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Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Avenue, N.W.
Washington, DC 20580

September 29, 2008

Re: Emerging Health Care Competition And Consumer Issues – Project No. P083901

Dear Commissioners:

The Novartis Group of companies (Novartis) is pleased to submit the enclosed response to the questions on the important subject of the competitive effects of Follow-on Biologics (FOBs), in response to the Federal Trade Commission's (Commission's) Federal Register Notice of September 3, 2008 (73 Fed. Reg. 51479).

Novartis, as a global leader in both innovative and generic medicines and the biosimilars pioneer, is uniquely positioned to contribute to the Commission's inquiry. Twenty-five percent of our new therapies under development are biologics, and our Sandoz generics business has received four (4) biosimilars approvals in Europe, as well as U.S. approval, under the existing 505(b)(2) pathway, for the first follow-on version of a recombinant biologic.

The needs of patients must be foremost in establishing a new regulatory pathway for interchangeable follow-on versions of Public Health Service Act (PHS Act) biologics in the U.S. In that regard, competition among safe and effective medicines, including innovative biologics and follow-on versions of those biologics that are off-patent, spurs innovation and expands access to more affordable biologics. In addition, by offering savings to government and private payors, FOBs will make available health care dollars for further investment, and validate the continued and beneficial, free-market pricing of all biologics.

Now is an exciting time for biotechnology. The industry is past proof-of-principle, and investment dollars freed up through competition will be well spent on research and development of exciting new medicines addressing unmet medical needs. In this context, it is time to upgrade our regulatory approaches and enable the U.S. Food and Drug Administration (FDA) to approve all products based on data derived from state-of the-art science, rather than constraining FDA's ability to evaluate medicines with unduly rigid data requirements or artificial barriers to entry codified in a statute.

As we and other companies have demonstrated through approvals under the European Union (EU) biosimilars pathway, science and technology have progressed to enable the development and manufacture of safe and effective, lower-cost versions of off-patent biologics. Significantly, the EU biosimilars pathway uses a regulatory approach based on the internationally-accepted standard of comparability, which initially was developed by FDA in collaboration with the biopharmaceutical industry in the mid-1990's to enable manufacturing changes to these previously-approved biologics. An equally-straightforward legislative approach to a pathway for FOBs based on these same regulatory concepts is readily-available in the U.S. and could be enacted with very simple legislative provisions. Indeed, such an approach was use by FDA in May 2006 for approval of Omnitrope, Sandoz' follow-on human growth hormone, in connection with which FDA cited 28 times the highly-similar standard by which comparability is defined.

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As reflected in our enclosed answers to the Commission's questions, Novartis supports a balanced position on FOBs that enables rigorous regulatory standards to be applied consistently by FDA to all products, including innovator and follow-on biologics; one that respects intellectual property rights; and, finally, one that provides an appropriate exclusivity period for innovator biologics.

Central to achieving a reasonable balance is preserving the existing system for resolving patent disputes involving PHS Act biologics. The Patent Code already contains all the necessary prohibitions on patent infringement and grounds upon which patent rights can be adequately and appropriately defended. Accordingly, we have consistently advocated for decoupling of the biosimilars review and approval processes and patent litigation. However, as described more fully in our enclosed response, we would suggest a requirement that the FOB applicant provide notice at the time of FOB approval to the Biologics License Application (BLA) holder of the Reference biologic before marketing the FOB. With a post-approval stay on launch of the FOB for say 45 or 90 days, such a procedure would provide an orderly opportunity for the BLA holder to seek an appropriate remedy in court, or otherwise, should patent infringement be alleged. Of course, maintaining the separation of the regulatory review process from the patent system and balancing the equities would be best served by establishing a fair exclusivity period for innovator biologics.

To implement a patent linkage system as exists today for generic drugs under Hatch-Waxman could prematurely risk the patent rights of U.S. patent holders and the commercial value of the biotech portfolios defined by those patent rights, and do so unnecessarily. In such a system, there is no net competitive or other benefit for patients – who are the consumers for whom FOBs, as well as innovator biologics, are being developed. Indeed, as detailed in our comments, patent linkage can be expected to foster extensive litigation that is not only hostile to patent rights and the innovation they promote but also not pro-competitive nor enhancing of patient access. The adverse consequences flowing from such pre-approval litigation are contrary to the basic principles of competition and access underlying FOBs and include: (i) unnecessary litigation costs during FOB development when capital is better directed at R&D and production of both innovator biologics and FOBs; (ii) a slowdown and potentially-indefinite delay in the FDA regulatory review and approval processes even though biotech patent litigation and FDA approval are wholly unrelated; and (iii) the creation of disincentives to the further development of FOBs during the term of innovator patents due to the risks associated with prolonged and complex biotech patent litigation, and the potential required disclosure of FOB applicants' trade secret and confidential information to the innovator, which will discourage many qualified FOB applicants from developing competing products.

We commend the Commission for focusing its resources on the positive role FOBs can play in generating the competition necessary to stimulate biotech innovation and to expand access to safe and effective therapeutic biologics. I hope you find our data and perspective useful, and we look forward to working with the Commission as it plans the upcoming workshop.

Kind regards,

Robert Pelzer

Enclosure

COMMENTS IN RESPONSE TO FEDERAL TRADE COMMISSION QUESTIONS ON FOLLOW-ON BIOLOGICS
Emerging Health Care Competition And Consumer Issues – Project No. P083901
(September 30, 2008)

I. Competition Issues Involving Follow-on Biologic Drugs[1]

A. Regulatory Exclusivities and Follow-on Biologic Drug Competition

1. 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 reference and follow-on products in European markets? Would reference product manufacturers lower their prices, offer discounts, and/or engage in enhanced marketing activities?

The market entry of Follow-on Biologics (FOBs) will have a competitive effect as a result of natural market forces regardless of whether one or multiple FOB competitors enter the market, although the full extent of that competitive effect is likely to be dependent upon the actual number of competitors. Moreover, the Novartis Group of companies believes that implementation of a pathway to enable FOBs competition will itself have competitive effects, albeit discrete and less noticeable than those triggered by the actual competition itself, as the marketplace prepares for the advent of competition in segments that, until now, have not experienced it. It generally is anticipated that, at least in the early years of implementation, there probably would be fewer FOB competitors against any given previously-licensed biologic because the investment per FOB generally is expected to be significant in relative terms. Moreover, FOB competitors may enter the market over staggered time periods, depending upon whether there is patent linkage to the regulatory review process (which, as discussed below, the Novartis Group of companies does not believe there should be), as there may not be a patent-based date-certain for FDA licensure and/or sponsor launch of a FOB competitor to a given biologic reference product. Nonetheless, even with the foregoing variables potentially affecting the number and timing of FOB competitors' market entry, and despite the fact that many biologics are used to treat relatively-smaller patient populations, the substantially-higher unit cost of biologics for payors represents a significant incentive for market entrants.[2,3,4] That competitive incentive will be

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[1] As the company that achieved with Sandoz' Omnitrope the first recombinant follow-on biologic drug approval to a recombinant reference listed drug (see http://www fda.gov/CDER/drug/infopage/somatropin/default.htm), the Novartis Group of companies noted with interest the Commission's use of the term "biologic drug" in the title of this section. The term "biologic drug" often is applied to those products such as rhGH which are biologics in science but that are approved by the U.S. Food and Drug Administration ("FDA") as drugs under the Federal Food, Drug, and Cosmetics Act ("FD&C Act"). Given that a pathway already exists for competitive biologic drugs and FDA is approving competing versions of biologic drugs, it is assumed here that the term is meant to apply in this context to those products which are biologics in science but that are approved under the Public Health Service Act ("PHS Act").

[2] "*Economic Issues With Follow-On Protein Products*," Lanthier, Behrman, & Nardinelli, NATURE REVIEWS/DRUG DISCOVERY, Volume 7 (Sep. 2008).

enhanced as and when the regulatory pathway for FOBs becomes clearer over time and with experience, thereby enabling investments to be made more predictably.

There currently is no established empirical model that could predict the competitive effects of FOBs. In terms of experience in the highly-regulated markets, it is derived from the European experience base with their biosimilars pathway, which is growing rapidly.[5] In Europe, multiple marketing authorization applications have been reported to date for biosimilar competitors to three currently-approved and marketed European reference medicinal products – somatropin, epoetin alfa, and filgrastim. According to published data, there have been a total of 11 applications that have been acted upon favorably, resulting in seven marketing authorizations as well as four positive opinions that are awaiting conversion to full marketing authorizations.[6]

Biosimilar products in Europe have been launched selectively to date into a community of 27 countries. Those countries maintain varying health care systems and distinctive pricing and reimbursement systems (including national and regional systems and combinations of public and private payors), which generally do not apply free-market pricing and are rather variable on patient access, with some countries and certain payors using a tender (bidding) process to facilitate the acquisition of reference biologics and biosimilars based on price. Thus, important lessons can be learned from Europe, particularly in terms of the competitive impact of a FOBs pathway and the market entry of FOBs. Nonetheless, because of the decentralized and distinctive reimbursement systems prevalent in Europe, there are limits to the parallels that can be drawn.

Recognizing these inherent limitations, nonetheless, the experience to date in Europe is informative. Following the launch of competing biosimilars, the reference product sponsors indeed have lowered their price. What is most notable in this regard is that this competitive effect has not been limited just to the individual reference product. Instead, the European experience thus far reflects that every sponsor with a product in the same "class" also has lowered their prices, thereby achieving significant savings for healthcare systems in Europe (Figure 1).[7]

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[3] Issue Analysis: "*Healthy Competition: The Case for Generic and Follow-On Biologics*," Conko, Competitive Enterprise Institute (May 22, 2007).

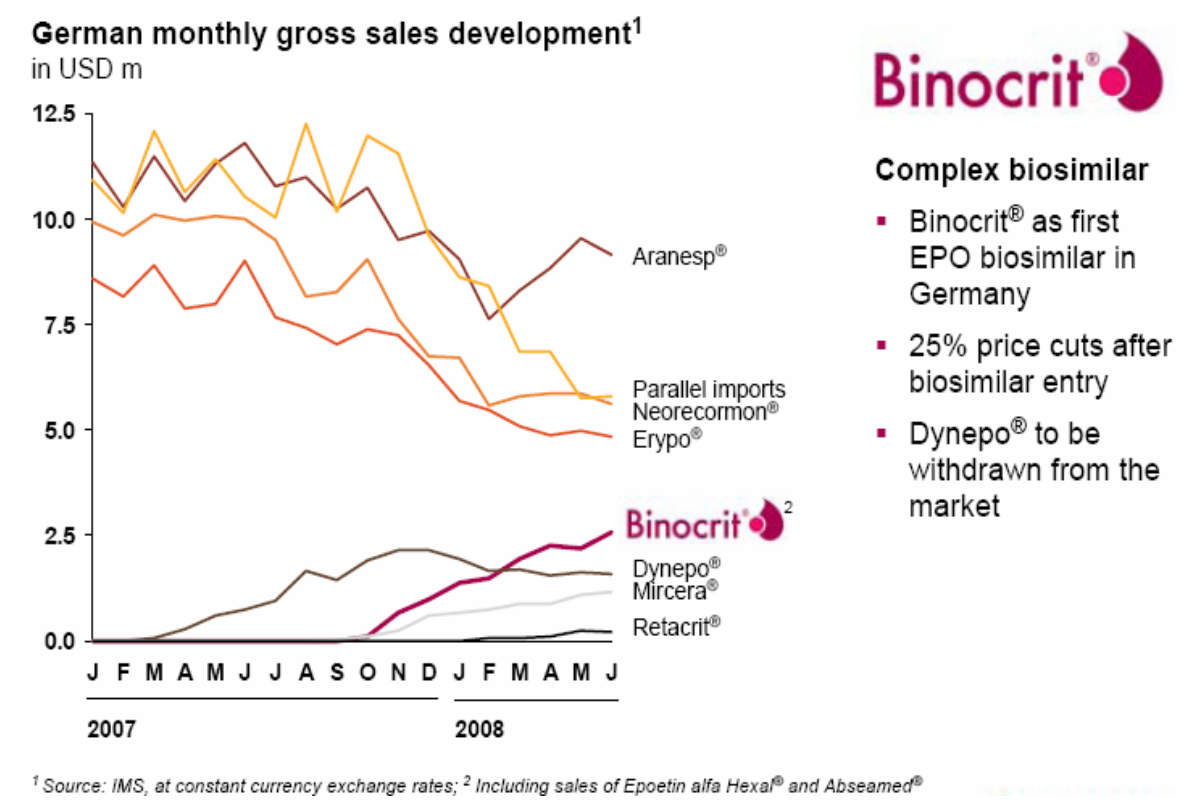
[4] "*Biogenerics: What They Are, Why They Are Important, and Their Economic Value to Taxpayers and Consumers*," Erlich & Wright, Citizens Against Government Waste (May 2, 2007).

[5] "*What Follow-on Biologics Mean for the Future of the Biotechnology Industry*," Hussain & Woollett, BIOPHARM INTERNATIONAL (Nov. 2007), at 32-40.

[6] Centralized approval of medicines in Europe follows a two-step process: after the regulatory authority, the European Medicines Agency ("EMEA"), through its expert medicines reviewers on the Committee for Human Medicinal Products ("CHMP"), renders a positive opinion on an application, the actual marketing authorization is granted by the European Commission. The transition between these two steps historically has operated quite smoothly. Indeed, we are only aware of two glitches in this process – the first occurred with Omnitrope, and the second occurred this year with the recently-authorized filgrastim biosimilar applications.

[7] Sandoz Day Investors' Event, Presentation By Hannes Teissl, Head Biopharmaceuticals BU Sandoz International, *available at* http://www novartis.com/downloads/investors/presentations-events/other-events/2008/2008-09-Sandoz-Day_Teissl-Presentation.pdf, Slide 10/11 (last accessed Sep. 22, 2008).

Figure 1



[1] Source: IMS, at constant currency exchange rates; [2] Including sales of Epoetin alfa Hexal® and Abseamed®

The issues of class for biologics are discussed in greater detail below in connection with the Commission's questions on interchangeability designations for biosimilars, although it is worth noting here that these issues have been brought to the fore in Europe as a result of the absence of such interchangeability designations.

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

Marketplace competition will be enhanced when patents expire if FDA is authorized to designate safe and effective FOBs as interchangeable. Interchangeability of biologics has been established scientifically, and FDA even has made interchangeability determinations for several PHS Act biologics, and safety is decidedly not an issue. Implementing a regulatory pathway that permits such interchangeable biologics to be licensed is the optimal mechanism for allowing market forces to operate because it will enable direct, head-to-head competition to occur based on price factoring in the "front-loaded" investment in the research and development of a FOB without the additional cost of a "back-loaded" investment in the advertising, promotion, and detailing of a FOB. Consequently, competing FOBs that are designated as interchangeable can be anticipated to achieve more rapid and ultimately more substantial market share

penetration that those that are not. The resulting reduction in prices caused by multiple FOB sponsors entering the market and competing when patents expire will incent further innovation for new products as well as better manufacturing science itself. The latter incentive for enhanced and innovative biologics manufacturing capacity is an oft-forgotten but critically-important aspect of innovation particularly in the context of biologics, and it is one that can enable a direct reduction in the cost of goods and an increased durability of supply.

Interchangeability, as that term recently has been discussed in the context of proposed FOBs legislation in the U.S., is a regulatory designation that would embody the expert scientific conclusions of FDA[8] – the only authority in the system that has the requisite expertise and access to a FOB sponsor's actual data on which to evaluate the interchangeability of a FOB and its reference product at the analytical, non-clinical, and, where appropriate, clinical levels.[9] The current trend in the proposed U.S. legislation is to establish a two-step process to interchangeability rather than having interchangeability be inherent in the FOB approval itself. Thus, in order to be approved, the sponsor of a FOB must demonstrate that it is comparable to a reference biologic (one previously-licensed under the PHS Act), and separately, in order to be designated as interchangeable, meet certain additional, as-yet-unspecified criteria. The reasonableness of such a two-step approach should be considered in the context of the long-standing and well-established comparability standard as defined in ICH Q5E.[10] When that international comparability standard is applied to a reference (pioneer) biologic undergoing a manufacturing change, interchangeability between the "old" and "new" biologic products is presupposed, and the "new" product is not labeled as being "different" or even having been "changed". The basis for applying a different outcome to a FOBs sponsor meeting that same international comparability standard is unclear.

In the regulatory context of an FDA interchangeability determination, confusion increasingly occurs at the interface between FDA and healthcare providers (physicians, pharmacists, and other healthcare professionals who prescribe or dispense medicines). This is because, as a federal regulatory authority, FDA is responsible for the review and approval[11] or licensure[12] of products that enables their introduction into interstate commerce, whereas the use and dispensing of those products in the practices of medicine and pharmacy is the responsibility

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8 "*Paving the Critical Path for Innovation to Thrive in the Biotechnology Industry Through Comparable Innovation in the US Regulatory Framework*," Hussain, Pomerantz, & Rummelt, THE RPM REPORT (Feb. 2006).

9 "*The FDA's Assessment Of Follow-On Protein Products: A Historical Perspective*," Woodcock et al, NATURE REVIEWS DRUG DISCOVERY (published online Apr. 13, 2007).

10 The US, EU, Japan shared regulatory guidance, ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process (*available at* http://www.ich.org/LOB/media/MEDIA1196.pdf (last accessed Sep. 16, 2008)), defines comparable as, "A conclusion that products have highly similar quality attributes before and after manufacturing process changes and that no adverse impact on the safety or efficacy, including immunogenicity, of the drug product occurred. This conclusion can be based on an analysis of product quality attributes. In some cases, nonclinical or clinical data might contribute to the conclusion." FDA's familiarity with the expression "highly similar" is reflected by its use of the term 28 times in the Agency's denial of the BIO, Pfizer, and Genentech Citizen Petitions that sought to prevent the Omnitrope approval (*available at* http://www fda.gov/ohrms/dockets/dockets/04P0231/04P-0231-pdn0001.pdf (last accessed Sep. 16, 2008)).

11 Approval is a term that generally is applied to FD&C Act drugs and biologic drugs.

12 Licensure is a term that generally is applied to PHS Act biologics.

of state boards of medicine and state boards of pharmacy, respectively. Increasingly, this interface is graying as healthcare systems, public and private, develop recommendations on the usage of prescriptions drugs and biologics, and professional organizations develop standards of care. Consequently, there often can be incentives for physicians and other healthcare providers to utilize different products according to a hierarchy of priorities that already is impacted by multiple factors, including economics factor such as cost. While such broader aspects of the U.S. healthcare system go beyond these FOB-specific comments, they nonetheless merit consideration in the context of a formal interchangeability designation by FDA, as that designation would introduce a science-based and data-driven competitive economic force into the biologics segments of the American healthcare system and can be expected to enhance the use of FOBs. Moreover, enabling such an FDA designation will benefit health plans administrators as well as providers because an FDA designation of interchangeability can be applied immediately and does not necessarily require payors or providers to undertake an independent formulary assessment and decision-making process. [13] Specifically, an interchangeability designation by FDA could enable substitution to occur as permitted under each state's laws and regulations, with the prescribing physician always having the option to override substitution based upon the unique medical circumstances of an individual patient.

Notably, the European experience reflects that the ultimate market penetration and economic impact of a safe and effective FOB that is not designated as interchangeable (the European legislation is silent on interchangeability) ultimately could prove to be much more extensive than otherwise might be anticipated because the FOB could impact the entire "class" of products to which it belongs, and not just the single reference biologic to which it demonstrates comparability. In the context of FOBs/biosimilars, "class" increasingly is a commonly-used term, but it is rarely defined. In Europe, the various biosimilar guidelines adopted by EMEA apply the term "class" to products that share active ingredient, and also to collections of products with different active ingredients that share the same mechanism of action. Consequently, ironically, the lack of a formal designation of a biosimilar as substitutable for its reference product is likely to lead to substitution across "class" to a greater degree than might otherwise be the case. Indeed, even outside the biosimilars context, this issue also has arisen with independently approved biologics in Europe for which no biosimilars exist, such as recombinant Factor VIII.[14]

Finally, with respect to the Commission's question regarding so-called "Authorized Biologics," there is no experience in the one major FOBs market (the EU) upon which to definitively project the potential for such a phenomenon to occur. Nonetheless, it can be posited that the unique economic factors associated with FOBs – including the anticipated substantial investment incurred over a significant period of time by a FOBs sponsor and the potential for FOBs regulatory review decoupled from patent litigation such that the reference BLA holder may be unaware of the of the FOBs sponsor's development program as is the case for biosimilars in the EU as well as the state of patent law for biotechnology products more generally today in the U.S. – there may be little or no incentive for "authorized FOBs".

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[13] "*Welcome to the P&T Committee: Reining in Biotech Prices*," THE RPM REPORT (July/Aug 2006).

[14] "*Considering all the Factors*," BIOCENTURY, THE BERNSTEIN REPORT ON BIOBUSINESS, Vol. 15, Number 37 (Aug. 20, 2007).

In this regard, decoupling and the concomitant lack of patent listings and notifications (discussed more fully below) may have an additional economic benefit, namely discouraging "authorized FOBs."

3. What competitive concerns are raised by joint research and development, supply, licensing, marketing, and distribution agreements between referenced biologic manufacturers and their follow-on biologic competitors? What would be the likely impact of a requirement that agreements between reference drug product manufacturers and follow-on biologic applicants be filed with the FTC and the Department of Justice Antitrust Division?

In light of biologics research and development and production capacity both in the U.S. and overseas, as well as the current state of supply, licensing, marketing, and distribution agreements across the biotechnology industry in both the U.S. and abroad, there are no apparent competitive concerns in these regards that would necessitate legislative or regulatory action. While only somewhat informative for the reasons outlined above, the state of biosimilars competition in the EU has not suggested that there are any competitive concerns in this segment. Moreover, against the backdrop of the vast array of collaborative agreements among academia, biotech companies, and the broader biopharmaceuticals industry, it is noteworthy that the nature and extent of those agreements have not presented any broadly-applicable competitive concerns. In the emerging FOBs segment, in those instances where such agreements currently exist in the U.S., they appear to be confined largely to facilitating biologics development – whether according to the existing regulatory pathway and/or in preparation for a new biosimilars pathway. Whether, and how, this might change would depend on the specifics of any new pathway. Both the current market conditions as well as the traditional history of biologics – which generally have been researched, developed, manufactured, and supplied by a single sponsor from essentially a single supply chain, often with some contribution from academia licensed in, and perhaps the assistance of a partner for marketing and distribution – suggest that change may be unlikely. In contrast to current market conditions and historical trends for small molecule chemical drugs, intermediates for biologics are not traded as commodities. Moreover, unlike drug manufacturing plants, biologic production facilities historically have been dedicated as a result of the FDA establishment licensing procedure imposed to get a new facility on-line or even a change in supplier.

Historically, therefore, biologics were "trapped" by their original suppliers and within their original production methods because, prior to the development of the regulatory concept of comparability to facilitate manufacturing changes, any change in raw materials or method(s) of manufacture could result in the requirement of an entirely new development program and new license. In 1996, working with the innovator biopharmaceuticals industry, FDA introduced the concept of Comparability Protocols through guidance – a pre-approval

approach to enabling manufacturing changes.[15] Comparability has enabled greater flexibility in securing FDA concurrence on the implementation of changes in biopharmaceuticals manufacturing, particularly for those products based on recombinant biotechnology, which generally can be well characterized more readily.

While dedicated facilities for biologics production can require a significant financial investment,[16] the era of comparability and advances in state-of-the-art biologics manufacturing technology have combined to facilitate evolution in multi-use facilities and more extensive use of contract manufacturing (including utilization of multiple suppliers of components). Nonetheless, the nature of biologics, the requirement for unique cell lines, and the necessity for specifically-designed purification regimes and sterile manufacturing conditions all result in expensive facilities and high production costs. Consequently, even when taking into account the capabilities represented by contract manufacturers, the facilities in which GMP commercial batches of biologics can be produced are still limited. This capacity limitation impacting some current (pioneer) manufacturers will apply similarly to some FOBs manufacturers, and perhaps even more so after FOBs sponsors obtain their initial FDA license for their FOB. Although these inherent capacity constraints may corollary impacts on competition, it is essential that quality considerations for all biologics are maintained and consistently applied. As technology stands today, certain of these limitations are inherent in the products themselves, but, they can be expected to evolve over time as, for instance, production technology continues advancing and the capacity of analytics to assure quality continues evolving.

In light of the foregoing technological and capacity considerations, and pending enactment and implementation of a FOBs pathway in the U.S., it seems it may be too early to suggest what agreements should be filed with the FTC and the Department of Justice Antitrust Division (beyond those required to be filed under current law).

4. 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?

It is a reasonable expectation that imminent competition to off-patent biologics will strongly encourage individual companies and the biotech industry as a whole to expand existing portfolios and to accelerate research into additional breakthrough therapies, as well as improvements to existing biologics where an originator is likely to have a unique

[15] FDA's comparability guidance (*available at* http://www fda.gov/cder/Guidance/compare htm (last accessed Sep. 16, 2008)) ultimately evolved into ICH Q5E (*available at* http://www.ich.org/LOB/media/MEDIA1196.pdf (last accessed Sep. 16, 2008)), and its comparability standard, subsequently were adopted as the foundation of the EU biosimilars framework. Regulation (EC) No 726/2004, *available at* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (last accessed Sep. 16, 2008).

[16] The costs associated with the development of innovator biopharmaceuticals are discussed in the PhRMA Annual Industry Profile (*available at* http://www.phrma.org/files/2008%20Profile.pdf (last accessed Sep. 16, 2008)).

advantage. New biologics that can be developed and approved as a result of such R&D initiatives will represent innovation that benefits the healthcare system generally and patients in particular. To the extent such innovation results in patentable subject matter, new patents estates claiming those new products can be established in their own right, which will have the long-term effect of expanding the pipeline of FOBs that can be developed in the future when those newly-issued patents expire. Experience demonstrates that this "cycle of innovation" works and works well across the biopharmaceutical industry. For biologics, however, this cycle can only truly begin when a pathway for FOBs is established. Absent the threat and subsequent advent of head-to-head competition when patents expire, there is only limited incentive to innovate, and biologics with limited or no patent protection can maintain *de facto* monopolies in their respective segment. Thus, for example, the inability of competing versions of PHS Act biologics to reach the market as a result of the absence of a FOBs pathway is evidenced in some cases by the absence of any material change in price of an individual innovator biologic after its patents expire.

Claims to the contrary, premised upon competition bringing about the demise of the biotech industry, simply are not plausible. All the arguments currently being made about the uniquely-vulnerable and precarious position of the U.S. biotech industry were made in a similar manner for the small molecule drug industry prior to enactment of the Hatch-Waxman Act in 1984.[17] The argument was misguided then and remains so today. Not only did the projected demise of the innovator pharmaceutical industry *not* occur, the industry experienced a true renaissance and manifested a wealth of innovation over the ensuing decades. The pharmaceutical industry's constant replaying of the "cycle of innovation" following Hatch-Waxman's enactment benefitted patients tremendously and enabled the industry to withstand fierce competition from the generic drug industry. As a result, to the extent there once were clear lines between the innovator and generic drug industries, they both flourished in a competitive U.S. marketplace applying market-based pricing to each side's drug products throughout the 1980's and 1990's. More importantly, patients and payors likewise benefited from the head-to-head competition and expanded access to competitively-priced drug products, as well as from the ensuing innovation and subsequent generations of newer and better drug products – all of which has produced greater health care choices for all stakeholders.

There is no reason to believe that the short-term consequences or long-term outcomes will be any different for the biotechnology-based biopharmaceuticals industry[18] – many of whom are the very same companies that responded with so many innovative drug successes after 1984. Indeed, the experience to date in Europe suggests that the predicted demise of the biotech industry may is exaggerated. Despite multiple biosimilar competitors entering various European markets for one of the biggest biotech blockbusters (EPO), and despite the class effects of that competition across all EPO products even though the biosimilars all share a

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[17] "*Overview of the Hatch-Waxman Act and Its Impact on the Drug Development Process*," Gerald J. Mossinghoff, FOOD AND DRUG LAW JOURNAL, *available at* http://www fdli.org/pubs/Journal%20Online/54_2/art2.pdf (last accessed Sep. 21, 2008).

[18] "*Orphaning Biotech? The Impact of Biosimilars on Biotech Investment*," Baghdadi, THE RPM REPORT (Jan. 2008).

single reference medicinal product, the European biotech industry appears to have flourished in the five years since the European Parliament initially adopted biosimilars legislation. Indeed, in contrast to its U.S. counterpart, the EU biotech industry has continued marshalling its R&D and secured numerous marketing authorizations for multiple innovative products to which patients in Europe have gained access as a result. We believe that most of the biotechnology industry will prosper in a world of competition precisely because competition will enable the innovation it inspires (in terms of both new products and more efficient and cost-effective manufacturing) to be recognized and valued.

The U.S. led the world in pharmaceutical and biotechnology innovation from the early 1980s onward. With the first biotech product having been approved in 1982, however, patents are now conspicuously expiring. With over one-third of all medicines in development now being biotech-based,[19] the economic significance of biologics in healthcare is becoming more apparent to all stakeholders. Indeed, it is the very success of biologics, now 18.5% of the prescription drug budget in the U.S.[20] and growing at a rate of 15-20%,[21] which has attracted stakeholders' increased attention to the need for competition when patents expire. Biologics are showing no moderation in costs, and as was recently noted by AARP, the average annual increase for specialty prescription drugs was three times the general inflation rate in 2007.[22] The now-conspicuous market driver of expiring patents on products for which there is no head-to-head competition will increase with time and be compounded by the increasing proportion of the healthcare dollar consumed by prescription drugs.

Various arguments have been made as to why the biotechnology-based biopharmaceuticals industry in the U.S. purportedly would be unable to achieve a return on investment in the context of an interchangeable FOBs pathway based upon the on-market patent life of biologics.[23] Such arguments include the implicit or express premise of a justification of premium, market-based pricing during the remaining patent terms in order to enable the return on high research and development investments to be realized. The challenge is integrating these related points concurrently and weighting them fairly, particularly if, in opposing a FOBs pathway, one also asserts as some have that FOBs will not be cheaper and there will be limited to no savings.[24] In fact, the U.S. experience over the past 25 years with

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[19] "*PhRMA, Biotechnology Medicines in Development Survey"* (2006), *available at* http://www.phrma.org/medicines_in_development_for_biotechnology/ (last accessed Sep. 21, 2008).

[20] According to CMS, the total prescription drug spend was $216.7 billion in 2006. See http://www.cms.hhs.gov/NationalHealthExpendData/downloads/highlights.pdf (last accessed Sep. 25, 2008). According to CBO, the biologics spend in 2006 was $40 billion (see note 20, *infra*).

[21] "*S. 1695 Biologics Price Competition and Innovation Act of 2007*," Congressional Budget Office Estimate (Jun. 25, 2008), *available at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf (last accessed Sep. 25, 2008).

[22] "In 2007 the average annual increase in manufacturing prices [ ] for 144 brand and generic specialty prescription drugs [ ] was 8.7%, or three times the general inflation rate of 2.7%." AARP Public Policy Institute, "*Rx Watchdog Report: Trends in Manufacturing Prices of Specialty Prescription Drugs Used by Medicare Beneficiaries 2004-2007*," *available at* http://assets.aarp.org/rgcenter/health/2008_15_specialty_q407.pdf (last accessed Sep. 26, 2008).

[23] According to PhRMA, the average post-approval on-market patent life is 11.5 years. *See* PhRMA Industry Profile 2008, *available at* http://www.phrma.org/files/2008%20Profile.pdf (last accessed Sep. 22, 2008).

[24] BIO Paper, "*Recent Studies of Follow-On Biologics Are Based on Seriously Flawed Assumptions*," Edward (Ted) Buckley. *available at* http://www.bio.org/healthcare/followon/20070222.pdf (last accessed Sep. 25, 2008).

innovative pharmaceuticals and generic drugs and Europe's recent experience over the past several years with innovative biologics and biosimilars reflect that innovation and competition can co-exist and indeed flourish.

However, absent a FOBs pathway when patents expire (irrespective of any new exclusivity that it offers), that homeostasis cannot be achieved, as the sponsors of safe and effective FOBs will have no viable pathway to the U.S. market for interchangeable products. In short, the effect of the current regulatory system is to confer exclusivity independent of patent rights or non-patent exclusivity. With no market access, there is only limited incentive to make safe and effective competing products (which, under current law, could not be designated as interchangeable even if approved), and there is only limited incentive to expand the market with new indications.[25] In addition, there is no meaningful stimulus to implement more efficient and cost-effective manufacturing[26] that potentially can enable reductions in costs of goods. Most significantly, truly innovative companies are not fully motivated to pursue marketplace advantages through the introduction of new products whose high R&D costs cannot be justified when margins can be maintained on existing products without incurring additional marginal costs. Consequently, the absence of a FOBs pathway undermines innovation at multiple levels, and this is contrary to the interests of patients and other consumers of the biopharmaceutical industry's products.

5. How does the method used by Medicare for reimbursement of biologic drug products affect pricing and competition of referenced biologic products? What factors are important for this effect and why? How would the Medicare reimbursement system likely affect prices for both the referenced and follow-on biologic products? For example, does Medicare reimburse Part B drugs, including biological drugs, based on the Average Sales Price of all the biological drugs whose National Drug Codes (NDCs) reference the same Biologic License Application (BLA)? If so, how would a follow-on biologic drug that does not reference the BLA of the reference drug affect the Medicare reimbursed price for referenced drug product? How will these and other Medicare reimbursement methodologies likely affect models of price competition after follow-on biologic drug entry?

Prior to the enactment and implementation of a defined pathway for FOBs, it is not possible to speculate whether or to what extent Medicare reimbursement might affect their pricing and competition. While various models have been constructed to project the anticipated savings to Medicare and other insurance programs from FOBs based on economic assumptions regarding projected discounting and market share,[27, 28, 29, 30, 31]

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[25] PhRMA paper, "*Post-Approval Research on Biotech Medicines Leads to Key Medical Advances*," (Oct. 2007), *available at* http://www.innovation.org/documents/File/PhRMA_Post-Approval_Research_FINAL.pdf (last accessed Sep. 16, 2008).

[26] "*A Call To Arms: Next Generation Pharmaceuticals*," *available at* http://www.gdspublishing.com/ic_pdf/ngp/fda3.pdf (last accessed Sep. 20, 2008).

[27] PCMA, "*PCMA: Medicare Part B Program Could Save $14 Billion in Prescription Drug Costs through Biogenerics*" (Jan. 4, 2007), *available at* http://pcmanet.org/pcma-medicare-part-b-program-could-save-14-billion-in-prescription-drug-costs-through-biogenerics/ (last accessed Sep. 25, 2008).

there does not appear to be a viable approach to constructing the reverse model that can project the impact of Medicare reimbursement on FOBs pricing – which is likely to be intrinsically linked to the requirements of the pathway, the R&D required to utilize that pathway, and the nature of the biologic segment in which a particular FOB will compete.

Unquestionably, any number of elements of legislation establishing a new pathway for PHS Act FOBs can have a significant impact on pricing and competition. Foremost among these probably will be FDA's authority to designate safe and effective FOBs as interchangeable. A related factor is whether, as in various legislative proposals, interchangeability is a second and distinct step segregated from FDA approval of a FOB, or whether the approval inherently encompasses an interchangeability determination. It should also be noted that FDA and CMS, while separate agencies within the Department of Health and Human Services, work synergistically to enable coverage decisions.[32] The manner in which the Medicare program and other payors will manage these and a myriad of related factors at a coding and payment level obviously will impact the competitive position of FOBs and their reference products. However, modeling those effects is best deferred until the specifics of a pathway are in place.

6. 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)?

As a general matter, the historical record suggests that, at a macro level, the patent estates of biologics have been distinct from the patent estates of chemical drugs in several significant respects. Thus, biologics and their relationship to the biotech patent estates at issue are unique. First, some biologics are not protected by patents. Second, the patent estates that do cover biologics generally have tended to be broader, both in terms of the sheer number of patents and the number of claims allowed in those patents, as compared to FD&C Act drugs. Third, biologic patent estates often are not focused exclusively, or even necessarily primarily, on a biologic therapeutic, but instead may claim multiple products in the marketplace that are of commercial value to the patentee, such as a research tool, a manufacturing platform, a diagnostic, and/or a combination product such as a biologic-device combination. Fourth, because many biotech products have roots in academia, there can be multiple parties holding patents

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[28] Avalere, "*Avalere Health Analyzes Factors Influencing Federal Budget Impact of Follow-on Biologics*" (Mar. 14, 2007), *available at* http://www.avalerehealth.net/wm/show.php?c=1&id=738 (last accessed Sep. 25, 2008).

[29] ExpressScripts, "*Can We Afford Biologic Drugs: A Payers Perspective*," Presentation by Stephen Miller, M.D., M.B.A., Biosimilars2007 Conference, *available at* http://www.biosimilarstoday.com/Miller.pdf (last accessed Sep. 26, 2008).

[30] Insmed, "*The Potential American Market for Generic Biological Treatments and the Associated Cost Savings*," Shapiro, Singh, & Mukim (Feb. 2008), *available at* insmed.com (last accessed Sep. 25, 2008).

[31] "*S. 1695 Biologics Price Competition and Innovation Act of 2007*," Congressional Budget Office Estimate (Jun. 25, 2008), *available at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf (last accessed Sep. 25, 2008).

[32] "*FDA, CMS in sync on ESAs*," Usdin, BIOCENTURY (Oct. 22, 2007).

claiming PHS Act biologics, adding to the complexity of their estates. Finally, due to the inherent nature of biologics, their patent estates tend to include many more process patents than typically would be found in the patent estates of FD&C Act drugs. Beyond these broad generalities, it is difficult ascertain the patent estate around a given PHS Act biologic marketed in the U.S. Notably, throughout the history of the biotech industry, a decoupled patent-enforcement system has prevailed. Thus, for biotech patent estates, U.S. law has enabled the FDA regulatory review and approval process to proceed and prosecution of infringement claims and non-infringement/invalidity defenses to ensue post-approval in the context of approved biologics and market-based competition. In this and many other respects, the U.S. Constitution-based patent system has proved invaluable to the creation and continued innovation of the biotech industry – a vigorous and risky, but also very successful, sector of the U.S. economy. The present absence of patent linkage between biotech patent estates and FDA regulatory review is a critical distinction from chemical drug patent estates, and one that should be maintained going forward in implementing a FOBs pathway. However, in order to enable an orderly, post-approval patent-litigation to be initiated efficiently, potentially in advance of market entry, we would recommend a statutory notification process, in which the FOB applicant must notify the reference product BLA sponsor at the time of approval, with a statutory deferral of 45 - 90 days, during which the reference product sponsor can pursue its traditional patent remedies against the FOB if it has a good faith basis for doing so.

As historically has been the case at the outset of any U.S. industry, the launch of the biotechnology industry made the role of patents for biologics significant – and considerably more so than had been the case for naturally-sourced biologics. Biotech approvals themselves, and then entire companies, as well as the very nature of the products developed, became dependent on patents, down to the actual research tools used to develop them. As the biotech industry moves beyond a focus on the simple replacement of naturally-occurring human proteins for those few individuals suffering the misfortune of a temporary, partial or life-long deficiency, and begins developing uniquely designed and larger molecules, there is likely to be an expectation of more composition-of-matter patents for biologics. Indeed, as analytical technology evolves and the ability to define and design biologics beyond those found in nature becomes increasingly apparent,[33] patent estates for PHS Act biologics could expand significantly. Appropriately, therefore, patents are anticipated to remain critical to the biotechnology industry throughout biotech's continuing evolution.

In the meantime, as the currently-issued patents in the patent estates of the first biotechnology-based products begin to expire, Congress is confronting the issues of how and on what terms to enable market-based competition for biotechnology-derived PHS Act biologics in the U.S. In that context, while recognizing that biotechnology patent estates can

[33] Perhaps the first example of a designer molecule is the insulin analog Humalog. Lilly explicitly designed this non-naturally occurring designer recombinant molecule to be a rapid-acting insulin analogue. It was engineered through recombinant DNA technology so that the penultimate lysine and proline residues on the C-terminal end of the B-chain were reversed. This modification did not alter receptor binding, but blocked the formation of insulin dimers and hexamers. This allowed larger amounts of active monomeric insulin to be available for postprandial (after meal) injections, and thus provided clear clinical advantages to patients http://www fda.gov/cder/foi/label/2007/020563s075,021017s040,021018s034lbl.pdf (last accessed Sep. 26, 2008).

be complex, it is equally important to acknowledge the industry's history of realizing the value of those patent estates through the utilization of traditional patent remedies outside the context of the FDA licensure process. In short, in addition to its many other remarkable successes, the biotechnology industry has demonstrated that, for PHS Act biologics, there is no need for patent linkage to FDA review and approval. For all PHS Act biologic applications – pioneer and FOB alike – the FDA regulatory review process can and should proceed as it exists under current law. All parties should maintain their patent claims and defenses and fully litigate them, post-approval, at that point at which the courts have jurisdiction under current law over a claim of alleged infringement by the sponsor of a PHS Act biologic.[34]

The case for such "decoupling" is reinforced by the complexity of biotech patent estates, which remain intrinsically uncertain – an uncertainty that would be exacerbated if litigation on innovators' patents is initiated prior to approval of a PHS Act FOB. In order to maximize predictability around biotech patent estates, the U.S. patent laws applicable to PHS Act biologics should remain in force as they are, unamended. Generic drugs should remain the exception for linking the patent-litigation process with regulatory review, as that system – unique to generic drugs – was justified by the very different state of development of the generic drugs industry in 1984 compared to that of the biotechnology and biosimilar industries today. We would recommend, however, inclusion of a notification process so that the sponsor of the innovator product receives a notice when a FOB is approved (with a statutory bar on launch of 45 - 90 days, during which the innovator biologic sponsor can pursue its traditional patent remedies). Such a process can an enable an orderly, albeit post-approval, resolution of patent issues and minimize the risk that the precipitous launch of a FOB would irreparably harm the innovator – a prospect that seems to be undermined by the innovator industry's own arguments that FOBs will not produce significant savings.

Recognizing that those FOBs sponsors who do a poor job of evaluating their freedom to operate will risk traditional patent damages if sued by the innovator, it also is important to recognize that, today, in the U.S. (and EU) patent climate in which biotechnology has lived and prospered to date, no innovator sponsor of a PHS Act biologic receives notification of a regulatory filing or approval of a subsequent biologic that may infringe any of its patents. This model has served the biotechnology industry, and there is no justifying need to deviate from it in the context of FOBs. Biotech patents need not be litigated until there is an act of infringement as recognized under current law that would violate a patent right and give rise to a cause of action. While the market dynamics today – where there can be multiple "innovator" biologics on the market – differ from those in a post-FOBs environment, this change is not a rational basis for departing from the standard patent system that every industry lives by – other than the innovator chemical drug and generic drug industry. Some have argued, however, that because a FOB is "similar to," and not necessarily the "same as," the innovator, a FOB sponsor could secure approval of a product that is outside the claim scope of the innovator's patents. Even if this were the case, it is not a credible basis for imposing linkage in legislation that applies the "highly similar" standard (used for innovator

[34] "*Research Use Of Patented Knowledge – A Review*," Dent, Jensen, Waller, & Webster, Intellectual Property Research Institute of Australia (IPRIA), OECD STI Working Paper Series, *available at* http://www.oecd.org/dataoecd/15/16/36311146.pdf (last accessed Sep. 21, 2008).

comparability for over a decade) as the basis for FDA approval of a FOB. The cumbersome and increasingly-unworkable nature of the controversial Hatch-Waxman patent listing/certification/litigation process is neither necessary nor desirable as a model for FOBs, because of the even greater complexity of IP rights around biologics. Moreover, developments in the law reflect that such mechanisms are not essential, as U.S. courts can address and have rectified irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch. Thus, the Constitutionally-protected patent rights that have enabled the biotechnology industry to grow and succeed should remain unaltered when codifying a straightforward grant of authority to FDA to review and approve safe and effective interchangeable FOBs.

7. 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?

The Hatch-Waxman Amendments to the FD&C Act provide a five-year period of non-patent data exclusivity for a new chemical entity (NCE) running from its date of approval. The five-year NCE exclusivity applies against 505(j) ANDAs and 505(b)(2) NDAs, but it does not block stand-alone 505(b)(1) NDAs. Hatch-Waxman also provides for additional three-year periods of market exclusivity if an NCE sponsor subsequently (post-approval) secures clearance to market a new indication, or a new form of the product, or the like, based on new clinical studies essential to the approval. Three-year market exclusivity only precludes approval of 505(j) ANDAs and 505(b)(2) NDAs for the post-approval change (e.g., the new indication), but submission of such applications can occur during the three-year exclusivity period. As reflected by the contemporary judgment of the European Parliament in adopting an 8+2+1 data and market exclusivity period for all medicinal products (biologics and drugs) in the EU,[35] the Hatch-Waxman five-year and three-year exclusivity periods are considered too short and an insufficient period to enable recovery of R&D and manufacturing costs associated with development of an innovative biologic.

[35] DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004 amending Directive 2001/83/EC on the Community code relating to medicinal products for human. "The ten-year period [ ] shall be extended to a maximum of eleven years if, during the first eight years of those ten years, the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. [ ] In addition [ ] where an application is made for a new indication for a well-established substance, a non-cumulative period of one year of data exclusivity shall be granted, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication." See Directive 2004/27/EC at page 6, *available at* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2004:136:0034:0057:EN:PDF (last accessed Sep. 26, 2008).

Relative to the patent term that generally pertains at the point of initial approval,[36] the Hatch-Waxman exclusivity periods applicable to FD&C Act drugs are considerably shorter. Because development of a PHS Act biologic is generally regarded to take more time and require more financial and other resources on average than the development of a small molecule drug, arguments about longer periods of exclusivity for biologics than drugs are readily understandable in the context of incentivizing development and approval of innovator biologics.[37] The 8+2+1 exclusivity period in Europe provides useful experience to consider for the U.S., but other differences in the healthcare systems of the two regions mean that the length of time for exclusivity for PHS Act biologics in the U.S. must be carefully evaluated in a U.S.-specific context. Given the substantial investments necessary to develop innovator biologics, a minimum of 12 years of exclusivity is essential, and there may be sound arguments for more. The balance that must be achieved should provide certainty that the period of time on the market for any PHS Act biologic to gain a return on investment will be sufficient to maintain investment, while enabling subsequent sponsors to reasonably anticipate when they will be able to offer competing products to patients and other consumers in the healthcare system.

8. 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?

It is important to enable the "cycle of innovation" by stimulating competition while also assuring an appropriate return on investment. However, it is very difficult to predict in advance and in a vacuum how a given segment of the U.S. marketplace will respond to such opportunities, and how the effects might vary for different PHS Act biologics. Conceptually, although it may be theoretically possible to stagger non-patent exclusivity periods based on factors such as those identified in the question, Congress has not taken that step before and seems unlikely to do so in the future. Similarly, when the European Parliament initially adopted the EU biosimilars legislation in 2003, the exclusivity periods for all medicines prospectively became a ten-year period across-the-board with the potential for an additional one year for a single, clinically-significant new indication approved during the first eight years post-approval.[38] These terms are fixed and do not vary (except as it relates to additional exclusivity periods for which an

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[36] According to PhRMA, the average post-approval on-market patent life is 11.5 years. PhRMA Industry Profile 2008, *available at* http://www.phrma.org/files/2008%20Profile.pdf (last accessed Sep. 22, 2008).

[37] Henry Grabowski, Duke University Department of Economics Working Paper, "*Data Exclusivity for New Biological Entities*" (June 2007), *available at* http://www.innovation.org/documents/File/Grabowski_Data_Exclusivity_for_New_Biological_Entities_FINAL.pdf (last accessed Sep. 18, 2008). See also Overview, *available at* http://www.innovation.org/documents/File/Grabowski_Data_Exclusivity_for_New_Biological_Entities_Overview.pdf (last accessed Sep. 18, 2008).

[38] Boston Consulting Group White Paper (sponsored by PhRMA), "*Continued Development of Approved Biological Drugs – A Quantitative Study of Additional Indications Approved Postlaunch in the United States*" (Dec. 2007), *available at* http://www.bcg.com/impact_expertise/publications/files/Biologics_Dec07_final.pdf (last accessed Sep. 18, 2008).

innovator may become eligible), and all stakeholders make their decisions accordingly. The introduction of staggered or otherwise-fluctuating exclusivity periods would introduce uncertainty that would adversely impact both innovative investment as well as preparations for competitive market entry.

Non-patent exclusivity that is appropriately established can provide a period of certainty against use of the innovator product as a reference by a subsequent sponsor, and thereby complements patents and increases the probability of further and sustained innovation. Patents and exclusivity are both valuable as stimuli to further investment and hence further innovation. While periods of patent protection and exclusivity may overlap significantly for a given product, the assurance that each provides to a sponsor of an innovator product is distinctive and both are necessary. While discovery and development of the next generation of innovator products is essential to the existence of both the innovator and follow-on biopharmaceutical industry, the cost/uncertainty element of patent disputes should not be underestimated. Consequently, a defined exclusivity period provides additional value by reducing this cost to the overall healthcare system.

The European system, originally adopted in 2003 in conjunction with establish of the EU's biosimilars pathway, reflects this principle. The EU's 8+2+1 exclusivity provisions preclude filing of any generic drug or biosimilar application for eight years, the approval of any such application for 10 years, and a potential further deferral of approval for an additional year if a clinically-significant new indication is approved. The Novartis Group of companies supports at a minimum exclusivity for innovator products comparable to that provided in Europe.

9. 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?

Europe has been the first jurisdiction to create a formal and specific pathway to accommodate FOBs – the EU's biosimilars pathway.[39,40] Although the EU pathway is by no means abbreviated, and nor should any U.S. system be abbreviated, both should enable "expedited" applications and Europe's leadership and experience has been an important resource for subsequent jurisdictions such as the U.S. to consider. Its value is enhanced by the trend towards development of biomedical products for a global marketplace, which can generate significant financial and time savings through harmonization of regulatory requirements imposed on sponsors accessing global marketplaces, which can enable those sponsors to develop a single global dossier.[41] Enhancing patients' access worldwide to lifesaving biological medicines that are increasingly manufactured for that global marketplace is a sound policy goal applicable

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[39] Directive 2004/27/EC, *available at* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf (last accessed Sep. 13, 2008).

[40] Regulation (EC) No 726/2004, *available at* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/reg_2004_726/reg_2004_726_en.pdf (last accessed Sep. 13, 2008).

[41] ICH Q5E, "Comparability of Biotechnological/Biological Products Subject to Changes in Their Manufacturing Process," *available at* http://www.ich.org/LOB/media/MEDIA1196.pdf (last accessed Sep. 22, 2008).

to both innovator and follow-on biologics.[42] However, because the U.S. represents a distinctive healthcare system and reimbursement model, it is most appropriate to consider the European approach as a reasonable place to start with respect to exclusivity considerations. Europe now has a single market exclusivity approach that applies to every medicine, whether small molecule drug or biologic, that provides for 10 and potentially 11 years of exclusivity. Presently, none of the proposals for a FOBs pathway in the U.S. have provided for such a unified exclusivity approach.

The EU represents 27 countries which share certain regulatory approaches that are very similar to those in the U.S., such as centralized review of medicines prior to marketing (while national reviews and mutual recognition are possible for some products, all biotechnology products use the centralized procedure). The centralized EU process includes an assessment of the quality, safety, and efficacy of all biotechnology products including biosimilars – the same criteria as apply to all other medicinal products in Europe.[43] Europe has a mixture of reimbursement systems that are applied individually within each Member State with the potential, subsequent to regulatory marketing authorization, to affect how quickly authorized products are made available to which patients, as well as the amount biopharmaceutical manufactures are paid for them.

In this context, there is no question that availability of the biosimilars pathway in the EU is leading to those products being reviewed, approved, and made available in the marketplace to European patients.[44] Availability of biosimilars in Europe is resulting in reductions in prices and greater access to important off-patent medicines that cannot presently occur in the U.S. unless subsequent sponsors are prepared to invest in and undertake a complete biologics development program and file a "full" BLA. The European biosimilars experience reinforces the importance of establishing at a minimum the same exclusivity period in the U.S. With Europe having established such incentives and encouraging innovator companies to invest in the next generation of products, the lack of at least comparable incentives in the U.S. will affect where biologics are researched, developed, and first marketed – in essence, it will determine where the innovation and innovation-spend occurs. The best outcome for patients in the U.S. and the biopharmaceutical industry that serves them is to provide at least the same level of encouragement under U.S. law.

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[42] See, e.g., World Health Organization, Expert Committee On Biological Standardization, Draft "*WHO guideline for abbreviated licensing pathways for certain biological therapeutic products,*" WHO/BS/08.BS number, Draft *available at* http://www.insidehealthpolicy.com/secure/data_extra/dir_08/he2008_1837.pdf (subscription required) (last accessed Sep. 29, 2008).

[43] DIRECTIVE 2004/27/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 31 March 2004, amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, *available at* http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2004_27/dir_2004_27_en.pdf (last accessed Sep. 10, 2008).

[44] "*What Follow-On Biologics Mean For The Future Of The Biotechnology Industry*," Hussain & Woollett, BIOPHARM INTERNATIONAL (Nov. 2007).

10. Is a marketing exclusivity period necessary to encourage companies to develop follow-on biologics and to seek their approval by the FDA? If so, why, and how should such an exclusivity period be structured?

Depending on the terms of FOBs legislation that is adopted, the nature of the regulatory pathway(s) for safe and effective FOBs that is created, and the imposition of a significant additional regulatory burden to achieve FDA designation as an interchangeable FOB subsequent to initial licensure of the FOB itself, sound public policy would suggest that it may be appropriate to provide an express incentive to FOB sponsors to seek an interchangeability designation. To date, none of the U.S. legislative proposals for FOBs would grant exclusivity to a non-interchangeable FOB. An interchangeability designation is currently considered the most effective way to introduce head-to-head market-based competition with currently-licensed PHS Act biologics. However, pursuit of an interchangeability designation necessarily will be a balance for sponsors between the cost of achieving it versus its value in the marketplace (i.e., whether it enables greater and/or more rapid market penetration without detailing expenses). Preliminary data from Europe suggests that the model for biologics will be different, and that "class"-based market penetration increasingly will become more important as patients get switched by providers to products in a class that are anticipated to come off-patent first.

Exclusivity for the first interchangeable FOB, as has been proposed in some legislative proposals, can incentivize sponsors of FOBs to seek the additional recognition by FDA that their product can be interchanged safely and effectively with the reference product.[45] This regulatory designation embodying FDA's expert conclusions could have some value to a FOBs sponsor. It is not possible to speculate at this juncture, however, on the magnitude of that value or the extent to which it will be appreciated. For business reasons, different FOBs sponsors may wish to pursue the designations or not depending on their company's specific business model, including such factors as whether the company intends to detail and promote its FOBs and to whom. Consequently, there may be value in a distinction between FOBs and interchangeable FOBs, and in the associated exclusivity regimes.

However, irrespective of the manner in which these regulatory pathway and exclusivity opportunities are configured for FOBs in the U.S., a key distinction needs to be drawn from the generic drug model, and that is to decouple any follow-on exclusivity period from a

[45] It should be recognized that the comparability standard is already defined in ICH Q5E, *available at* http://www.ich.org/LOB/media/MEDIA1196.pdf (last accessed Sep. 22, 2008). Comparability also provides the regulatory history and experience for the "highly similar" term-of-art that has been used in various U.S. legislative proposals as well as for the European biosimilars pathway. This established comparability standard is applied to an innovator product undergoing a manufacturing change such that interchangeability of the pre- and post-manufacturing change products already is presumed, and the product is not labeled as having been "changed." Hence, it is not evident what additional requirements FDA could impose that allow for the same regulatory standard to be applied differently to FOBs and innovator products, and yet it is the nature of these requirements that could determine the need for exclusivity to incentivize a FOB sponsor to pursue the further regulatory hurdle of becoming an interchangeable FOB. As a scientific and regulatory matter, the distinction between a FOB and an interchangeable FOB is inappropriate if the "highly similar" standard is the one being applied. Furthermore, the regulators cannot be applying the same standard if, for a FOB, any unknown is assumed to be different while, for an innovator product undergoing a manufacturing change, any unknown is assumed to be the same.

patent notification and litigation system linked to FDA review and approval. Given the uniqueness of biotechnology patent estates, any patent listing and notification system inevitably will be cumbersome and necessarily incomplete.[46] As a matter of sound public policy, it will be much simpler, clearer, and efficient to leave patent rights implicating PHS Act biologics as they currently stand. Decoupling will avoid premature challenges to biotech patent estates ahead of the prospect of imminent commercialization, and current law provides robust protection for those rights when infringement occurs. Indeed, throughout its history, the biotechnology industry has prospered without patent linkage and does not need it now any more than the sponsors of FOBs need patent linkage. As has always been the case for PHS Act biologics, the net result of continuing such "decoupling" for FOBs will be to allow FDA to concentrate its scientific expertise where it is best suited – on the evaluation of medicinal products – and it will reduce the concerns already articulated by the Commission that patent linkage may encourage sponsors to enter anticompetitive patent settlements.[47]

B. Patent Dispute Resolution Issues

1. 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?

The Constitutionally-protected patent rights that have enabled the biotechnology industry to grow and succeed would be unaltered by the straightforward grant of authority to FDA to review and approve safe and effective interchangeable FOBs. Legislation to establish such a regulatory pathway can simply give FDA a clear mandate allowing the Agency to manage the regulatory review and approval process for FOBs (using the same standards of safety, purity, and potency as FDA has used for innovator products for 100 years), and thereby enable competing products to reach the U.S. marketplace. It is the absence of such a pathway that is creating this inability to access the U.S. marketplace and causing a competition deficit that is contributing to the serious access issues experienced by patients. In remedying this regulatory artifact, there is absolutely no need, and indeed there would be serious downsides, to coupling FDA's regulatory review of FOBs to the exercise of patent rights. However, in order to enable an orderly, post-approval patent-litigation system to function, potentially in advance of market entry, we would recommend a statutory notification process, in which the FOB applicant must notify the reference product BLA sponsor at the time of approval, with a statutory deferral of 45 - 90 days, during which the reference product sponsor can pursue its traditional patent remedies in court if it elects to do so. Linkage of patent rights (which will remain unaffected by FOBs and continue to be reconciled by the courts as needed) to regulatory review of FOBs would add a level of complexity that is unnecessary for biologics and impose an additional burden on FDA and/or FOBs

[46] Perhaps most notably, no legislative proposal has managed to provide a thorough and appropriate mechanism for dealing with third-party patents.

[47] See FTC response to House E&C questions (May 2, 2008), *available at* http://energycommerce house.gov/Press_110/110-ltr.050208 respto040308.FTC.pdf (last accessed Sep. 26, 2008).

sponsors if applied to PHS Act biologics. Moreover, patent linkage indisputably would delay a user-fee based approval process for BLAs for FOBs – which would be subject to PDUFA 10-month "clocks" – and require FOBs sponsors to disclose the confidential commercial information surrounding the filing of their BLA (a step that is not routinely made public by FDA or by innovators filing applications). In short, linking patents and BLAs by enabling patent litigation concurrent with regulatory review, is unnecessary, achieves no sound public policy objective, is open to confusion and abuse, and therefore is simply unwise, particularly given the greater complexity of IP rights around biologics. This conclusion is reinforced by developments in the law, which reflect that paten linkage is not essential to prevent market destruction, as U.S. courts can address and have rectified irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch. Thus, the Constitutionally-protected patent rights that have enabled the biotechnology industry to grow and succeed should remain unaltered when codifying a straightforward grant of authority to FDA to review and approve safe and effective interchangeable FOBs.

When any biologic is approved and marketed, as a follow-on or as an innovator product, any patent holder can determine whether or not they believe that they hold a patent that is infringed. If so, the patentee can sue. If this system is carried over into a new Congressionally-authorized FOBs pathway, nothing would change for PHS Act biologics. Instead, FOBs would follow exactly the same patent-litigation course as any other FDA-approved biologic – with the potential for litigation by another BLA holder or a third-party patent holder (who may or may not have licensed those patents to the sponsor of the innovator biologic). In each case, the patentee(s) can choose to sue, or not, any approved BLA holder whom the patentee reasonably believes has infringed its patent(s). Today, no innovator sponsor receives notification of a regulatory filing or approval of a subsequent product that may infringe any of its patents. This model has served the biotechnology industry, and there is no justifying need to deviate from it in the context of FOBs. Biotech patents need not be litigated until there is an act of infringement as recognized under current law that would violate a patent right and give rise to a cause of action. While the market dynamics today – where there can be multiple "innovators" on the market with patent rights at stake – differ from those in a post-FOBs environment, this change is not a rationale basis for departing from the standard patent system that every industry lives by – other than the innovator chemical drug and generic drug industry. Some have argued, however, that because a FOB is "similar to," and not necessarily the "same as," the innovator, a FOB sponsor could secure approval of a product that is outside the claim scope of the innovator's patents. Even if this were the case, it is not a credible basis for imposing Hatch-Waxman-like linkage in legislation that applies the "highly similar" standard (used for innovator comparability for over a decade) as the basis for FDA approval of a FOB. Separately, iterative improvements developed by innovators that create different products while innovating around patents (requiring a "Full BLA" for approval) can and indeed should continue to be encouraged, with their place in the market based on the value of these differences in an increasingly-competitive world.

Creating an artificial act of infringement could unnecessarily put the patent estate of the innovator, and others from whom they have licensed patents, at risk artificially early. Because of the breadth of biotech patent estates (with a biotech patent estate, the same patent claiming a biologic medicinal product also could claim another product or technology, e.g., a platform or an out-licensed diagnostic), a biotech patentee should not be compelled to put its entire bundle of rights at risk to address a premature, pre-commercialization artificial act of infringement. Considering the many potential uses to which individual biotech patents are put, such a system could be particularly antagonistic to biotech patent estates. In particular, early FOB litigation could become a mechanism for testing patents early in a setting (pre-approval of a FOB) that is of relatively-minor commercial value to the patentee. However, because biotech patentees may have more to protect than just a biologic medicinal product, such early litigation could put at risk other technologies and products embodied within the same patent(s). Biotech patentees should not be compelled to put any such broadly-applicable patents or other commercially-significant revenue streams at risk in a pre-approval litigation scheme for FOBs. Moreover, given the generally recognized complexity of patent estates for PHS Act biologics, the notion of "early" litigation does not assure a FOB sponsor of an early resolution of patent rights, because other patents held by other patentees could be enforced at any time, before or after FDA approves the FOB. It is unlikely that any such disputes would be comprehensively resolved such that a launch would be free from any form of risk. Hence, "early" litigation does not offer any real guarantee to subsequent sponsors, and it seriously compromises the patent rights of innovators.

In short, the very real potential of triggering serial litigation benefits no one – not patentees, not FOBs sponsors, and not the patients or the healthcare system they serve. Each FOB sponsor must perform a freedom-to-operate assessment, just like that any routine BLA sponsor. Enabling early litigation by creating new artificial acts of infringement provides no meaningful assurances for any party, is of dubious value as a public policy objective, and will not enhance competition and access.

As an alternative to pre-approval linkage, the Novartis Group of companies has advanced a proposal that it believes is useful and fair to all stakeholders in FOBs legislation that enables legitimate and lawful competition to occur when patent terms expire. Specifically, we suggest that, immediately subsequent to FDA approval of a FOB, the FOB sponsor provide the reference BLA holder notice (of 45 - 90 days) of the approval and impending launch of the FOB, and couple that notice with a statutory stay on launch during that post-approval window to enable patentees to sue if they have a good faith basis for asserting patent rights have been infringed. Such a post-approval process would grant a reference BLA holder an additional opportunity to assert its rights, while also enabling the FOB sponsor to secure an asset that has value, namely the FDA biologics license. At the conclusion of the statutory stay, the FOB sponsor can launch at risk if not sued and/or absent a preliminary injunction, thereby enabling the FOB sponsor (rather than a patentee or an artificial statutory clock) to control its entry into the U.S. marketplace. Enabling FOBs sponsors to make this purely business decision to launch at risk or not is sound public policy. However, it requires FOBs sponsors to have a pathway to obtain an FDA biologics license without the interference, cost, and disincentive of pre-approval litigation. That biologics license per se does not take

anything from the reference product holder, who retains all patent rights and may simply need to defend them as it would do today against any other BLA holder. Moreover, such a post-approval process can enable an orderly resolution of patent issues and minimize the risk that the precipitous launch of a FOB would irreparably harm the innovator – a prospect that seems to be undermined by the innovator industry's own arguments that FOBs will not produce significant savings.

Accordingly, generic drugs should remain the exception for linking the patent-litigation process with regulatory review, as that system unique to generic drugs was justified by the very different state of development of the generic drug industry in 1984 compared to that of the biotechnology and biosimilar industries today. The current state of the law should hold particularly because the cumbersome and increasingly-unworkable nature of the Hatch-Waxman patent listing/certification/litigation process is neither necessary nor desirable as a model for FOBs, because of the even greater complexity of IP rights around biologics. Moreover, developments in the law reflect that such mechanisms are not essential, as U.S. courts address and rectify the irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch. Thus, the Constitutionally-protected patent rights that have enabled the biotechnology industry to grow and succeed should remain unaltered when codifying a straightforward grant of authority to FDA to review and approve safe and effective interchangeable FOBs.

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

If FOBs are subject to user fees, as has been proposed in all the U.S. legislative proposals to date, then they will be treated to the same 10-month review clock as innovator products - and the FDA will receive directly from the FOB sponsor the resources needed to accommodate review on that schedule. The review of each biologic application takes significant FDA resources, and, while a FOB application will include a different data set from that of an innovator product, it still will require careful and thorough review by the experts at the Agency. User fees consistent with those for current full BLAs will more than suffice.

The application for an FOB will contain data provided by the FOB sponsor that the FOB sponsor has developed with their own independently-developed product in head-to-head studies against their chosen reference innovator product. Thus, the follow-on sponsor's regulatory filing will include data on both the innovator product as well as the FOB that the FDA never will have seen before. It will not contain any of the innovator's data, but will refer to public information on the reference product and to its use as reflected in the scientific and medical literature. However, while complete in and of itself, it is not anticipated that an application for a FOB will be as extensive as that of a traditional "full" BLA because a great

deal already will be known from the analysis and previous use of the reference product, such as dosing. So, for example, Phase II clinical studies on FOBs generally will be unnecessary.

Should FDA decide that guidance documents would be useful for purposes of development and/or licensure of FOBs in the U.S., the Agency can develop them just as FDA has done for new classes of molecules and other topics on which it has deemed guidance to be necessary and appropriate. Many of the issues that might be addressed in any guidance would apply to all biologics, particularly given the ongoing and rapid evolution of the technology, and may not be specific to FOBs even if that is where they are first applied. Moreover, some FOBs sponsors already have experience with much of the current guidance, which has been utilized for purposes of EU applications and/or in anticipation of a pathway in the U.S., as FOBs ultimately are first and foremost biologics.[48] Thus, while additional guidance may ultimately be useful, there is no reason to presuppose that it is needed, nor that it should in anyway hold up the review and approval of FOBs in the meantime. Indeed, in the Europe the process used for the development of the European Guidelines for their biosimilars, both general[49] and class-specific[50], has proceeded concurrently with the submission, review and issuance of positive opinions and full marketing authorizations for biosimilars, and the regulators have been able to learn from the initiatives of the FOBs sponsors as much as the other way around. The US will be able to consider the lessons learned in Europe and may well not need to "reinvent the wheel" on guidance, not least because the global biopharmaceutical industry who would likely engage with FDA on the drafting of guidance documents have already contributed extensively to the European guidelines.

It is fair to conclude that the unopposed provisions embodied in all U.S. legislative proposals to date, that a standard user fee be applied to any FOB application (unlike a generic drug application which does not currently pay a user fee), should cover the incremental costs of the implementation of the new regulatory pathway for safe and effective interchangeable follow-on versions of PHS Act reference biologics. There is no reasonable basis to believe that FDA will not be able to review and license FOBs within the period provided for all other products (currently 10 months under FDAAA).[51] If no other blocking components, such as the mandatory new regulations or guidance documents, are built into legislation authorizing FDA to review FOBs, it is reasonable to expect that some FOBs could be licensed and available to patients and other healthcare consumers within one year of enactment of legislation.

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[48] Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (Feb. 2006), *available at* http://www.emea.europa.eu/pdfs/human/biosimilar/4934805en.pdf (last accessed Sep. 14, 2008); Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues (Feb. 2006), *available at* http://www.emea.europa.eu/pdfs/human/biosimilar/4283205en.pdf (last accessed Sep. 14, 2008).

[49] Guideline on Similar Biological Medicinal Products (Sep. 2005), *available at* http://www.emea.europa.eu/pdfs/human/biosimilar/043704en.pdf (last accessed Sep. 14, 2008).

[50] EMEA has published a series of product-specific biosimilar Guidelines, including Guidelines for somatropin, insulin, GCSF, and epoetins, all of which are available from the EMEA website. See http://www.emea.europa.eu.

[51] PDUFA Reauthorization Performance Goals And Procedures, Fiscal Years 2008 Through 2012, *accompanying* Transmittal Letter to Congress (Sep 27, 2007), *available at* http://www fda.gov/oc/pdufa4/pdufa4goals html.

3. 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?

Sponsors of biologics, as well as other individuals such as those in academia, have pursued and secured extensive patent estates, and these have been asserted and vigorously contested in some instances. The patent system has proven invaluable to the creation and generation of worth in the biotech industry, a vigorous and risky, but also very successful sector of the U.S. economy.[52] However, there is no reason to presuppose how long patent litigation for biologics, including any related to FOBs enabled by an as yet unspecified new regulatory pathway will take, or if it will be any different from any other patent litigation, including that for small molecule drugs (albeit the latter is unique in terms of its pre-approval commencement as a result of the novel provisions of Hatch-Waxman). The quality and overall number of the individual patents in the patent estates concerned ultimately will be what determines the path of the litigation, and to some extent its duration. As long as legislation creating a new FOBs pathway does not allow/encourage patent litigation to delay the FDA review and licensure of FOBs, it should have minimal impact of the timely availability of FOBs. If Hatch-Waxman-like linkage is imposed and regulatory review is coupled with patent litigation, there could be a compelling incentive for a given reference product holder to litigate, in series, every available patent. In any case, whether patents are litigated in series or in parallel during the FDA review process, significant delays in the availability of every FOB can be anticipated if innovators, or any other patentee, can pursue patent challenges pre-approval. Likewise, FOBs sponsors could be incented to litigate early on what otherwise may be irrelevant patents in order to qualify for exclusivities (as can happen today under Hatch-Waxman) or to otherwise impact the marketplace (e.g., discourage subsequent but perhaps more robust FOBs applications). In addition, third-party patent-holders with patent claims that may be only marginally tenable could be invited to support such ongoing litigation in a manner that is currently unpredictable (as Hatch-Waxman, unlike some FOBs legislative proposals, does not even enable third-party patent litigation). Decoupling, particularly when "coupled" with data exclusivity for the innovator, creates a date certain, post-approval, when a FOB can be approved because expiration of the exclusivity is unambiguous. When decoupling is contrasted with the various patent-linkage proposals, however, it should be apparent that no patent-linkage system can provide such certainty for any stakeholder, and, short of expiry of all patents in a patent estate, linkage simply is unable to provide a clear date for a FOB to launch that is without any risk of patent infringement. This is true regardless of how early in the FOBs review process patent notification and litigation are commenced; an early start to patent litigation does not mean an early end. Indeed, enabling early litigation by creating artificial acts of infringement provides no meaningful assurances for any party. Instead, in order to

[52] According to CBO, there was $40 billion in expenditures on biologics in 2006. See "*S. 1695 Biologics Price Competition and Innovation Act of 2007*," Congressional Budget Office Estimate (Jun. 25, 2008), *available at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf (last accessed Sep. 25, 2008).

maximize predictability around the protection afforded by biotech patent estates, the U.S. patent laws applicable to PHS Act biologics should remain in force unamended. An orderly resolution of patent issues can be enabled through a post-approval process, providing notice to the reference BLA holder coupled with a statutory stay (45 - 90 days) enabling patentees to initiate litigation if they have a good faith basis for doing so. In that post-approval litigation context, developments in the law reflect that U.S. courts can address and rectify the irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch.

Patents are anticipated to remain critical to the biotechnology industry. While biotechnology patent estates can be more complex that those for small molecule drugs, the history of the industry has shown they have value, and that it continues to be important that they can be disputed in the courts without interfering with the concurrent FDA approval process. Even those who suggest that patents are not sufficient to sustain the industry[53] do not suggest that the industry wants to forego the protection that patents offer. Indeed, exclusivity is a complementary concept, and not, in any form, a substitute for patents (not least because exclusivities are product-specific, whereas patents may not be, and for biologics this may more often be the case than for drugs).

Complex patent estates will always remain intrinsically uncertain, and this is made more so if litigation on the innovators' patents can be initiated by the subsequent potential infringer prior to any actual or even imminent commercialization of the subsequent product, and with minimal risk to that potential infringer. Litigation, enabled by the artificial act of infringement created in Hatch-Waxman, does result in the earlier initiation of patent litigation, and this is a source of uncertainty, and is necessarily a cost for the innovator industry, and the results can apply to a portfolio of products. An early start to litigation may or may not enable resolution of all patent issues "early," as the complexity of the estates, the number of technologies that may be entailed, and the potential multiplicity of patent holders, including third parties, may result in serial litigation of protracted duration. It is also a cost for the subsequent sponsor, and the incentives created by any patent-challenge-based exclusivity could almost force the approach on those sponsors. Patent litigation can be essentially a "tax" on both sides of the industry. It does not necessarily result in an early end to litigation, only an early beginning. Decoupling will reduce uncertainty for both innovators and the sponsors of follow-on biologics and expedite appropriately-timely market entry of subsequent products without undermining the legitimate rights of innovators.

The exceptional linkage process created under Hatch-Waxman does not presently apply to PHS Act biologics, and there is no need to establish a comparable patent linkage system for FOBs. The patent laws that apply to biotechnology products should remain the same as they

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[53] "Biologic patents are not strong enough to protect innovator biologics from competition, said Audrey Phillips, executive director of public policy for Johnson & Johnson, because they apply to the manufacturing process, not the molecule or active ingredient in the drug." *Brand Industry Worries Generics Can Skirt Biologic Patents*, INSIDEHEALTHPOLICY (Apr. 13, 2007).

are for every other product from any other industry, and generic drugs should remain the exception for linking patent litigation with the regulatory approval process.

No compelling case has been made for the need and value of patent linkage, let alone for how it will facilitate the availability of more biologic products by more sponsors able to compete in the market to the benefit of patients. Instead, such proposals simply appear to be extrapolations from the current Hatch-Waxman system uniquely created in 1984 for small molecule drugs when the state of the innovator and generic industries was very different and the needs of both were likewise completely unlike those of the innovator biopharma and biotech industries today. Indeed, unlike the chemical drug industry, there is unlikely to be a clear distinction between the sponsors of innovator biologics and FOBs – as already evidenced by those companies that have succeeded with biosimilars in Europe being sponsors of both innovator and follow-on biologic products. The net effect of patent linkage for FOBs will be delay as a result of the attendant litigation and the accompanying ambiguity and confusion surrounding innovators' patent estates. We would recommend, however, inclusion of a notification process so that the sponsor of the innovator product receives a notice when a FOB is approved (with a statutory bar on launch of 45 - 90 days, during which the innovator biologic sponsor can pursue its traditional patent remedies). Such a process can an enable an orderly, albeit post-approval, resolution of patent issues and minimize the risk that the precipitous launch of a FOB would irreparably harm the innovator – a prospect that seems to be undermined by the innovator industry's own arguments that FOBs will not produce significant savings.[54]

Recognizing that those FOBs sponsors' who do a poor job of evaluating their freedom to operate will risk traditional patent damages if sued by the innovator, it also is important to recognize that, today, in the U.S. (and EU) patent climate in which biotechnology has lived and prospered to date, no innovator sponsor of a PHS Act biologic receives notification of a regulatory filing or approval of a subsequent biologic that may infringe any of its patents. This model has served the biotechnology industry, and there is no justifying need to deviate from it in the context of FOBs. Moreover, developments in the law reflect that pre-approval patent linkage mechanisms are not essential to prevent market destruction, as U.S. courts can address and have rectified irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch. Thus, the Constitutionally-protected patent rights that have enabled the biotechnology industry to grow and succeed should remain unaltered when codifying a straightforward grant of authority to FDA to review and approve safe and effective interchangeable FOBs.

The present "decoupled" system for PHS Act biologics represents a balance that is valuable to both innovators and the manufacturers of subsequent biologics, whether they are FOBs *per se* or simply other innovator products using similar, and potentially patent-infringing, technology. Without patent-linkage, the FDA regulatory process can continue. At the point

[54] BIO, "*The Economics of Follow-On Biologics*," Edward (Ted) Buckley, Presentation at Biosimilars2007 (Sep. 25, 2007), *available at* http://www.biosimilarstoday.com/Buckley.pdf (last accessed Sep. 26, 2008).

at which FDA has completed its review and a FOB sponsor has secured an FDA-issued biologics license authorizing it to ship its FOB in interstate commerce, the FOB sponsor can make its own business assessment as to whether it wants to launch at risk and the patentee(s) can assess whether they have a good faith basis for a patent infringement lawsuit. That balanced system is good enough for every other U.S. industry, it has served the U.S. biotechnology industry, and it works in the EU for biologics and biosimilars as well as for brand chemical and generic drugs.

4. 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?

It may not be helpful to try to presuppose what the interests of the FOBs sponsors and the innovator sponsors will be on the timing of patent resolution when every biologic will raise very different issues for the different stakeholders depending on numerous factors from the size of the market for each of the products, the size/strengths of the companies involved, the quality of the patent(s), and the number of potential competitors. An assessment of strength of each patent will have to be made by each patent holder/licensee and the sponsor of any FOB, just as those assessments are made today for every potentially-infringing biologic (such as a second-generation products). Consequently, it is far better to opt for the simplicity of ensuring that the Constitutional rights of every patent holder, be they product sponsor or independent inventor, is not undermined in a new FOBs pathway. Instead, those rights should be left unamended, to be enforced independently through the courts – just as they are for every industry, other than innovator chemical and generic drugs, including other FDA-regulated products requiring pre-market approval, such as diagnostics. This simply means leaving well alone in terms of maintaining the longstanding practice of keeping patents out of the PHS Act biologics realm pre-approval, and not "coupling" the regulatory review and approval process with a patent notification/litigation system that encumbers FDA or its review in any way. Separate and apart from FOBs and outside the context of legislation creating a new pathway for FOBs in the U.S., we would support adoption of a patent opposition system in the U.S. akin to that in Europe. In particular, Congress could consider establishing a new, post-grant review proceeding to provide an additional administrative forum for challenging patent validity based upon "clear and convincing evidence" outside of the court system. In the FOBs context, however, we would note that patent listing/notification, dossier-sharing, and comparable complex administrative procedures associated with patent linkage have proven challenging for small molecule drugs under Hatch-Waxman, with accusations from both sides and others of "gaming."[55] It is not unreasonable to anticipate that such processes would be even more cumbersome and challenging in the context of complex patent estates and multiple patentees applicable to biologics.

[55] See FTC response to House E&C Committee questions (May 2, 2008), *available at* http://energycommerce house.gov/Press_110/110-ltr.050208 respto040308.FTC.pdf (last accessed Sep. 26, 2008).

There is no attribute unique of the biotechnology industry in the U.S. that makes biotech patent holders unable to use the courts as effectively as they have over the past 25 years to continue enforcing their patent rights in a post-FOBs environment in the same manner as every other U.S. industry enforces patent rights against competitors. In fact, throughout the entirety of the very successful history of the U.S. biotechnology industry, patent litigation has proceeded on this basis when a threat to patented rights has arisen. Indeed, the very rational for a new FOBs pathway is that the expiration of patents on PHS Act biologics has not resulted in marketplace competition or enabled greater patient/payor access at lower cost post-expiry. The FDA review and approval process for PHS Act biologics always has proceeded free and clear of patent litigation, irrespective of the patent estates claiming those biologics or potentially infringed by them.

Just as there is no need or justification for a special level of protection for current biologics patent holders, there likewise is no need for potential-infringers to be able to utilize a Hatch-Waxman-like system for FOBs in order to precipitate patent litigation prematurely – i.e., prior to FDA approval of a commercializable product. That is not to say that other reforms, outside the context of FOBs, should not be pursued. In particular, Congress should give consideration, on a separate track, to establishment of a patent opposition system that would provide a new, post-grant review proceeding for challenging patent validity based upon "clear and convincing evidence" outside of the courts.

The fundamental premise of the U.S. patent system is that it grants the holder a right to preclude others from practicing the protected invention. In the context of FOBs, that generally will not occur prior to FDA approval because of the "Bolar amendment" provisions in section 271(e) of the Patent Code. It is for this very reason that Hatch-Waxman had to establish an "artificial" act of infringement in order to vest the U.S. courts with jurisdiction over pre-approval patent litigation. The question now is whether yet another "artificial" act of infringement needs to be created and yet another barrier to entry established for competitive biologics – purportedly on the basis of some overwhelming public policy need to enable premature litigation. The Novartis Group of companies does not perceive an overwhelming need for such a system. To the contrary, we believe premature litigation of biologics patents presents some very serious downsides that would outweigh even theoretical advantages. The most significant risk by far, of creating yet another "artificial" act of infringement, is that it can engender unnecessary patent litigation in which one or more parties seek to "test the water" in court in an effort to clear-up potential uncertainty in the patent estates of biologics when these patents may apply to an entire technology and not just one product. Any such litigation can become a stalking horse with minimal risk to those involved, some of whom may merely be interested in avoiding risk rather than advancing competition in the marketplace and making products available to consumers.

Throughout the entire public policy debate on FOBs, one of the most fundamental mistakes has been the failure to question the assumption that an early start to patent litigation means an early end to litigation. It is indisputable that it is the conclusion of patent litigation that matters most and that will be more important in determining whether and when competing FOBs enter the market. Absent a fully transparent compulsory process requiring disclosure

of the entirety of the patent estate for any given biologic (including all third-party patents), or a public-policy decision to consider cutting off patent rights (which can present serious Constitutional issues and which we certainly do not support), it simply is not possible to know when litigation will end. Similarly, it is not possible to get to the much-heralded "certainty" that those supporting patent linkage assert is the primary benefit of linkage. Consequently, if it is impossible to predict an end to litigation, it makes no sense to in any way hold up or interfere with FDA review and approval and undermine the ability of FOBs sponsors to enter the litigation setting with an FDA-issued biologics license in hand. Any pre-approval litigation process would incent premature, protracted, and potentially-serial patent litigation, while risking attacks on valuable patents prematurely. Accordingly, the Novartis Group of companies believe it is far better to leave all patent issues up to individual patent holders and their competitors to assess and address in accordance with the existing provisions of the Patent Code.

5. 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?

The fundamental rights created in the Constitution for patent holders, which have enabled the biotechnology industry to grow and prosper without patent linkage, would remain unaltered by simple, straightforward legislation granting FDA authority to review and approve safe and effective interchangeable follow-on biologics. If patent issues are not coupled with the regulatory review process, a FOB sponsor could only be sued when an act of infringement occurs under current law, which typically would arise after FDA approval of their FOB. Similarly, with that FDA approval in hand, an interest/intent on selling that FOB in the U.S., and reasonable apprehension of suit by the reference biologic BLA holder and/or other patentees, FDA approval also should enable a FOB sponsor to pursue its patent law remedies under the Declaratory Judgment Act if the FOB approval does not result in initiation of litigation by a patent holder. Just as there is no special need to protect biotech patent holders with special pre-infringement notification and litigation rights, there is similarly no need for doing so for FOB sponsors pursuing FDA approval of potentially-infringing products. All parties should be left to their existing remedies under current law without the introduction, and unnecessary complication, of new systems and new rules for FOBs. This enables a level playing field for all parties developing PHS Act biologics and/or holding patents claiming those products. Accordingly, the Novartis Group of companies does not believe any new declaratory judgment provisions should be codified in connection with the establishment of a new FOBs pathway.

When any PHS Act biologic is approved (as a FOB or as an innovator product) and then marketed, any patent holder can decide whether or not they have a good faith basis for believing a patent(s) is infringed. If so, they can sue as provided for under current law. In the context of FOBs, with decoupling, this would be precisely the same situation as presently applies to biotech patents, irrespective of whether the patent holder or competitor is the sponsor of an innovator biologic BLA, in academia, or an individual inventor. Today, no

innovator BLA holder or other patentee receives any notification of a BLA submission or notice of approval of a competing product that may infringe any of their patents. Despite the absence of notice, the patent estates of PHS Act biologics have continued to demonstrate value and support product and/or royalty income for their owners.

This independence of FDA regulatory processes from patents is the model which applies to biotechnology, and it has been applied to PHS Act biologics to date (as it has been to every other industry in the U.S. except generic drugs). As evidenced by the myriad of non-patent-litigation issues spawned by the Hatch-Waxman patent notice/litigation provisions over the past 25 years, the current model for biotech is the appropriate model for this industry because it respects IP, it retains the full value of patent rights, it avoids unnecessary and costly litigation before litigation otherwise would occur, and it enables the regulatory review process to proceed free and clear of interference from patent litigation. This existing system should be continued for *all* PHS Act biologics. Otherwise, with patent linkage, the breadth and complexity of biotech patent estates inevitably would give rise, pre-approval, to even more non-patent-infringement issues and greater delays than have been generated by the patent certification/litigation process under Hatch-Waxman. The best thing for biotech is to avoid these unnecessary complications and retain current law as it presently stands relative to the patent law/BLA interface.

Outside of the BLA review and approval process, the Novartis Group of companies consistently has advocated for a post-approval mechanism that we believe could be useful and efficient for all stakeholders to resolve patent disputes once a FOB sponsor completes the approval requirements of the new pathway. Our proposal is to require a FOB sponsor, upon receipt of its FDA approval letter, to provide notice of the approval to the reference product BLA holder with a statutory stay on launch of 45 - 90 days, during which any patentee(s) could initiate suit if they have a good-faith belief that a patent(s) has been infringed. Such a post-approval mechanism would allow the reference product holder to assert its patent rights with the added protection of notice of the approval, while also enabling an FOB applicant to secure a tangible asset that has meaningful value and that can be launched at risk at the end of the pre-launch window absent a preliminary injunction obtained by a patentee. Enabling a FOB sponsor to make the purely business judgment regarding an at-risk launch is sound public policy, and giving exceptional but not too burdensome notice to the reference product BLA holder does not unnecessarily encumber the FOB sponsor's business decision. Together, these mechanisms also should have the effect of enabling a FOB sponsor to pursue a declaratory judgment action if no suit is filed against them during the minimal statutory stay on launch.

6. Are regulatory exclusivities needed to encourage follow-on biologic applicants to challenge patents?[56] Why or why not?

Depending on the terms of the FOBs legislation that is enacted, the nature of the regulatory pathway(s) for FOBs that is created, and the imposition of a significant additional regulatory burden to achieve FDA designation as an interchangeable FOB subsequent to initial licensure of the FOB itself, sound public policy would suggest that it may be appropriate to provide an express incentive to FOB sponsors to seek an interchangeability designation since interchangeability is considered the most effective way to introduce head-to-head market-based competition. The incentive under such a system would be directed at encouraging interchangeability status rather than challenging patents. Such interchangeability exclusivity can be particularly important in the context of a FOBs pathway for which the standards for interchangeability are not (as they should not be) delineated in the statute but are instead (appropriately) a matter of discretion determined by the scientific experts at FDA. With respect to challenging patents, the most direct incentives are, and will always be, the same as those which apply today to any biologic sponsor willing to make a competing biologic product. Those existing patent-challenge incentives revolve around the product's complexity, the magnitude of the product segment in the U.S. marketplace, and the margins available to a company that can supply that segment (especially if that company can achieve a like-quality product at a significantly-reduced manufacturing cost). As reflected by the fact that it is the success of biologics such as the top five biotechnology products – each of which have worldwide sales approaching $5 billion – which is driving the public policy debate on FOBs, it seems apparent that the foregoing types of commercial considerations will remain a primary motivation for both product selection as well as patent challenges.

Exclusivity for the first interchangeable FOB, as would be established under some U.S. legislative proposals, can incentivize sponsors of FOBs to seek the additional recognition by FDA that their product can be interchanged safely and effectively with the reference product.[57] This regulatory designation embodying FDA's expert conclusions could have some value to a FOBs sponsor. It is not possible to speculate at this juncture, however, on the magnitude of that value or the extent to which it will be appreciated. For business reasons, different FOBs sponsors may wish to pursue the designation or not depending on

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[56] We are assuming that this question refers to exclusivities that might be granted to a FOB sponsor for securing approval of the first FOB to a given reference product as occurs for generic chemical drugs under Hatch-Waxman. In the U.S. legislative proposals introduced to date, such exclusivity would apply only to the first interchangeable FOB and would not block market entry during the exclusive term of subsequently-licensed, non-interchangeable FOBs. The comments in the main text accordingly focus on such FOB interchangeability exclusivity.

[57] The comparability standard already is defined in ICH Q5E, *available at* http://www.ich.org/LOB/media/MEDIA1196.pdf (last accessed Sep. 22, 2008). Comparability also provides the regulatory history and experience for the "highly similar" term-of-art that has been used in various U.S. legislative proposals as well as for the European biosimilars pathway. This established comparability standard is applied to an innovator product undergoing a manufacturing change such that interchangeability of the pre- and post-manufacturing change products already is presumed, and the product is not labeled as having been "changed." As a scientific and regulatory matter, the distinction between a FOB and an interchangeable FOB is inappropriate if the "highly similar" standard is the one being applied.

their company's specific business model, including such factors as whether the company intends to detail and promote its FOBs and to whom. Consequently, there may be value in a distinction between FOBs and interchangeable FOBs, and in the associated exclusivity regimes.

However, the idea being fostered by some that a FOB meeting the "highly similar" standard of comparability means "not the same" so as to create leeway to avoid patents is entirely misplaced. "Highly similar" is an extremely high regulatory standard, currently applied to innovators making manufacturing changes to their own products. Patents claiming manufacturing methods for PHS Act biologics potentially may be easier to innovate around simply because manufacturing technology has made such significant progress over the last several decades that older, patented methods are no longer relevant. The vast progress in manufacturing science may represent the greatest opportunity and value of FOBs beyond marketplace competition, as the opportunities for manufacturing innovation and significantly reduced cost-of-goods abound. The ability of FOBs sponsors to competitively price their products due to manufacturing efficiencies could make an additional significant contribution from a FOBs pathway – namely, a stimulus for the better application of optimal biomanufacturing science for all biologics.

The Novartis Group of companies is a proponent of respect for all legitimate IP including patents, and the incentives created in legislation establishing a FOBs pathway are not in conflict with this *per se* given that a pathway is about regulatory access to a market, and, in its simplest form, would not alter current IP rights in any manner. However, regardless of the manner in which these regulatory pathway and exclusivity opportunities are configured for FOBs in the U.S., it is not necessary to incent patent challenges as part of a FOBs pathway, because the principle objective of the pathway is to enable market access for competing products where currently there is none even for those products on which all blocking patents already have expired. Consequently, we support continuation of the existing "decoupled" system for PHS Act biologics, in which the regulatory process at FDA is not linked to patent rights or the patent-litigation system. Therefore, all that is required is to confer the additional authority on FDA to review and approve FOBs without altering the extant provisions of the Patent Code or otherwise affecting the patent rights held by the sponsors of innovative or follow-on versions of PHS Act biologics. Decoupling will avoid premature challenges to biotech patent estates, and current law provides robust protection for those rights when infringement occurs, as has consistently been shown to be the case throughout the history of the biotech industry. Moreover, developments in the law reflect that U.S. courts can address and have rectified irreparable injury caused by market entry and cannibalization (as in the generic Plavix case). Although historically it may not have been possible to redress market destruction caused by generic entry, the Plavix case suggests that is no longer an absolute even post-launch, and the Mircera case demonstrates that adequate remedies can be applied pre-launch.

7. What opportunities will biologic drug manufacturers and follow-on applicants have to manipulate proposed new regulatory obligations (*e.g.*, application notification obligations, declarations of patents claiming biologic drugs, etc.) and exclusivity periods surrounding a

concurrent patent resolution process? What are the prospects for the improper use of citizen petitions to delay approval of follow-on biologic applications?

If the regulatory review and approval process and the patent systems remain decoupled for FOBs, just as they have for PHS Act biologics throughout the history of the biotechnology industry, then they can continue to each proceed at their own pace, unencumbered by tactics such as those identified in the Commission's question. Under decoupling, such tactics become irrelevant. Implementing a decoupled solution for FOBs only requires the simplest of regulatory authorities granting FDA the ability to approve subsequent applications for safe and effective interchangeable versions of PHS Act biologics referencing FDA's prior approval of a biologic already licensed under the Act.

There is no need for a complex statute that revisits multiple historical areas of contention that emerged for small molecule drugs after Hatch-Waxman was enacted in 1984. Acknowledgement that linking patents and regulatory approval processes is inherently cumbersome and open to confusion (and manipulation by some) is long overdue, particularly in light of the documented expense and delay it imposes on all sponsors and the delay in competition and access it imposes on patients and the healthcare system. Simplicity can achieve the pro-competitive outcome that safe and effective FOBs will enable. An appropriate pathway can be enunciated in just a few pages, and need not get bogged down in dozens and dozens of pages of complex and necessarily-confusing provisions linking patent litigation and regulatory review. These are necessarily two very different issues that require completely different oversight – the one by FDA and the other by the courts – and that oversight should occur independently (i.e., with regulatory review decoupled from patent litigation).

8. How might referenced biologic product manufacturers and follow-on biologic applicants structure patent settlement agreements given the competitive dynamics arising from the marketing of follow-on biologic drugs? What incentives might exist for these companies to enter anticompetitive settlements? Should patent settlement agreements be filed with the antitrust agencies? What would be the likely effect of the filing requirement on settlements?

There unquestionably are many lessons to be learned from Hatch-Waxman. However, most of those lessons are not entirely relevant or applicable to PHS Act biologics. In the debate on FOBs, there has been a tendency to presuppose that the provisions of Hatch-Waxman should form the foundation for any legislation to authorize interchangeable PHS Act FOBs, but this is the wrong place to start. Such a Hatch-Waxman-oriented mindset has led to excessive complexity and unduly lengthy legislative proposals to date (especially when one considers that the PHS Act provisions establishing the criteria for approval amount to nothing more than a couple of subparagraphs). As a matter of sound public policy, it is better and more appropriate to focus on why legislation is needed to enable interchangeable PHS Act FOBs, and what elements such legislation must contain to achieve that public policy objective. If legislation is limited to granting authority to FDA to approve safe and effective

interchangeable FOBs that reference a previously-approved PHS Act biologic, there is no need to enable, nor therefore expect, any form of wholesale disruption of the successful biotechnology industry.

The success of the biotech industry over the past decades is emblematic of the natural progression seen in every industry, namely, the ongoing development of new products in the context of the expiration of patents on highly-successful but older products, which culminates in the public policy need to enable competition in the marketplace against those older products on which patents have expired. The marketplace for medicines is unique in this regard as a result of the requirement for securing prior FDA approval to enter the U.S. marketplace as an innovator and as a subsequent competitor. While this is possible for interchangeable generic drugs, it is not currently an option for interchangeable follow-on versions of PHS Act biologics. This results in the appearance of a market failure for biologics in the U.S. in the face of its apparent solution in Europe with the EU biosimilars pathway, because comparable competition is not currently able to commence in the U.S. as it is now occurring in Europe. Hence, the issue for Congress to address is FDA's authority to enable market entry for competitors to old biotechnology products on which patents have expired (the contesting of unexpired patents being a post-approval issue).

How the legislation in written, and what it includes in addition to creating a statutory pathway for FOBs, ultimately will determine whether there are potential sponsors interested in developing and manufacturing FOBs. These sponsors will respond to the opportunities created and ultimately will determine any particular patent is worth and what sort of agreement if any they are interested in executing. It is impossible to pre-judge how the competitive dynamics will play out in this regard, but there is no reason to presuppose that they will be radically different from the great variety of licensing and settlement arrangements that occur today between government, academic, industrial and individual biotech patent stakeholders even absent a FOBs pathway. After all, the greatest significance of a FOBs pathway is for those products on which there are no outstanding patents.

Nonetheless, the availability of a pathway for safe and effective interchangeable FOBs to be evaluated by FDA actually could make the patent estates held by various stakeholders more meaningful, particularly because the expiration of the patents will have consequences in terms of determining when competitors enter the market. At the moment, patents matter to the biotechnology industry, but not as a way of limiting head-to-head competition so much as in terms of blocking market access for products that share certain features representative of manufacturing technology or use. In the future, depending on the availability of a new pathway and the incentives associated with it, it may be that products will be evaluated to be indistinguishable in terms of their clinical consequences, and, absent authority for FDA to designate them as interchangeable, actual market forces could emerge that ultimately place greater or lesser value on structural identity and the patents associated with it. In any case, pending enactment and implementation of a FOBs pathway in the U.S., it seems it may be too early to suggest what agreements should be filed with the antitrust authorities (beyond those required to be filed under current law).