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Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Avenue, NW
Washington, DC 20580

[submitted at <http://secure.commentworks.com/ftc-healthcarecompetition>]

Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901 (Federal Register, September 3, 2008, Volume 73, Number 171, pp. 51479-51482, “Notice of Public Workshops and Roundtables and Opportunity for Comment”)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Federal Trade Commission (FTC) for the opportunity to respond to FTC’s questions regarding competition provided by developing a regulatory approval pathway for follow-on biologic (FOB) drugs. BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, renewable sources of energy, and a cleaner and safer environment.

A. Regulatory Exclusivities and Follow-on Biologic Drug Competition

A1. What is the likely competitive effect of the market entry of a follow-on biologic competitor? Are there empirical models that predict the nature of this competition based on existing biologic drug product competition? How has competition developed between referenced and follow-on products in European markets? Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?

The Congressional Budget Office (CBO) has estimated the savings to the federal government of S. 1695, the Biologics Price and Competition and Innovation Act of 2007, to be \$5.9 billion over

the 10-year scoring window. The findings of the study confirm many of the points made below in further response to this question. The CBO score can be found at: <http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf>.

While BIO has not, itself, analyzed what the competitive nature of a follow-on biologics market may look like, we believe that a framework developed by Henry Grabowski and the Analysis Group can help to inform this question.¹

This paper explains that the competitive effect of the market entry of follow-on biologic competitors will reflect the impact of an expedited approval process on both prices and utilization of each affected reference biologic product. While there is considerable heterogeneity among these innovator biologics, the paper identifies a number of critical factors that will drive these market outcomes:

- The timing of patent expiry for these products and the nature of their intellectual property protection
- The time required to develop a United States (U.S.) Food and Drug Administration (FDA) regulatory scheme, testing requirements, and any product-class guidelines following passage of any legislation
- The time required for FOB manufacturers to obtain regulatory approval (three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval) and to bring manufacturing capacity on-line (four to six years, likely developed concurrently with product development schedule)
- The evolution of utilization of currently approved biologics, driven by:
 - Demographics, disease incidence, medical practice, and regulatory and reimbursement practice
 - The pace and extent of uptake of next generation patent-protected products in markets where follow-on biologics have entered (limiting longer-term uptake of follow-on biologics in markets with unmet medical need)
- The nature of the competitive model in markets for biologics that experience entry by follow-on biologics (likely to be driven by the marketing of branded, proprietary products rather than the “commodity” competition based on price alone seen among generic small molecule generic drugs), and its effect on:
 - The pace and extent of uptake of follow-on products for currently marketed branded products (likely slower and less extensive than for many small-molecule drugs, or 10% to 45% follow-on product share)
 - The price impact of entry by follow-on products (limited discounts of 10% to 30% off brand, due to fewer likely market entrants than in generic drug market², among other factors)

¹ Grabowski, Henry, *et al.* “The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions,” White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

² Due to the higher expected development costs for a FOB product versus a generic drug, fewer market entrants are expected in the FOB market than in the generic drug market. The higher development costs associated with the development of a FOB product include, but are not limited to, manufacturing costs, costs associated with clinical trials and potentially post-marketing surveillance. For a more detailed description, please see Grabowski, Henry, *et*

The paper concludes that, with respect to cost savings in the federal budget, the magnitude of such savings is highly uncertain and very sensitive not only to the specific legislative language that emerges, but also to a range of critical assumptions about scientific, regulatory, and clinical issues, the nature of competition in markets for specific biologics, as well as future intellectual property protection, and related litigation and the development of case law.

For more detailed information, the study can be found at:

http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

In addition, BIO has critiqued two studies (PCMA and Express Scripts) that claimed large cost savings from a follow-on biologics pathway. The studies overestimated the savings due to, among other factors:

- Misguided estimates of the timing when savings would begin to accrue
- Unreasonable assumptions on interchangeability
- Mathematical errors

BIO's critique may be found at: <http://www.bio.org/healthcare/followon/20070222.pdf>.

A more recent study by Sonecon, which also suggested large savings, suffers from many of the same issues as the studies by PCMA and Express Scripts. Further, it contains a methodological error that results in an overestimate of savings of at least 110%.

The discussion above focuses on the short term. In the long run, the savings estimates are more difficult to make and depend on a number of factors, including scientific advancement.

Concerning, "*How has competition developed between referenced and follow-on products in European markets,*" the European experience to date may be of only limited value in informing what the U.S. experience will be due to the fact that very little time has elapsed since the introduction of the first biosimilar in Europe and the different ways that reimbursement occurs in Europe versus the U.S.

Concerning the final part of the question, "*Would referenced product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?,*" as a trade association BIO cannot and does not discuss the strategic marketing and pricing decisions that individual member companies may or may not make.

A2. What is the likely impact of a follow-on biologic product being designated "interchangeable" (i.e., receiving an approval that would permit pharmacists, without physician authorization, to fill a prescription for the referenced product with the follow-on product)? What are the prospects for the use of "authorized follow-on biologics" in these

al. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions," White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

circumstances? Do the answers to these questions differ based on the type of biologic product involved?

The degree of competition and potential cost savings arising from a follow-on biologics approval pathway is likely to be dependent on numerous factors, including product quality, cost of production, price discounting, market penetration, number of market entrants, potential market size for any given product, etc. For more detail, please see our answer in response to Question # 1 above.

With respect to designations of interchangeability, it is BIO's position that patients and their physicians should decide the proper course of treatment, including which medicine to take. All biologics should be dispensed as written and prescribed by brand name. We are urging Congress to ensure this approach in any legislation. Indeed, FDA recently stated:

With protein products, as of today, the FDA has not determined how interchangeability can be established for complex proteins.³

The complex nature of biological manufacturing methods means that the manufacturing process used by a follow-on manufacturer will be different from the manufacturing process of the innovator. Because a follow-on manufacturer can never exactly duplicate the innovator's process, differences in process may result in differences in the protein product and, significantly, different effects in the clinic. In fact, even when innovator companies make changes in their *own* manufacturing processes, unanticipated changes in the product can and have occurred. For specific examples of such situations, please see our comments to the European Medicines Agency (EMA) and FDA, available at <http://www.bio.org/healthcare/followon/> (e.g., BIO Comments to 2004N-0355, "Scientific Considerations," December 13, 2004, pp. 18-37). Based on the experience of innovators, BIO agrees with FDA that it has not been determined how interchangeability can be established for complex proteins made by separate manufacturers.

If pharmacists were able, without physician authorization, to substitute the follow-on product for the reference product, patients might not only be dispensed a follow-on biologic rather than the prescribed biologic, but they might be switched back-and-forth among several products over time. Although switching among the innovator small-molecule drug and its generic versions normally raises few concerns, switching among biologics that are "similar" – rather than the same – involves particular risks. As FDA notes:

For many follow-on protein products – and in particular, the more complex proteins – there is a significant potential for repeated switches between products to have a negative impact on the safety and/or effectiveness. Therefore, the ability to make determinations of substitutability for follow-on protein products may be limited.⁴

³ <http://www.fda.gov/cder/news/biosimilars.htm>, Possible International Non-proprietary Name (INN) Policies for Biosimilars, September 1, 2006

⁴ <http://www.fda.gov/ola/2007/protein32607.html>, Statement of Janet Woodcock, M.D., before House Committee on Oversight and Government Reform, March 26, 2007

EMA and certain member states of the European Union likewise have recognized the fundamental differences between drugs and biologics with respect to substitutability. Recently, EMA issued a statement that “[s]ince biosimilar and biological reference medicines are similar but not identical, the decision to treat a patient with a reference or a biosimilar medicine should be taken following the opinion of a qualified healthcare professional.” BIO believes that, consistent with the policies of EMA and many European countries, patients should receive the product expressly prescribed by a physician.

It is important to note that substitution has been a problem for certain small molecule generics. For example, levothyroxine, the generic form of certain medications treating hypothyroidism, is only safe and effective at a very narrowly defined dose. The American Thyroid Association has issued a public statement noting that patients should be alerted by their physicians or pharmacists that their levothyroxine preparation might be switched at the pharmacy, that patients should ask to remain on their current levothyroxine preparation, and that they should inform their physicians if their thyroid hormone is changed to a generic preparation because, following such a switch, thyroid function should be re-checked. This concern is even more relevant for biologics, which are often hundreds or thousands of times larger and more complex than traditional chemical drugs. The kinds and sizes of studies that would have to be done to address doubts about substitutability – including the risks of switching – would be so large that the dataset presented for approval would likely be larger than that required to be presented by an innovator.

As Secretary Leavitt noted in a letter to Senator Kennedy:

[I]n light of the current scientific limitations on the ability to make determinations for interchangeability, and because it is critical to protect patient safety, the Administration believes that patients should not be switched from the innovator biological product to a follow-on biological product (or vice versa) without the express consent and advice of the patient’s physician, and legislation should not allow for determinations of interchangeability at this time.⁵

Finally, we caution that the term “interchangeability” is not defined by FDA and has no settled legal or regulatory meaning at this time. We note that some use this word to describe products that are not “substitutable” or “therapeutically equivalent,” but which, under a physician’s supervision, could be used to treat the same disease or condition in the same patient.

Concerning the question, “*What are the prospects for the use of ‘authorized follow-on biologics’ in these circumstances?*,” as a trade association, BIO cannot and does not discuss the strategic marketing and pricing decisions that individual member companies may or may not make.

A4. How would the prospect of competition from follow-on biologic drugs influence research and development for new biologic drugs, improvements to existing biologic drugs, and the timing and rollout of new and/or improved biologic drugs? Does the market experience with non-biologic generic pharmaceutical drug products provide insights into these issues?

⁵ Letter from HHS Secretary Michael O. Leavitt to Senator Edward M Kennedy, June 26, 2007

When discussing future innovation, it is helpful to understand what biotechnological innovation has accomplished to date. Biotechnology has created hundreds of new therapies and vaccines, including products to treat cancer, diabetes, HIV/AIDS and autoimmune disorders, and many other rare and unmet medical conditions. In fact, between 1995 and 2005, 160 different medicines were approved to treat rare diseases that affect 200,000 or fewer patients. Biotechnology also is responsible for hundreds of medical diagnostic tests that keep the blood supply safe and detect other conditions early enough to be successfully treated.

This spectacular innovation depends on an environment where companies can attract the capital needed to continue massive research and development (R&D) investment. Over the past 25 years, the average R&D intensity (R&D spending to total firm assets) for biotechnology was 38%. By comparison, the average R&D intensity for all industries was only about 3%.⁶ According to Ernst and Young, “Global Year in Review 2006,” the biotechnology industry has increased the amount of money it devotes to R&D by more than 120% since 1994.⁷ Biotechnology is one of the most research-intensive industries in the world. The U.S. biotech industry spent \$19.8 billion on research and development in 2005 alone.

In this regard, it bears emphasis that the biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies – many of which will never see a product come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology companies (all biotechnology companies but the top 10) account for two-thirds of the industry’s future clinical pipeline.*⁸

This enormous reservoir of biotech innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients. Thus, in crafting a follow-on biologics approval pathway, it is important to err on the side of incentivizing innovation, particularly in light of the unique elements of the biotechnology industry. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research – which is particularly difficult in the current economic environment. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted follow-on biologics regime.

The statistics speak to the challenges this emerging industry faces. Biologics research and development is a high-risk endeavor, with higher capital costs, higher material costs, greater

⁶ Golec, Joseph H. and John A. Vernon. “Financial Risk in the Biotechnology Industry,” NBER Working Paper 13604.

⁷ Ernst & Young LLP, annual biotechnology industry reports, 1993–2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies; constant 2005 dollars.

⁸ The Boston Consulting Group: [Rising to the Productivity Challenge](#), July 2004.

manufacturing costs and uncertainties, longer development times, and lower late-stage success rates than compared to small molecule drugs. In fact, from 2001–2005, the success rate of a Phase III trial for the average biotechnology product was just slightly more than 50%.⁹ These failures occur at the last stage of product development – after years of research and hundreds of millions of dollars may have been spent.

The industry’s heavy reliance on private equity also is notable. In 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:^{10,11}

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Net Loss (\$B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	1.4	3.5

This situation is very much *unlike* the situation involving the traditional small molecule pharmaceutical market at the time that the Hatch-Waxman Act created a generic drug pathway in 1984 – a market that was dominated by mature and profitable companies with substantial revenues to reinvest in pharmaceutical R&D. Thus, the risk of driving research investment out of the industry, and quite possibly out of the U.S., is substantial if a follow-on biologics approval pathway does not contain sufficient incentives for continued innovation.

Given these unique challenges, patent protection alone (even including patent term restoration under current law) is not sufficient to ensure such adequate incentives under a follow-on biologics regime. Under a statutory framework allowing for follow-on biologics, there is a very real potential that the manufacturer of a follow-on product may be able to secure regulatory approval based at least in part on the innovator’s prior approval, and, at the same time, avoid infringing patents that protect the innovator’s product. That likelihood exists because of the confluence of critical factors not present in the Hatch-Waxman Act construct for generic small molecule drugs. Unlike a generic drug which must be the same as an innovator product, a follow-on biologic will only be required to be “comparable,” “similar” or “highly similar” to the corresponding innovator product. Compared to generic drugs, the emerging follow-on biologics framework thus provides applicants with significantly more leeway to design around the patents that claim the reference product and make products that are sufficiently different to avoid patent infringement, but sufficiently similar to get abbreviated regulatory approval.

⁹ Parexel’s Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007.

¹⁰ Ernst and Young LLP, annual biotechnology industry reports, 1995 – 2007. Financial data based primarily on fiscal-year financial statements of publicly-traded companies.

¹¹ Only about 20 biotech companies are currently profitable: Parexel’s Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

In light of this increased risk due to the scientific and regulatory facts related to biologics, data exclusivity must be substantially longer than the five years currently afforded to small molecule drugs under the Hatch-Waxman Act. Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time. Without sufficient data protection, companies and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – \$1.2 billion in research and development costs that are necessary to bring a biologic to market.¹² This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment.

This decrease in biotechnology R&D investment will be detrimental not just to biotechnology companies, but also to American universities, as less of their cutting-edge research and fewer of their technologies will be licensed because companies will not be able to recoup the R&D investment necessary to take a licensed technology from the laboratory to the marketplace. Investors will turn to other less risky ventures, and cutting-edge research (including the substantial public investment in basic research through the National Institutes of Health) will sit on laboratory shelves, as it often did prior to the Bayh-Dole Act and the Hatch-Waxman Act patent term restoration provisions.

If this occurs, society as a whole will suffer. New treatments in the pipeline hold the promise of continued progress against our most pressing medical challenges. At present, more than 400 biotechnology medicines and vaccines are in development, targeting more than 200 diseases, including various cancers, Alzheimer's disease, heart disease, diabetes, multiple sclerosis, AIDS, and arthritis. Specifically, there are:

- 210 for cancer and related conditions
- 22 for cardiovascular disease
- 15 for diabetes and related conditions

These innovative treatments include:

- Monoclonal antibodies to treat asthma, Crohn's disease, and lupus
- Therapeutic vaccines for AIDS
- Recombinant proteins to treat autoimmune disorders

Without adequate incentives these – and many other – breakthrough cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions may either take longer to come to fruition or not come to be realized at all.

¹² DiMasi, Joseph and Henry Grabowski. "The cost of biopharmaceutical R&D: is biotech different?" *Managerial and Decision Economics* 28(4-5), pages: 469-479 (2007).

A properly developed follow-on biologic pathway will ensure that the incentives needed to encourage research and development of new, innovative therapies remain in place. BIO believes that, to accomplish this result, the best data available support a 14-year period of data exclusivity for biologics under a follow-on biologics regime. We emphasize that data exclusivity does not interfere with the existing competition among biologic innovators today, and we are not seeking “marketing exclusivity” to prevent such competition. Rather, data exclusivity only prevents, during this time period, a follow-on manufacturer from short-circuiting the normal FDA approval process by basing its FDA application on the safety and efficacy of the innovator product rather than its own full application.

Several independent factors support BIO’s position on the appropriate data exclusivity period. First, we know that the breakeven point for return on investment in a biologic occurs after it has been on the market between 12.9 and 16.2 years,¹³ and thus competition from follow-on biologics prior to that time period would clearly undermine incentives for such investment in the first place. Second, in 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval. This time period was selected so that “research intensive companies will have the necessary incentive to increase their research and development activities.”¹⁴ As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years,¹⁵ and new molecular entities are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition.¹⁶ A similar length of protection should be available for biologics. For a fuller discussion of these data and the justification for 14 years of data exclusivity, please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

In addition, a follow-on biologics pathway must maintain incentives for the development of second-generation products.¹⁷ A second-generation product must go through the same rigorous FDA approval process as a first generation product. It requires development and submission of full clinical safety and efficacy data to support FDA review and approval of the complete marketing application (Biologics License Application (BLA) or New Drug Application (NDA)). Accordingly, FDA approval of a second-generation product should be rewarded with full data

¹³ Grabowski, Henry. “Data Exclusivity for New Biological Entities,” Duke University Department of Economics Working Paper. June 2007.

¹⁴ H.R. Rep. No. 98-857, at 41 (1984).

¹⁵ Congressional Budget Office, A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry, July 1998, Chapter Four, “The Effects of the Hatch-Waxman Act on the Returns from Innovation.”

¹⁶ Grabowski, Henry and Margaret Kyle. “Generic Competition and Market Exclusivity Periods in Pharmaceuticals,” *Managerial and Decision Economics* 28(4-5), pages: 491-502 (2007).

¹⁷ “...second-generation products – those with structural differences designed to improve performance while maintaining the same mechanism of action as the original product – are not conventionally considered as follow-on products.” Woodcock, J., “The FDA’s Assessment of Follow-on Protein Products: A Historical Perspective,” *Nature Reviews Drug Discovery* 6: 437-442, June 2007.

exclusivity as well. Such exclusivity is necessary to enable manufacturers to invest in the development of such innovative second-generation products and to enable patients to benefit from these treatment advances. Simply put, without sufficient data exclusivity of their own, second generation products will not be developed if a follow-on biologics pathway is enacted. Such a result would be a “lose-lose-lose” situation. A loss for innovators who would not pursue product improvements, a loss for follow-on manufacturers who would not have second-generation products to select from, and most important, a loss for patients who would not have the benefit of improved products.

For new indications, there should be an additional data exclusivity period for the original innovative product (e.g., 2 additional years) as an incentive for innovators to invest in such advances. Data exclusivity for new indications is critical in areas such as cancer research, where initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies most often occur much later in time. Without this additional exclusivity, there would be little incentive to research and obtain approval for these new indications.

BIO notes that data protection for a second-generation product will in no way affect the ability of a follow-on biologic to enter the market based on the original innovative product. The success of the second-generation product will depend on its benefits for patients and price compared to the follow-on and other competitive marketed products. If the second-generation product’s benefit is minor in comparison to existing products, then it is unlikely – particularly in today’s price-sensitive payer market – that granting data exclusivity to the second-generation product will impact the marketplace in any meaningful way. However, without any separate data exclusivity for second-generation products, major advances will be stymied.

A6. How are the patent portfolios claiming biologic drugs similar or dissimilar to the patent portfolios that claim small molecule (nonbiologic) drugs approved under the federal Food, Drug, and Cosmetic Act (FDCA)?

There is less public information available about patent portfolios for biologics than for small molecule drugs. However, certain inferences about such patent portfolios can be drawn from current biotechnology patent practice, and from biotechnology patents known to cover existing FDA approved biologics.

Like small molecule drugs, biologics are protected by different classes of patent claims, but there are critical distinctions:

(a) Compound claims. Claims to the active molecule, such as a specific peptide or antibody, exist for biologics, as they do for small molecule drugs. The way in which these active molecules are claimed, however, is often significantly different. For example, unlike small molecules, biologics are often claimed with reference to specific amino acid and/or nucleic acid sequences, and more often include functional claim limitations.¹⁸

¹⁸ For example, an antibody claim that includes a sequence limitation in addition to multiple functional limitations could be drafted in the following form:

(b) Claims to methods of treatment (use of the compound in a specific indication; dose, route, or schedule of administration, etc.) exist, as they do for small molecule drugs.¹⁹

(c) Drug product claims (formulation, dosage form) exist, as they do for small molecule drugs.²⁰

(d) Product by process claims are more prevalent and important in biotechnology than in small molecule medicinal chemistry. In a biotechnology product-by-process claim, the claimed molecule is defined not (or not solely) by its molecular structure or by its function, but as the product resulting from following the steps of a biotechnological process. Such claims are useful in cases where important characteristics of the claimed molecule depend on the process by which it was made (see below), but where it may not be possible or feasible to otherwise describe all such characteristics in structural and functional terms. This is sometimes the case for inventions that comprise complex mixtures of different compounds (e.g., a vaccine).²¹

(e) Claims that protect manufacturing technology: Process claims. Claims to manufacturing processes are more important in biotechnology than they are in the small molecule space.²² The

“An isolated human antibody, or an antigen-binding portion thereof, that dissociates from human [antigen] with a K_d of 1×10^{-8} M or less and a K_{off} rate constant of 1×10^{-3} or less, both determined by surface plasmon resonance, and neutralizes human [antigen] cytotoxicity in a standard in vitro L929 assay with an IC_{50} of 1×10^{-7} M or less, said antibody comprising a heavy chain variable region comprising a contiguous sequence from CDR1 through CDR3 as represented in SEQ ID NO:14.”

In such a claim, the reader would consult the attached patent specification to identify the specific sequence of amino acids that make up the critical portion of the claimed antibody.

¹⁹ An example of a biotechnology claim to a method of treatment could be drafted in the following form:

“A method for inhibiting the growth of human tumor cells that express human [factor] receptors and are mitogenically stimulated by [factor], the method comprising administering an effective amount of an anti-neoplastic agent and an effective amount of a monoclonal antibody to a human cancer patient having said tumor cells; (i) wherein said antibody binds to the extra-cellular domain of the human [factor] receptor of said tumor cell; (ii) wherein the antibody is not conjugated to the anti-neoplastic agent; and (iii) wherein the antibody inhibits the binding of [factor] to the [factor] receptor.”

²⁰ An example of a biological composition claim could be as follows:

“A pharmaceutical composition for parenteral administration to a human patient comprising human [enzyme] with catalytic activity and in a therapeutically effective dosage to treat a patient suffering from [syndrome]; and a pharmaceutical carrier, the composition being free of other human proteins present in its natural environment.”

²¹ An example of a biological product-by-process claim could be:

“A bacterin-toxoid vaccine against [bacterial strain] infection produced by culturing [bacterial strain] for a time sufficient for said culture to reach the late-logarithmic phase of growth; harvesting culture supernatant therefrom comprising leukotoxin, capsular antigen, soluble antigens, and [bacterial] cells at a density ranging from about 10^3 to about 10^8 cells per ml; and adding an inactivating agent.”

²² An example of a biotechnological process claim could be drafted as follows:

processes by which biologics are made are highly specific, complex, and determine many of the biologic's functional and structural characteristics, such as the way the protein is folded; the presence and position of sugar or fatty acid side chains; the way proteins aggregate; the way both ends of the protein's amino acid chain are truncated or extended; the presence of protein isoforms in the final preparation, or its impurity profile, and the like. Such product characteristics can often be expected to affect the product's safety, purity, and efficacy profile, and thus are integral to the approval of the product itself. Thus, many important inventions are made as biologics manufacturers work out optimal processes to reliably and reproducibly make, purify, and process a biologic molecule. In contrast to the Hatch-Waxman Act, which does not permit listing of process patents and excludes them from the Act's patent resolution procedures, FOBs legislation should contain adequate provisions to account for the importance of process patents in the biologics space, and allow for the pre-marketing resolution of disputes over such patents.

(f) Claims that protect manufacturing technology: Non-process claims. The high importance of process technology is also illustrated by the existence of patents on inventions that must be practiced as part of the technology platform necessary to make and use the biologic, such as claims to the isolated and purified DNA or RNA polynucleotide that encodes the recombinant protein, to the vector used to insert it into host cells, to the host cell that secretes it, to the promoter that drives its expression, and the like. The existence and importance of such claims relate to the way biotechnology inventions are made as the technology progresses through clinical and process development to market approval. The discovery of a new receptor on certain cancer cells, for example, may lead to the isolation and purification of the receptor protein and the sequencing of its amino acid sequence and of the gene that encodes it. To transform such basic discoveries into real-world therapeutic products, biologics manufacturers must develop a technology platform that can involve a number of independently patentable inventions, such as hybridoma cells that secrete antibodies to the drug target, the construction of vectors useful to transfer it to cultured cells, techniques to regulate its expression, and the like. This way, developing, making and using a biotechnology product can involve multiple patentable inventions that all must be practiced together. Patents on such inventions play a more prominent role in the portfolios that protect biologic drugs compared to the small molecule sector.²³ Despite

"A process of making a conjugate that comprises a [protein] glycoprotein having an N-terminal alpha-amino group and one poly(ethylene glycol); said process comprising: a) expressing and fermenting a recombinant [protein] that has an N-terminal peptidic extension that includes a proteolytic cleavage sequence, b) protecting the .epsilon.-amino groups, c) proteolytically cleaving the N-terminal peptidic extension, d) pegylating the N-terminal .alpha.-amino group, and e) deprotecting the .epsilon.-amino groups of the [protein] glycoprotein; wherein the recombinant [protein] comprises a sequence selected from the group consisting of the amino acid sequences SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO 4: and SEQ ID NO: 5."

²³ Examples of DNA or host cell claims that are part of the technology platform for manufacturing a therapeutic protein could be drafted as follows:

"An isolated DNA molecule encoding a protein comprising a sequence of amino acids selected from the group consisting of amino acids 1-142 of SEQ ID NO:1 and amino acids 1-226 of SEQ ID NO:3, wherein said protein is capable of binding [receptor]."

"A eukaryotic host cell containing DNA encoding an antibody molecule, said antibody being capable of being expressed in said eukaryotic host by said DNA, wherein said antibody has specificity for the antigen bound by the

their importance to the protection of biologics process technology today, it is possible that the relevance of such patents would be diminished under a FOBs regime where many FOB products would be produced overseas, as more fully explained in BIO's answer to Question #3 in the patent section, below.

Deposits of biological material are another aspect without correlate in the small molecule space. Every patent must contain a technical disclosure sufficient to enable other skilled persons to make and use the invention without undue experimentation. In biotechnology, however, inventions may not always be easily reproducible. For example, during a transfection experiment (a form of experimental gene transfer) it is not possible to predict exactly where, and how, a piece of foreign DNA will be integrated into the chromosomes of the host cell. Each successfully transfected cell will be unique in its own way, and may be near impossible to exactly reproduce by repeating the experiment. Other biotechnology inventions involve complex biological materials that cannot sufficiently be described by words alone. In such situations, the patent law requirement that a patent "enable" other skilled persons to make and use the invention can be satisfied by providing a sample of the biological material to a depository that is approved by the World Intellectual Property Organization, such as, for example, the American Type Culture Collection, where it can be accessed and studied by others. Some biologic drug claims that reference deposited biologic materials are narrowly limited in their scope to only what was deposited.²⁴

Other aspects of patent law, too, impact the way biologic drugs are claimed and the amount of experimental work that must be done to obtain comprehensive patent protection. Patent applicants who seek broader biotechnology claims must often conduct more experiments, do more work, and provide more in-depth explanation of the underlying biological processes and structure-function relationships than their colleagues in the small molecule field. This work must be done to satisfy the so-called "written description" and "enablement" requirements – a task that can be particularly difficult in biotechnology, where the unpredictability of biological processes may not allow other scientists to extrapolate from just a few described examples to the full scope of a broadly-claimed invention, and to practice it across its full scope without undue experimentation. Many biotechnology patent practitioners feel that the "written description" and "enablement" requirements operate to limit the breadth of claims available to patent applicants.²⁵ Stringent application of these requirements by patent examiners may also force patent applicants to retreat from an initially broader claim scope to a much narrower claim scope during the course of patent examination. Because such surrendered claim scope can be difficult or impossible to

antibody produced by hybridoma [###] as deposited with the ATCC, and wherein said antibody has cytolytic activity."

²⁴ An example of a biotechnology claim that includes a limitation to a specific deposit could be drafted as follows:

"A method for treatment of [specific cancer] comprising the step of administering a therapeutically effective amount of immunologically active anti-[antigen] antibody to a patient in need thereof, said antibody being derived from a hybridoma as deposited with the ATCC, deposit number [###]."

²⁵ For a recent interpretation of the so-called "written description" requirement, see *Carnegie Mellon University et al. v. Hoffmann-La Roche Inc. et al.*, Slip op. (Fed Cir. Sept. 8, 2008); available at: <http://www.cafc.uscourts.gov/opinions/07-1266.pdf>.

regain during enforcement in later litigation, patentees may find themselves confined to the literal limits of their issued claims, and unable to assert that even a close equivalent of their own, patented product infringes the patent.²⁶

In summary, while sharing some common features with small molecule patents, biologics patents more commonly include functional claim limitations, may be limited in scope to specific deposited biological materials or specific recited sequences, and often face unique challenges in meeting the written description and enablement requirements. When viewed as a whole, the patent portfolios that protect biologic drugs today are often more complex than those found in the small molecule space. These differences cannot be disregarded when crafting any follow-on biologics approval pathway. However, for the reasons set forth in BIO's answer to Question #3 in the patent section, below, it does not follow that higher complexity in the innovators' patent estates would always translate into more complex patent litigation. Instead, differences in the way patent disputes would be resolved would predominantly be grounded not in portfolio complexity, but in the way these portfolios operate under different approval standards for generic drugs and FOBs. In the small molecule space, a patent that claims an innovator's new molecular entity almost certainly also covers the generic drug applicant's molecule, because both must, by law, be "the same." Under a follow-on biologics regime, FOB products would likely be approvable under a less stringent standard that may provide FOB applicants with significantly wider latitude to design around innovator patents, and to manufacture FOB products that are different enough to avoid patent infringement, yet similar enough to benefit from the reference product's safety and efficacy record and obtain abbreviated approval. Thus, the differences between patent portfolios that claim small molecule drugs and biologics must always be examined in the regulatory context in which these portfolios will be brought to bear. This context must be taken into account when designing patent resolution procedures in any FOBs regime.

A7. Are the regulatory exclusivities currently provided to pharmaceutical drug products in the FDCA appropriate for new biologic drugs and/or significant improvements to existing biologic products? Are they appropriate for specific types of biologics? Why or why not?

BIO believes that the balance between innovation and generic competition struck by the Hatch-Waxman Act can provide valuable insights for the development of a follow-on biologics approval pathway. The Hatch-Waxman Act provides innovators and generic competitors a range of statutory, patent, and litigation-based incentives that, as described in response to a previous question, operate to create de facto protection against generic competition for, on average, 13.5 years. However, to achieve that same balance in the follow-on biologics context, the law must reflect the differences between small molecule drugs and biologics and differences between generic drugs and follow-on biologics. Under the 1984 Hatch-Waxman Act, a generic version of a small molecule drug may be approved for marketing only if its active ingredient is the "same" as in the innovator product. Thus, the patents that cover the innovator's active ingredient generally will apply to the generic version. Accordingly, the generic drug manufacturer cannot

²⁶ For a recent discussion of developments in the patent law doctrines relating to prosecution history estoppel and equivalence, see, e.g., John R. Allison and Mark A. Lemley, *The (Unnoticed) Demise of the Doctrine of Equivalents*, 59 *Stan. L. Rev.* 955 (2007).

gain FDA approval of its product by demonstrating that the active ingredient is the same as the innovator product and then claim in the patent context that it is different from the innovator's drug. In addition, the Hatch-Waxman Act contains provisions that can extend the term of an innovator patent to cover a period of 14 years following approval of an innovative drug. As noted above, new molecular entities today do not face generic market competition until 13.5 years post-FDA approval on average, evidencing that the mix of policy tools employed by the Hatch-Waxman Act has come remarkably close to achieving the 14-year mark deemed appropriate under the Act for innovators to recoup their substantial investments prior to generic entry.

In contrast, under the various statutory frameworks being considered for follow-on biologics, a follow-on will not be required to be the "same" as the innovator product due to the high degree of complexity of biologics. Instead, the follow-on product will only have to be similar or highly similar to the innovator product. This similarity standard for follow-on biologics creates a significant risk that a follow-on competitor will circumvent or "design around" the innovator's biotech patents – meaning that the follow-on may be outside of the scope of the innovator's patent claim. As a result, a follow-on biologic may be sufficiently similar to the innovator biologic to rely to some degree on the safety and effectiveness of the innovator product and thus receive abbreviated regulatory approval. Yet, it may still be different enough from the innovator product to avoid a patent infringement claim and, thus, reach the market well in advance of innovator patent expiration. For these reasons, patents may provide less comprehensive protection for innovative biologics under a follow-on biologics regime than they do for small molecules in the generic drug context.

Accordingly, if data exclusivity in a follow-on biologics regime were limited to the 5 years under the Hatch-Waxman Act, it would severely undermine incentives to invest in biotech innovation. Instead, BIO believes that a 14-year period of data exclusivity should be granted for biologics in any follow-on biologics regime. Such an approach would ensure that biologics receive the same degree of effective market protection from follow-on competition that small molecules receive today from generics, as described above. For more detailed information, please see BIO's response to Questions #4 above and #8 below, as well as our white paper on exclusivity and patent protection in a follow-on biologics regime, found at the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

A8. What are the appropriate factors to consider when determining the optimal length of regulatory exclusivity periods for biologic drug products? Do these factors change based on the type of referenced product involved, the extent of competition facing the referenced product, or patent portfolios claiming the referenced product, and if so, how?

The biotechnology industry in the U.S. is still relatively nascent and largely unprofitable: the companies that comprise it are primarily small, private start-ups heavily reliant on venture capital and years away from product commercialization. It is these small companies – many of which will never see a product come to market or turn a profit – that are undertaking the bulk of early development gambles, challenging the boundaries of current medical knowledge toward new and exciting mechanisms of disease treatment amid overwhelming odds. *In fact, small biotechnology*

companies (all biotechnology companies but the top ten) account for two-thirds of the industry's future clinical pipeline.²⁷

This enormous reservoir of biotech innovation is critically important to the future of healthcare, the U.S. economy, the biotechnology industry, and, of course, patients. Thus, in crafting a follow-on biologics approval pathway, it is important to err on the side of incentivizing innovation, particularly in light of the unique elements of the biotechnology industry. These companies already bear enormous costs and a very high degree of uncertainty, not only in product development and manufacturing, but also in raising the necessary capital to fund innovative research. Thus, as compared to the broader pharmaceutical industry, biotechnology companies are more vulnerable to the type of changes in investment incentives that could result from a poorly-crafted follow-on biologics regime.

The industry's heavy reliance on private equity also is notable. In 2005, there were 1,415 biotechnology companies in the U.S., but only 329 were publicly traded. In aggregate, even the publicly traded companies have not yet turned a profit:^{28,29}

Year	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Net Loss (\$B)	3.6	4.1	4.6	4.5	4.1	4.4	5.6	4.6	9.4	5.4	6.8	1.4	3.5

Given these unique challenges, patent protection (including patent term restoration under current law) is not sufficient to ensure adequate incentives for biotech innovation under a follow-on biologics regime. Rather, any statutory pathway for follow-on biologics must establish a substantial period of data exclusivity to preserve incentives for research, development, manufacture, and approval of new biologic therapies. As discussed in response to Questions #4, 6 and 7, this is necessary because, under a statutory framework allowing for follow-on biologics, there is a very real risk that the manufacturer of a follow-on product may be able to secure abbreviated regulatory approval based at least in part on the innovator's prior approval, and, at the same time, avoid infringing the patents that protect the innovator's product. That likelihood exists because of the confluence of critical factors not present in the Hatch-Waxman Act construct for generic small molecule drugs. Unlike a generic drug which must be the same as an innovator product, a follow-on biologic will only be required to be "comparable," "similar" or "highly similar" to the corresponding innovator product. Compared to generic drugs, the emerging follow-on biologics framework thus provides applicants with significantly more leeway to design around the patents that claim the reference product and make products that are

²⁷ The Boston Consulting Group: Rising to the Productivity Challenge, July 2004.

²⁸ Ernst and Young LLP, Annual biotechnology industry reports, 1995 – 2006. Financial data based primarily on fiscal-year financial statements of publicly-traded companies.

²⁹ Only about 20 biotech companies are currently profitable: Parexel's Bio/Pharmaceutical Statistical Sourcebook 2006/2007, pg. 39.

sufficiently different to avoid patent infringement, but sufficiently similar to get abbreviated regulatory approval.

In light of this potential gap in patent protection for biologics under a follow-on biologics regime, data exclusivity must be substantially longer than the five years currently afforded to small molecule drugs under the Hatch-Waxman Act. Failure to provide substantial data exclusivity would fundamentally alter the ability of biotechnology companies to continue to innovate because these companies, in order to secure the necessary resources from venture capital firms and other funding sources, must have some certainty that they can prevent free-riding on their investment in the development of new breakthrough therapies for a substantial period of time. Without sufficient data protection, companies and investors will have a great deal of uncertainty as to whether they will be able to recoup the – on average – \$1.2 billion in research and development costs that are necessary to bring a biologic to market.³⁰ This large amount of uncertainty will cause companies and investors to direct their investments to other areas where there is a higher degree of certainty that they will obtain a fair return on their investment. If this occurs, society as a whole will suffer, as fewer cures and therapies for cancer, Alzheimer's, Parkinson's, AIDS and many rare or unmet medical conditions will be developed.

As stated above, BIO believes that the best data available support a 14-year period of data exclusivity – not an “exclusive marketing” period – for biologics under a follow-on biologics regime. Several independent factors support this position. First, we know that the breakeven point for return on investment in a biologic occurs after it has been on the market between 12.9 and 16.2 years,³¹ and thus competition from follow-on biologics prior to that time period would clearly undermine incentives for such investment in the first place. Second, in 1984, Congress enacted patent term restoration provisions to provide pharmaceuticals with up to 14 years of patent protection following marketing approval. This time period was selected so that “research intensive companies will have the necessary incentive to increase their research and development activities.”³² As a result, the average period of time for marketing a drug product with patent protection now is 11.5 years,³³ and new molecular entities are, on average, marketed in the U.S. for 13.5 years before the entry of generic competition.³⁴

³⁰ DiMasi, Joseph and Henry Grabowski. “The cost of biopharmaceutical R&D: is biotech different?” *Managerial and Decision Economics* 28(4-5), pages: 469-479 (2007).

³¹ Grabowski, Henry. “Data Exclusivity for New Biological Entities,” Duke University Department of Economics Working Paper. June 2007.

³² H.R. Rep. No. 98-857, at 41 (1984).

³³ Congressional Budget Office, *A CBO Study: How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry*, July 1998, Chapter Four, “The Effects of the Hatch-Waxman Act on the Returns from Innovation.”

³⁴ Grabowski, Henry and Margaret Kyle. “Generic Competition and Market Exclusivity Periods in Pharmaceuticals,” *Managerial and Decision Economics* 28(4-5), pages: 491-502 (2007).

Thus, any statutory formula that allows for follow-on biologics should at least guarantee the same degree of effective market protection that Congress found necessary to maintain incentives for innovation in small molecule drugs – and, for the reasons discussed above, that protection can be accomplished most predictably through data exclusivity. Indeed, if the data exclusivity period for biologics is less than the number of years available to drugs under patent term restoration (that is, 14 years), then, because of the potential patent protection gap and the higher risks of biologics development, it will skew investment away from biotech innovation. Because data exclusivity would run concurrently with the patent term for the product, it therefore would create actual protection only in those instances where the follow-on manufacturer would be able to work around the patents held by the innovator but still gain abbreviated approval of its product.

For a fuller discussion of these data and the justification for 14 years of data exclusivity, please visit the following URL:

- http://bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf

A9. How does the European Medicines Agency's approach to regulatory exclusivities in its abbreviated regulatory approval pathway for follow-on biologics inform the U.S. approach?

As we state in our answers above, we believe that a 14-year base period of data exclusivity is necessary to avoid undermining incentives for the development of innovative biologics. And for the reasons explained more fully below, anything less would jeopardize the U.S.'s leadership role in producing innovative biotechnology medicines for the patients who need them.

The European Union provides eight years following innovator approval during which a generic or biosimilar application cannot be submitted, two further years (i.e., 10 years total) during which a generic or biosimilar cannot be marketed, and one further year if, during the first eight years of data exclusivity, the holder of the reference product obtains an authorization for new therapeutic indication(s) which bring(s) significant clinical benefit in comparison with existing therapies. While we believe that the length of data exclusivity provided in the European Union would be inadequate in the U.S. context, we strongly agree with the provision of a further exclusivity period for new indications, and we also note that the European Union provides 10 (or 11 if appropriate) years of data exclusivity to next- or second-generation products. (See BIO's Response to Question #4 above). We also strongly support the protection against the filing of biosimilar applications too soon after innovator approval, for the reasons described more fully in response to Question #1 below in the patent section).

We believe that if the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, the result will be substantially less investment in biotech innovation. Because the U.S. leads the world in this area, the economic impact of reduced investment will be particularly acute here in the U.S. The latest data from Burrill & Company show that the U.S. continues to dominate the biopharmaceutical market, whether the measure is sales, R&D, employees or public companies:

US, European, Canadian, Japanese, Canadian, and Australian Biotech: Global Activity Measures (2005, U.S. dollars)

	U.S.	Europe	Japan*	Canada	Australia
Sales/Revenue	\$71.5 B	\$7.5 B	\$0.82 B	\$1.7 B	\$1.0 B
Annual R&D	\$18.5 B	\$4.2 B	-	\$0.6 B	\$0.1 B
# of Companies	1,473	1,878	464	470	226
# of public companies	363	96	22	81	58
# of employees	146,100	32,470	4,171	7,440	6,393

*Japan – public companies only

The U.S.'s per capita biotech R&D expenditures are 574% higher than the European Union's (EU's) per capita biotech R&D expenditures.³⁵ It also should be noted that:³⁶

- The biotechnology industry's U.S. trade surplus grew from \$593 million in 2000 to \$1.8 billion in 2004 – an increase of almost 200%. Over the same period of time, overall U.S. trade in advanced-technology products decreased by more than 200% -- going from a net surplus to a net deficit.
- The biotechnology industry's U.S. exports grew from \$1.7 billion in 2000 to \$3.7 billion in 2004 – an increase of more than 100%.
- Between 2000 and 2004, U.S. jobs in the biopharmaceutical industry rose by 8.3%.
- The biopharmaceutical industry expands U.S. gross domestic product by at least \$27 billion annually, on a permanent basis, for every one-time R&D investment of \$15 billion. In 2005 alone, the U.S. biotechnology industry invested nearly \$20 billion in R&D.

Thus, a follow-on biologics pathway that does not preserve the necessary incentives for innovation (that is, 14 years of data exclusivity) would disproportionately and negatively affect the U.S., the world leader in biotechnology innovation, and would drive investment towards less risky ventures, including those outside of the U.S.

B. Patent Dispute Resolution Issues

B1. Would it be important to have the litigation of any patent disputes proceed concurrently with the abbreviated FDA approval process for follow-on biologics? Why or why not? What has been learned from the experience under Hatch-Waxman about the incentives necessary to encourage early resolution of patent issues?

It would be important to resolve patent disputes concurrently with the approval process, and prior to launch of, a follow-on biologic, because premature launches of such products carry numerous risks that significantly impact the public as well as the private interests of the parties.

³⁵ R&D figures are from Parexel's Bio/Pharmaceutical R&D Statistical Sourcebook 2006/2007. Population figures estimated as of July 2006.

³⁶ See URL: <http://www.nsf.gov/statistics/seind06/c6/tt06-03.htm> -- last accessed on February 1, 2008.

A judicial determination of patent infringement for a prematurely-launched FOB product would raise significant concerns about therapeutic disruption for patients. In fact, consistency of product availability is of great importance to patient health and physician prescribing practices and such consistency would be jeopardized by a premature launch without patent resolution.

Premature marketing would not only create unnecessary confusion among physicians, patients, payers and other market participants – it would also lead to great business uncertainty for both parties. From the reference product sponsor's perspective, a premature follow-on biologic launch may lead to a loss of market share and price erosion that cannot be reversed even if a court subsequently were to find the asserted patents valid and infringed. From the follow-on applicant's perspective, a judicial determination of patent infringement could lead to very significant damages awards which may or may not exceed the applicant's financial capacities.

Seen this way, launches of follow-on biologics prior to patent resolution entail huge business risk not only for the innovator, but also for the follow-on applicant – a risk that is exacerbated by the considerable financial investment in FOB development (much larger than the investment required for a generic drug submission) that would already have been made at that point. It stands to reason that only the biggest, financially strongest FOB applicants would tolerate the risk of losing their investment or facing large infringement damages awards. Thus, a FOB framework that routinely envisions patent resolution after FOB market entry would selectively disadvantage smaller, financially weaker FOB applicants and operate to create FOB markets that are dominated by only a few, financially strong players and FOB products.

Sufficient time for resolution of patent disputes prior to follow-on biologic approval must therefore be provided. Ideally, patent disputes would be resolved by the time the innovator statutory exclusivity period expires. This way, the patent resolution could take place without the need for special stays pending litigation during a time when the FOB product could otherwise be launched. Such timing of patent resolution would provide business certainty that a risk-free FOB launch could occur at a fixed point in time. Timing of patent resolution prior to the expiration of the innovator's statutory exclusivity period would also encourage full resolution of patent validity questions on the merits, rather than through settlement, thus providing more patent certainty for subsequent FOB applicants.

However, while patent resolution should be timed so as to be concluded within the innovator's statutory exclusivity period, it should not be timed so as to begin too early. The FOB applicant must be far enough down the road of developing its comprehensive data package, as well as its detailed manufacturing processes, needed for the FOB regulatory submission and for a full exploration of relevant patent-related issues. Further, in order to properly evaluate a FOB application and the heightened concerns regarding immunogenicity in the biologics arena, the FDA will need sufficient experience with the reference product in the marketplace.

It also must be kept in mind that the earliest date on which a FOB application can be submitted during an innovator's data exclusivity period should not be set so early that its final approval, upon expiration of the innovator's exclusivity, is so remote in time that the data on which it relies have become inapposite to the final FOB product due to, for example, subsequent changes to the FOB process technology used in commercial manufacturing. Finally, the likelihood that any

given FOB application would be approvable will be lower than it is today for generic drug applications, and the possibility that the Secretary may require additional clinical studies is greater. Thus, patent litigation would be premature if it were allowed to commence before a determination that the FOB application in question is complete and in condition for review without additional clinical studies.

A focus on triggering “patent challenges” at the earliest possible opportunity, possibly complemented by valuable regulatory exclusivity incentives for doing so, could thus lead to premature litigation as well as premature submission of FOB applications. The focus should be on incentivizing the timely submission of complete, high-quality, approvable FOB applications, not to reward the first “patent challenge.” Experience under the Hatch Waxman Act confirms that incentives for early resolution of patent disputes must be crafted carefully to avoid unintended consequences. Premature litigation, both with respect to timing and with respect to the merits, is commonplace today in the small molecule space. For example, a survey of active NDAs for New Molecular Entities (NMEs) approved after March 2000 for which a paragraph IV certification could have been submitted after March 2004³⁷ shows that about 42% of all NMEs in this sample faced a paragraph IV challenge between the fourth and the seventh year following NDA approval (average 4.6 years). This, it is submitted, is an extraordinarily high litigation burden on both innovators and generic drug applicants that should not occur within just a few years after NME launch, and need not occur at all under a FOBs regime. A rational FOB framework would instead create incentives for timely patent dispute resolution within the innovator’s statutory exclusivity period, to proceed in parallel with the FOB approval process, and would account for judicial determinations of patent validity and infringement by making the approval of the FOB application effective on the date of patent expiration or expiration of the innovator’s statutory exclusivity period, whichever occurs later.

B2. How long might the approval process for a follow-on biologic application take? What factors might influence this timing?

It has been estimated that the time required for follow-on biologic manufacturers to obtain regulatory approval likely will be three to five years for pre-clinical and clinical testing, and one-and-a-half to two years for FDA review and approval.³⁸ Note that it also takes four to six years to bring manufacturing capacity on-line (likely developed concurrently with product development schedule).

Following passage of any legislation, FDA will need to create a regulatory scheme, testing requirements, and product-class guidelines. However, we note that, in most cases, the European Union has completed product-group-specific guidance in 12-18 months. While FDA must conduct its own guidance development process, it will have the benefit of what has been and can be learned from the European Union and, in some cases, this may allow FDA to complete guidance in a shorter time. Furthermore, there are administrative processes FDA will have to put

³⁷ The time for which Paragraph IV certification dates are available from the FDA at <http://www.fda.gov/cder/ogd/ppiv.htm>

³⁸ Grabowski, Henry, *et al.* “The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions,” White Paper, August 2007. See URL: http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf

in place prior to approval of follow-on biologics; these will be separate from any guidance requirement. A guidance requirement would run concurrently with the establishment of these processes and thus would not create any additional delay.

B3. How might differences between patent portfolios for small molecule drugs and biologics affect patent litigation involving follow-on biologics? How long might patent litigation involving a follow-on biologic product take?

Compared to patent litigation under the Hatch-Waxman Act, biologics process patents would be expected to play a more prominent role in conjunction with other patents in the portfolio that protect the reference product. The main differences in the way in which patents would be litigated would, however, not be grounded in portfolio complexity, but in the way small molecule and biologics patent portfolios operate under different approval standards for generic drugs and FOBs. For example, because the reference product and the follow-on product would likely not need to be identical, there would be more frequent litigation of questions of noninfringement, doctrine of equivalents, and prosecution history estoppel. Claim construction would therefore be an even more important aspect of follow-on biologics patent litigation. In addition, it can be expected that the affirmative defenses of patent invalidity and unenforceability would be asserted at the same frequency at which they today occur during Hatch-Waxman litigation.

In another distinction from Hatch-Waxman litigation, biologics patent portfolios do not lend themselves to an Orange Book listing process of the kind relied on as the starting point for generic drug litigation today. Because a FOB product would likely not need to be the same as the reference biologic, and would invariably be made by a different manufacturing process, the innovator should not be forced to “guess” which of its product or process patents would probably cover a future FOB product and which ones might not, with potentially dire consequences for having guessed wrong. Instead, a mechanism that provides confidential access to follow-on product and process data for the sole purpose of identifying relevant patents would seem to be a more rational and practical approach.

Additional questions arise with respect to third parties who are likely to get involved in FOB patent litigation. Patent owners (such as university licensors) who have licensed relevant patents to the reference product sponsor, but who have reserved their patent enforcement rights, may need to be included in the patent resolution process. Early inclusion of such third party plaintiffs would seem to be necessary for a patent resolution process that provides legal certainty for innovators, patent holders, FOB applicants, and market participants prior to marketing of a FOB product.

It is not clear, however, that a relatively high degree of complexity of biologics patent portfolios, or the inclusion of third party patentees, would necessarily translate into a higher rate of litigation, or length of litigation, in the FOBs context. Industry experience over more than two decades of biotechnology patent litigation has shown that, while litigation involving biologic products can indeed be complex, such litigation has not been vastly more complicated than other high-stakes commercial litigation over other valuable products. Biotechnology patent disputes today can be adjudicated within a relatively stable doctrinal framework that is expected to

solidify further as biotechnology matures both as a science and as an industry. Further, some of the aspects that add complexity to biologics patent estates would not necessarily all come to bear in FOBs patent litigation. For example, composition-of-matter patents claiming the DNA that encodes the biologic protein, the host cell used for making it, or the promoter sequence used to drive its expression, etc., may not be relevant in U.S. patent litigation if the follow-on product is imported from India, China, or Europe. Third, the sheer rate of litigation per reference product is likely to be lower for biologics than it is for small molecule drugs. In the Hatch-Waxman context, a single reference product can get involved in multiple patent infringement suits against eight or more generic drug applicants.³⁹ Due to the complexities and cost inherent in developing biologic products, including FOBs, the number of potential FOB competitors – and the amount of litigation over multiple follow-on applications all referencing the same innovator product – will likely be smaller overall for at least a number of years. Finally, the length of reference product data exclusivity will be an important determinant of the numbers of “relevant” patents, because only patents that have a term longer than the reference product data protection would need to be adjudicated. It stands to reason that substantial periods of reference product data exclusivity would have the beneficial, if incidental, effect of simplifying litigation by taking those patents that expire during the innovator’s data exclusivity period “off the table.”

No good predictions can be made with respect to length of litigation. Patent litigation length depends on many factors that are highly specific to the parties, the legal issues in the case, the caseload of the court where the action was brought, the way the case is managed by the court, the individual judge to whom the case was assigned, and the like. To be sure, patent litigation generally does consume a lot of time. Experience from the small molecule sector, for example, suggests that the 30-month period envisioned by the Hatch-Waxman Act is not always sufficient to fully litigate a patent case on the merits. In any event, substantial reference product data exclusivity periods would likely be helpful in providing a litigation timeframe in which all key patent disputes could play out prior to FOB approval.

B4. When is it in the interest of a referenced biologic drug manufacturer to resolve patent issues prior to marketing by a follow-on applicant? When is it in the interest of a follow-on biologic applicant to resolve patent issues prior to marketing its follow-on biologic? When is it in the interest of either party to resolve patent issues following commercial marketing of the follow-on product?

For the reasons stated in BIO’s answer to Question #1 in the patent section above, both innovators and follow-on applicants would normally be expected to want to resolve patent disputes prior to launch of the FOB. For a more complete discussion of the disadvantages of a process that routinely envisions patent resolution after FOB launch, see BIO’s answer to Question #1 in the patent section as well.

³⁹ See, e.g., multiple infringement actions filed on August 12, 2008 by Hoffmann-La Roche, Inc. against Cobalt Pharmaceuticals Inc., 2:08-cv-04054; Gate Pharmaceuticals, 2:08-cv-04058; Mutual Pharmaceutical Company, Inc. 2:08-cv-04060; Genpharm Inc. 2:08-cv-04052; Teva Pharmaceuticals USA, Inc. 2:08-cv-04059; Orchid Chemicals & Pharmaceuticals Ltd. 2:08-cv-04051; Apotex Inc. 2:08-cv-04053; Dr. Reddy’s Laboratories, Ltd. 2:08-cv-04055; in the U.S. District Court for the District of New Jersey relating to defendants’ Paragraph IV certifications as part of ANDAs to manufacture generic versions of Roche’s Boniva® (ibandronate sodium) once-monthly tablets.

B5. What are the legal impediments facing a follow-on biologic applicant that has not been sued for infringement to obtaining a declaratory judgment on patent infringement or invalidity issues prior to commercial marketing of its follow-on product?

Appropriate follow-on biologics legislation would provide opportunities for innovators to protect their intellectual property rights – and for both parties to resolve disputes over them – before the FDA allows a follow-on product on the market. By making the filing of a FOB application an act of infringement, innovators and patentees would have a cause of action for infringement. Likewise, FOB applicants who have a justiciable case or controversy could seek legal and business certainty under the available Article III jurisdiction, as interpreted by the Supreme Court and the U.S. Court of Appeals for the Federal Circuit. By ensuring that these two complementary mechanisms would operate during the innovator’s statutory exclusivity period, patents that claim the FOB product could be tested in litigation, thus ensuring patent and business certainty for the FOB applicant and innovator, and market certainty for patients, providers, and payers.

B6. Are regulatory exclusivities needed to encourage follow-on biologic applicants to challenge patents? Why or why not?

The emphasis should not and need not be on “challenging patents.” The 180-day exclusivity under the Hatch-Waxman Act was designed to incentivize generic drug applicants to take on the cost of patent litigation because of free-rider concerns over other generic drug applicants that would benefit from this litigation investment. While it can fairly be asked whether the benefit of being able to exclusively market a first generic drug without significant price erosion for six months is commensurate with the cost of patent litigation,⁴⁰ many believe that the 180-day exclusivity has created an unnecessarily litigious environment by placing a high premium on bringing the earliest possible patent challenge, often by multiple filers who cannot afford to cede valuable generic exclusivity for a profitable drug to their generic competitors. 180-day exclusivity rewards the earliest possible challenge, not the one with the highest merits. In BIO’s view, the award of regulatory exclusivity or similarly powerful incentives merely for “challenging patents” carries a significant risk of operating in multiple unintended ways that, in the Hatch-Waxman context, have already led to significant litigation, regulatory scrutiny, and legislative intervention.

BIO cautions against the creation of such misguided and unwise patent litigation incentives. FOB legislation should encourage and facilitate investment in bringing FOB products to market rather than “challenging patents.” The logic for creating special patent challenge incentives under the Hatch-Waxman Act does not apply to FOBs because no two biologic drugs made by different manufacturers using different processes will be identical. Therefore, patent litigation over one FOB product will not necessarily apply to another FOB product, and the risk of

⁴⁰ This question can even more squarely be posed in light of the MMA Amendments of 2003, which confer 180-day exclusivity for the mere first filing of a paragraph IV certification, regardless of whether litigation ensues.

litigation free-riders faced in the generic context will be much diminished under a FOB framework.

Further, compared to a generic drug submission, the data package that will need to be assembled for a follow-on biologic application will be much more comprehensive and expensive. Also, regulatory approval of a follow-on biologic application will likely be less certain than it is for an average generic drug application, and further investment may be necessary to conduct any additional studies the Secretary may require, whether pre- or post-approval. In short, having made a very significant investment in its follow-on biologic technology, a follow-on applicant will be sufficiently motivated to challenge any patent barriers to entry even in the absence of artificial “patent challenge” incentives.

While it is thus unlikely that FOB applicants need special incentives to challenge patents, if Congress were to decide that a special regulatory exclusivity incentive is appropriate, the conditions under which such exclusivity would be triggered or forfeited would need to be carefully defined. In any case, such incentives should be designed to stimulate investment in FOB development and the submission of quality, approvable FOB applications, not the submission of naked patent challenges at the earliest possible opportunity.

Conclusion:

BIO appreciates this opportunity to respond to FTC’s questions regarding competition provided by developing a regulatory approval pathway for follow-on biologic drugs. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

John M. Taylor, III
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