higher costs of capital than larger, self-financed, well-established companies.
- More detailed responses to the FTC's critique of my *Nature* paper are presented in a separate, technically oriented document. However, the larger implication, that a reasonable sensitivity analysis using best-available information of the potential impact on investor decisions of significant changes in regulatory investment incentives should not be considered at all is simply not a proper or sound approach to public policy analysis. Furthermore, it is at odds with many reports emanating from public bodies like the Congressional Budget Office, the Office of Technology Assessment, and the Institute of Medicine that have utilized my research work on R&D costs and returns to assess public policy issues relating to innovation initiatives.

Conclusion: Data protection is an essential element for legislation on an abbreviated pathway for biosimilars to realize an appropriate balance between the objectives of cost savings and continued incentives for medical breakthroughs. This legislation is expected to have far-reaching implications for future advancements in public health. It is important that an abbreviated regulatory pathway for biosimilars not deter progress in biologic innovation.

The FTC recommendation that data protection be denied to innovators, except in extreme circumstances of no patent protection, exhibits an incomprehensible lack of balance and would lead to serious adverse implications for biological innovation. The FTC in the past has undertaken many carefully crafted economic analyses of the pharmaceutical industry competition, but in this case it has failed to provide an objective analysis that would assist Congress as it creates an abbreviated pathway for biologics.

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Summary of Response to Technical Mischaracterizations in the Federal Trade Commission Report Critique of the *Nature* Model in Appendix A

The *Nature* model provides a transparent, clear and appropriately streamlined representation of key economic factors impacting investor decisions in the development of innovative biologics. In presenting a simplified model of investor decision making the *Nature* model:

- Relies on all well-established available data sources
- Provides a transparent discussion of assumptions
- Applies reasonable sensitivity analyses to the assumptions

The FTC report presents several criticisms of the *Nature* model. These criticisms are not based in fact, misconstrue key industry characteristics, and focus on superfluous, hypothesized complexities. The following briefly summarizes the key errors and shortcomings of the FTC report's critique of the *Nature* model.

Responses to each area of specific criticism are presented below, but the larger implication, that a reasonable sensitivity analysis using best-available information of the potential impact on investor decisions of significant changes in regulatory investment incentives should not be considered at all, in light of the likely far-reaching implications of legislative change, is simply fundamentally incorrect.

Estimates of cost and revenues in the *Nature* model are not "Imprecise"

- The FTC report suggests that R&D cost and revenue estimates are imprecise because of sample size, but provides no evidence supporting this critique or alternative approach
 - Counter to the FTC's suggestion that the sample of biologics is unrepresentative (of past development decisions), this sample focuses on monoclonal antibodies and recombinant proteins, which are *more representative* of future biologic development than earlier, simpler biologics
 - In this way, relatively small, but representative data samples may be far more instructive in simulations than poorly selected, non-representative historical data samples that may be larger but not as relevant as indicators of future conditions
 - An extensive and well-established sample of biologics is relied on to estimate clinical trial success probabilities. However, there are no existing comprehensive data samples for biologics that include development costs by phase. As a result, the best available data must be relied upon from a smaller sample in a peer reviewed paper¹⁸, together with transparent and appropriate sensitivity analyses of key assumptions
- The FTC report speculates that R&D costs and expected revenues may be correlated, but provides no factual evidence supporting this critique.

¹⁸ DiMasi, J. and Grabowski H., 2007. "The Cost of Pharmaceutical R&D: Is Biotech Different?," *Managerial and Decision Economics* 28:469-479.

- R&D costs are incurred years in advance of realized revenues, so any correlation between costs and realized revenues is likely to be weak for most drugs, and not well-established in the minds of investors.¹⁹
- The *Nature* model conservatively excludes the lowest quintile of revenues, based on the hypothesis that many of these products may be those approved through the Orphan Drug Act, which removes one source where both R&D costs and expected revenues may be lower than average. If anything this exclusion causes computed break-even lifetimes to be biased downward, but a strong argument also can be made for including the full range of revenue outcomes, as noted above.
- The FTC report suggests that a separate cost of capital (CoC) estimate should be applied to each research phase.
 - The *Nature* model relies on industry average CoC estimates that includes public companies facing projects across research phases. This is mathematically equivalent to applying a phase-specific CoC for these public companies.
 - Further, in order to prevent undesired selection biases in early stage investment opportunities, companies typically rely for their decisions on a single average CoC estimate applied to all research phases to make investment decisions (not phase-specific CoC).
 - ***Due to very high implied cost of capital associated with venture capital-financed, early stage companies, limited data protection periods would likely deter investment disproportionately in small, early stage firms.*** As a result, the approach of using an average CoC may underestimate the negative investment impact of limited data protection

The *Nature* model is not necessarily predicated on perfectly “Inelastic Demand” (although it may be an appropriate assumption for many biology therapy markets and patient groups)

- The FTC report mistakenly suggests that the assumption that aggregate biologic market sales are the same before and after biosimilar entry is equivalent to an assumption of completely inelastic demand
 - In some markets (e.g., oncology products), demand for effective therapies may be close to perfectly inelastic. Demand for these drugs may be largely determined by clinical considerations (e.g., clinical guidelines, evolving standards of care) rather than by price. These markets reflect higher, value-based pricing, combined with patient assistance programs for those with inadequate insurance.
 - In other cases, the FTC report ignores a basic economic principal substantiated in the peer-reviewed literature that aggregate demand curves may shift with generic entry. Quantity supplied remains little changed at lower prices either if demand is inelastic, or if demand is elastic but the demand curve shifts inward (e.g., there is lower demand at the same market price due to reduced marketing investment from branded manufacturers).

¹⁹ Some correlation may exist at the extremes (i.e., for very large and very small expected markets)

- This phenomenon is consistent with research in the peer-reviewed economic literature on small molecule drug markets, which have experienced little or no increase in aggregate demand following generic entry despite much lower average prices, because the effect of reduced prices is approximately “cancelled out” by the effect of reduced marketing investment. For instance, some have found that the total amount of drug sold did not increase after generic entry for small-molecule drugs.²⁰ Other studies have found only a very small positive elasticity.²¹

The *Nature* model does not suffer from “Internal Inconsistencies”

- The FTC report claims that the *Nature* model assumptions regarding price decreases and market share declines following biosimilar entry are inconsistent with likely market dynamics
 - In the refinement to the original *Nature* model which incorporates the effect of data protection limitations, brand price decline sensitivities of 0%, 25%, and 40%, and biosimilar share sensitivities ranging from 25% to 55% were presented. All combinations of sensitivities were presented, as this is an area of high uncertainty for biosimilar entry some 10 to 20 years in the future
 - Table 3 of that paper provides the biosimilar share and price discount combinations assumed in other papers as a reference point – the assumptions used are generally in the range considered by others
- The FTC report erroneously associates the *Nature* model with relying heavily on an assumption that the brand price will be 40% below its pre-biosimilar price in four years.
 - This is incorrect. We consider a range of brand price decline assumptions including 0%, 25%, and 40%
- The FTC report erroneously associates the *Nature* model with an assumption that brand price will match biosimilar price.
 - This is incorrect. The *Nature* model as refined makes no assumption regarding the relationship between brand and FOB price.²²

The *Nature* model reflects economically appropriate, not “Excessive Aggregation”

- The FTC report suggests that revenues and costs associated with the initial biologic drug indication (at approval) should be analyzed separately from revenues and costs associated with subsequent, post-marketing indications
 - This is incorrect and does not reflect *ex ante* investor considerations. Investment decisions to develop new innovative biologic consider not only the R&D costs and revenues associated with the first indication(s) at approval, but also expected potential subsequent indications. The *Nature* model appropriately considers the full stream of costs and revenues to model investor decisions

²⁰ Caves, R., Whinston, M., & Hurwitz, M., “Patent Expiration, Entry, and Competition in the U.S. Pharmaceutical Industry,” Brookings Papers on Economic Activity: Microeconomics, 1 – 48 (1991).

²¹ Lichtenberg, F., “Importation and innovation,” *Economics of Innovation and New Technology*, forthcoming.

²² This appears to reflect the implementation by Alex Brill, an apparent misinterpretation of the CBO report, and misattributed to the *Nature* model and its refinements.

- The FTC report suggests that biologics with less than \$250 million in sales would not face biosimilar entry (at all, ever), and therefore should be excluded from the portfolio of biologic drugs used to determine typical revenue in the *Nature* model
 - A fundamental aspect of the investment decision is that investors do not know how successful a biologic will ultimately be at the time of the investment decision (i.e., whether or not it will earn more than \$250 million). The *Nature* model appropriately does not set an arbitrary threshold or assume greater investor foresight than is reasonable²³

The *Nature* model results are “Robust” in that they accurately reflect investor sensitivities to changes in economic factors

- The FTC report suggests that the *Nature* model is “too” sensitive to small changes in inputs, such as the cost of capital.
 - Sensitivity of investor decisions to changes in the cost of capital and contribution margin accurately reflects the long-term nature of investment in biologic drug development – to assume otherwise would be simply incorrect and misleading and the critique reflects a fundamental misunderstanding of the market and the objective of the model. This may be an inconvenient reality to those wishing to precisely model inherently sensitive long-term investment decisions, but it is an important reminder that what seem to be “small” changes in regulatory parameters may result in major behavioral responses over the long term. As a result, Congress should proceed carefully.
 - Consider a saver who invests \$100 in her 401k account. With an annual return of 10%, her initial investment is worth \$1,083 after 25 years. If that annual return rises by “only” one percentage point, to 11%, the same \$100 grow to \$1,359. A one percentage point difference in the discount rate is associated with more than a 20% difference in the end result. All long-lived investment decisions exhibit this phenomenon.
 - Similarly, change in market share, price and future revenues can be associated with large changes in the net present value calculation.
- There is a wide range of variable possibilities regarding competition in the biotechnology industry 10 to 20 years from now, and it is reasonable and expected that these different possibilities will yield variable results.
- The FTC report notes that the original *Nature* model fails to break even if the cost of capital is greater than 13.7%, but fails to consider the broader sensitivity analysis on this issue.
 - Under the original *Nature* model assumptions, the average biologic barely fails to break even if the cost of capital is assumed to be 13.7%, all other factors equal (i.e., an average investor would recover less than 1.4% of the NPV of costs with a 13.7% CoC) – this would be expected if the average cost of capital is approximately this level

²³ The *Nature* model does exclude the lowest quintile of biologic revenue from the portfolio analysis. However, one reason for excluding this group is that it was thought to represent biologics approved through the Orphan Drug Act and for those biologics there may be a priori somewhat different expected cost and revenue profiles. The exclusion of orphan drugs is conservative in that it likely biases break-even lifetimes *downward*.

- However, there are variations on the assumptions for key parameters like the contribution margin and the cost of capital that are relevant to particular firms and products; the *Nature* model does break even with a CoC of 13.7% if the contribution margin is increased by 1 percentage point from 50% to 51%. Given the importance of these parameters, a sensitivity analysis is included.

In summary, the FTC criticisms are flawed and not constructive in nature

- The FTC claims that a carefully crafted model, based on a legacy of peer reviewed articles and well established data sources, cannot provide any insights for the data protection issue, but offers no model of its own to guide public policy.

The FTC's opinion that there are no insights to be gained for public policy purposes from the Nature model is at odds with many prior analyses including those emanating from several government agencies

- The FTC's opinion on the value of the *Nature* model is at odds with prior public policy reports and studies emanating from government agencies and respected public organizations that have utilized this approach and my specific work on R&D costs and returns, including the Congressional Budget Office and the Office of Technology Assessment.²⁴
- The application of my research on pharmaceutical costs and returns to different public policy issues, such as the impact of generic competition on innovation, was initially developed based on research grants from the National Science Foundation and the FTC Bureau of Consumer Protection.²⁵

²⁴ See for example the US Congressional Budget Office, *How Increased Competition Has Affected Prices and Returns in the Pharmaceutical Industry*, Washington DC, 1998 <http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf>; US Congressional Budget Office, *How Health Care Reform Affects Pharmaceutical Research and Development*, Washington DC, June 1994 <http://www.cbo.gov/ftpdocs/48xx/doc4846/EntireReport.pdf>; US Congress, Office of Technology Assessment, *Pharmaceutical R&D: Costs, Risks and Reward*, Washington DC, February 1993.

²⁵ National Science Foundation grants to Duke University "The Effect of Product Quality Regulation on Innovation" (1975-1978) and "Studies on Drug Substitution, Patent Policy and Innovation" (1979-1982); FTC Bureau of Consumer Protection consulting project and report on "The Effect of Repealing Anti-Substitution Laws on Drug Innovation" (1977-1979).