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Emerging Health Care Competition and Consumer Issues – Comment
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Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Avenue, N.W.
Washington, D.C. 20580
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Dear Chairman Kovacic and Commissioners:

Thank you for providing Amgen with the opportunity to respond to your questions regarding biosimilars. As one of the world's first biotechnology companies, we believe we can offer a unique and valuable perspective on what is required to develop and manufacture safe and effective biologic drugs. We appreciate this opportunity to work with the Commission as it looks into the complex questions surrounding the establishment of an approval pathway for biosimilars (also known as "follow-on biologics").

Amgen discovers, develops, manufactures and delivers innovative human therapeutics. A biotechnology pioneer since 1980, Amgen was one of the first companies to realize the new science's promise by bringing safe and effective medicines from lab, to manufacturing plant, to patient. Amgen therapeutics have changed the practice of medicine, helping millions of people around the world in the fight against cancer, kidney disease, rheumatoid arthritis, and other serious illnesses. With a deep and broad pipeline of potential new medicines, Amgen remains committed to advancing science to dramatically improve people's lives.

In 2007, Amgen invested 3.2 billion dollars in research and development of new medicines, and we focus those research and development efforts on novel therapeutics for the treatment of grievous illness. Our innovations have helped millions of people worldwide who suffer from medical conditions for which there are few effective treatments. It is from this perspective that we submit our answers to the thoughtful questions posed by the Commission.

Please feel free to contact us should you require any additional information regarding the information described in these responses. We look forward to continuing this constructive dialogue and appreciate your interest in this important issue.

Sincerely,

David Beier
Senior Vice President,
Global Government Affairs

Executive Summary

An abbreviated approval pathway for biosimilar products (also referred to as "follow-on biologics") that limits the risk to patients can, and should, be developed. However, that pathway must be tailored to address the unique characteristics of biotechnology; otherwise, important consumer interests – namely patient safety and future medical innovation – will be compromised. Although the science of biotechnology is largely beyond the scope of the questions posed by the Federal Trade Commission (FTC), it has implications for several aspects of an approval pathway, and therefore for consumers.

Intellectual property is essential to the development of new cures for needy patients and a cornerstone of the information economy. Discovery and development of medical products from biotechnology is one of, if not the most complex inventive processes. Massively expensive, risky and lengthy development – on average, over $1 billion and 12 years – must occur before a therapeutic biological product can be approved and brought to patients. Moreover, this development is unpredictable and full of risk, as failure, rather than success, is the rule in terms of developing a product that is safe and effective. Every major developed nation that has allowed for follow-on biologics or biosimilars has recognized this reality by offering both patent protection and data exclusivity for innovative biotech products. The jurisdictions that have acted most recently (our trading partners and potential economic competitors) have a combination of patent and data exclusivity that far exceeds current U.S. law for small molecule drugs. This combination of rights is necessary because patents and data exclusivity protect different things. Patents protect inventions, whereas data exclusivity – as the name implies – protects the massive investment companies make to create the safety, efficacy and manufacturing data necessary to secure product approval. Without adequate periods of data exclusivity, those who follow in the wake of others' discoveries would be favored over innovators and scientific leaders. Such a choice would be detrimental to patient health and consumers as the relatively young biotech sector may be unable to continue to attract the investment needed to continue searching for much-needed cures.

Biosimilars are not identical to innovator products. Their safety profiles can also differ.
Biologics are manufactured from living cells or organisms by programming a cell line to produce a desired protein in a highly controlled environment. The manufacturing process for each biologic largely defines the clinical properties of the resulting biologic product. The end product is a highly complex, heterogeneous mixture that, for the most part, cannot be fully characterized with today's science. Small differences in manufacturing processes can cause significant differences in the end product. *No two biologics made using different cell lines or a different manufacturing process will be the same.*

A *biosimilar* version will be manufactured using a different cell line and process from that of the innovator biologic. Due to the innate complexity of biologics, this will inevitably lead to differences between the structures of the biosimilar and the innovator products and these differences could have significant clinical implications for patients. A biosimilar product could be more or less potent than the product it is imitating, or it could cause an immune response ("immunogenicity") not seen with the innovator product.

Automatic Substitution by pharmacists would compromise patient safety.
Due to the potential for immunogenicity and the attendant need for careful post market surveillance of biotech products, *substitution at the pharmacy level – without the consent of the physician – is not appropriate in the biotech context.* Biosimilars will not be identical to the reference product they attempt to copy and will be approved based on different clinical data than the innovator biologic. This being the case, only a physician with an in-depth knowledge of the patient's history can prudently choose to prescribe a specific biologic – whether biosimilar or innovator – that the physician deems appropriate for an individual patient. Additionally, it will be very difficult to trace adverse events to a particular product

if substitution occurs repeatedly and without the physician's involvement. Notably, the practice of substitution of a biologic by the pharmacist without the physician's consent has been rejected in more than half of the European Union (EU) member states (including France, Germany, the United Kingdom, Italy and Spain).

The future of biotech medicines depends upon adequate incentives for continued innovation. A model for approving biosimilars must include adequate protection for innovators who risk investing time and money in the very unpredictable and uncertain process of biotech medicine development or future cures may never materialize. The incentive structure provided by the Hatch-Waxman generic drug model is too complicated, has resulted in a vast increase in litigation, and is inapplicable to products that are "similar" rather than "identical" to the product they attempt to copy. The generic drug model would thus fail to provide adequate protections for biotech innovators, and therefore patients.

A model with sufficient incentives for ongoing biotech innovation would address both the timely resolution of patent disputes and adequate protection for the data developed to secure FDA approval of the innovator's product. First, an abbreviated approval model for biosimilars must permit resolution of patent disputes before a biosimilar product comes to market. Second, the data developed over many years and at great expense to the innovator must be protected from use by others for a period of time in order to give the innovator an opportunity to recover the investment. A period of 14 years of data exclusivity is appropriate and will encourage future innovation. The need to encourage research and development of new therapies includes providing the necessary incentive to research, develop, test and obtain FDA approval for new indications and other important developments emerging from existing biologics.

The approval pathway for biosimilars will have both commercial and therapeutic consequences. When assessing the potential for cost-savings of biosimilars, the difference in the science of biotechnology and of traditional pharmaceuticals is a crucial variable. The market dynamic and any associated savings from biosimilars are likely to be far different from the generic model, which consists of heavy discounting and rapid uptake of generics. According to highly credible analyses, savings estimates for biosimilars are modest over a ten-year time period when compared to the traditional generic model.

Any calculation of the economics of biotech medicines should include both the existence of productive competition by other innovative medicines and the contributions of the biotech industry to the U.S. economy and to the wellbeing of patients. It is inaccurate to assume that the only source of price competition in the market comes from efforts to make copies of new products. Innovators are also challenged by the arrival of new innovative products. Additionally, the U.S. leads the world in biotech research and innovation. It would be short sighted to undermine this productive, but fledgling industry when the U.S. is losing jobs to overseas competitors – and while millions of patients are still waiting for cures.

Finally, responsible legislation implementing an abbreviated approval pathway for biosimilars should be driven as much by patient safety and outcomes as by economics. In fact, the two are closely intertwined, since the commercial health of the biotech industry has a direct impact on the health and productivity of the patient population. *Without incentives to invest in innovation, the R&D pipeline of breakthrough therapies will be diminished and patient outcomes will be affected.* Beyond the human costs from chronic disease, the demise of innovation will have significant financial costs in terms of the lost work and productivity of patients.

I. Competition Issues Involving Follow-on Biologic Drugs

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

As a result of the difference in the science of biotechnology and traditional pharmaceuticals, the market dynamic and any associated savings from biosimilars is likely to be far different from the generic model that consists of heavy discounting and rapid uptake of generics. In fact, credible savings estimates, including one estimate recently released by the Congressional Budget Office (CBO), the official score keeper of Congress, are modest over a ten-year time period.

To date, a number of organizations have tried to quantify the savings potential from creating a biosimilar pathway. Most of these modeling attempts focus on estimating the timing of biosimilar entry, market uptake, and discounting levels, because these are the key drivers that influence the level of savings that will ultimately be available to consumers. The results of this research indicate that savings opportunities from creating a biosimilar pathway will be very different from the savings opportunities created from the Hatch-Waxman generic drug law in 1984.

On June 25, 2008 CBO released its cost estimate of S. 1695, the Biologics Price Competition and Innovation Act of 2007. That bill would create an abbreviated regulatory pathway for biosimilars.[1] As the official score keeper of Congress, CBO's role is to assess a legislative proposal's impact (cost or savings) on federal outlays over a ten-year time horizon. In its estimate of S. 1695, CBO found that direct spending by the federal government would decrease by $46 million over five years and by $5.9 billion over the ten year window (2009-2018). CBO found that approximately two-thirds of the savings would not occur until the last two years of the ten-year scoring window. Therefore, any savings would not be immediate.

In addition to the CBO estimate, three other studies have done a rigorous job of quantifying the impact of biosimilar entry into the market place and were conducted by Avalere Health, LLC, Henry Grabowski, Ph.D, and Howrey/CAP. Avalere Health, LLC, in its "CBO-style" estimate, calculated $3.6 billion in federal savings over ten years.[2] Henry Grabowski, Ph.D. simulated market entry rates and corresponding price discount levels and predicted that savings would be closer to or below Avalere's calculated savings estimate than other higher estimates, although he did not provide a specific number.[3] Howrey/CAP reviewed the assumptions made by the Pharmaceutical Care Management Association (PCMA) and Express Scripts studies and re-estimated savings at between $2.0 to $2.8 billion over a ten-year time period.[4]

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[1] "S. 1695, Biologics Price Competition and Innovation Act of 2007," Congressional Budget Office, June 25, 2008.

[2] Avalere Health, LLC, "Modeling Federal Cost Savings from Follow-on Biologics," (April 2007), at p. 10.

[3] Grabowski, Henry, *et al.*, "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at pp. 1-7, *available at* http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008).

[4] Howrey LLP, CAP Analysis & PhRMA, "The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports" (May 2007), at p. 6,

These three estimates are credible because they address, using different methodologies and approaches, the key components needed to assess any potential cost savings. Importantly, these studies taken collectively examine the implications that the complex nature of biotechnology has on the number of biosimilar competitors, which is then reflected in product pricing levels, the time lag between passage of a bill and promulgation of regulations and guidance, and the market uptake rates for biosimilar products.

Product pricing and market uptake will play important roles in assessing the potential cost savings if a biosimilar pathway is established. As these reports note,[5] the price of biosimilar products is likely to be close to that of the innovator product for several reasons. Biotech products are much more difficult and expensive to produce than most pharmaceuticals and often have higher fixed costs. Consequently, there will be far fewer biosimilar entrants than are usually seen with small-molecule generics.[6] The CBO analysis found that, "…CBO expects that certain drugs could face competition from several firms by 2018, although we believe it would be more typical for an innovator biologic to face competition from between one and three competitors."[7] This is far fewer than the average ten competitors normally seen in the traditional chemical generic space.[8] The combination of these factors will make it very unlikely that biosimilar products will bring about the price differential that generic products do.

Most estimates predict product savings of 10 to 25 percent, a savings range in line with the Generic Pharmaceutical Association's (GPhA) own expectations.[9] In fact, one biosimilar product on the market – Omnitrope® (somatropin recombinant) – has, according to the investment firm Griffiths McBurney, seen discounting levels of 20% to 25% in Germany, and 10% to 20% in the Australian human growth hormone market.[10] This is consistent with a report from Wachovia Capital Markets (10-20% discount).[11]

In recent testimony before the House Oversight and Government Reform Committee, Dr. Grabowski concluded that:

> Based on our analyses, we conclude that the costs of entry will be significantly higher for follow-on biologics than generic drugs. As a consequence, we expect fewer firms will

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available at http://www.howrey.com/files/News/6efa58d8-75a8-49e0-ac0f-512f45769c77/Presentation/NewsAttachment/13ce02b8-b57f-4f2f-b682-4d79c22d578a/Biologics%20White%20Paper%205-2-07.pdf (last visited April 18, 2008). at pp. 2-3.

[5] Avalere Health, LLC, "Modeling Federal Cost Savings from Follow-on Biologics," (April 2007), at p. 8, *available at* http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf (last visited April 18, 2008); Grabowski, Henry, *et al.,* "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at p. 7, *available at* http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008); Howrey LLP, CAP Analysis & PhRMA, "The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports" (May 2007), at p. 6, *available at* http://www.howrey.com/files/News/6efa58d8-75a8-49e0-ac0f-512f45769c77/Presentation/NewsAttachment/13ce02b8-b57f-4f2f-b682-4d79c22d578a/Biologics%20White%20Paper%205-2-07.pdf (last visited April 18, 2008).

[6] Grabowski, H. *et al.*, "Entry and Competition in Generic Biologics," *Managerial and Decision Economics*, 28: 439-451 (2007), at p. 449.

[7] "S. 1695, Biologics Price Competition and Innovation Act of 2007," Congressional Budget Office, June 25, 2008.

[8] "How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry," Congressional Budget Office, July 1998.

[9] GPhA, Press Release (Feb.14, 2007), *available at* http://www.gphaonline.org/AM/Template.cfm?Section=Press_Releases&TEMPLATE=/CM/ContentDisplay.cfm&CONTENTID=3202 (last accessed April 29, 2008).

[10] Ordonez, C. & T. Connolly, "Accretropin Receives FDA Approval," Griffiths McBurney (Jan. 25, 2008).

[11] Farmer G. et al., "Biogen Idec, Inc. BIIB: Shares unjustifiably rich on acquisition speculation," Wachovia Capital Markets LLC (Oct. 10, 2007).

> enter, and average prices will decline less for follow-on biologics than generic drugs. Consequently, conservative budgetary scoring is appropriate in terms of expected savings to the government programs and other payers.[12]

The science of biotechnology also has implications for market uptake. Market uptake for biosimilars will likely be gradual, meaning any potential savings will not materialize until years from now, a point CBO makes in its estimate. The limited clinical information that is likely to have been presented at the time of FDA approval may impact the readiness of physicians and patients to consider use of these products.[13]

Sales data reported by IMS and manufacturers show that Omnitrope®'s uptake in Australia (product launched in November 2005), the European Union (product authorized for marketing in April 2006), and the United States (product launched in March 2007) has been minimal. For example, a report of January 2008 sales data in the U.S. showed that Omnitrope® had no more than a 1.5% market share of prescription renewals (TRx).[14]

Several published estimates of the savings from biosimilars that are significantly higher than the CBO, Avalere, Grabowski and Howrey studies have used unrealistic assumptions around the timing of biosimilar entry, uptake rates, current innovator biologic patent expiry, and discounting levels.

The Biotechnology Industry Organization (BIO) has critiqued two of these studies (released by the PCMA and Express Scripts) that claimed large savings from a biosimilars pathway.[15] BIO determined that those studies overestimated the savings due to, among other things:

- Aggressive assumptions on interchangeability
- Inaccurate assessment of when savings would begin to accrue
- Mathematical errors

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?

Interchangeability of biotech medicines, as defined in this question, would compromise patient safety. There will always be differences between biotech medicines produced by different manufacturers using different cell lines and these differences could have clinical implications for patients. The question of interchangeability or automatic substitution by pharmacists has been addressed in the EU and, to date, the practice of substitution of a biologic by the pharmacist without the physician's consent has been rejected in more than half of the EU member states (including France, Germany, the United Kingdom, Italy and

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[12] Statement of Henry Grabowski, Ph.D., Duke University, before the House Oversight and Government Reform Committee, March 26, 2007.

[13] Grabowski, Henry, *et al.*, "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions" (Aug. 2007), at pp. 1-7, *available at* http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf (last visited April 18, 2008).

[14] Sinclair, A. and K. Scotcher, "Novo Nordisk: Initiating coverage with underweight and TP of DKK305," HSBC Global Research (March 27, 2008).

[15] Biotechnology Industry Association, "Recent Studies of Follow-on Biologics Are Based on Seriously Flawed Assumptions," (Feb. 22, 2007), *available at* www.bio.org/healthcare/followon/20070222.pdf (last visited May 1, 2008).

Spain). These rulings come out of experience, a concern for patient safety, and a commitment to maintaining the robustness of pharmacovigilance systems. It is inconsistent with the United States' commitment to public safety to assume that Congress would take a less rigorous position.

The rulings in Europe are blanket rulings that apply to all biologics, independent of their complexity. Furthermore, it was recognized that the concerns about pharmacovigilance, particularly for chronic therapies, could not be addressed by routine collection of data. Any systematic and uncontrolled substitution by pharmacists would significantly impair the ability of pharmacovigilance systems to accurately identify the root cause of any future safety or efficacy issues with that class of biologic.

The current system of generic substitution is predicated on the active ingredient in the substituted product being identical to the reference product. In other words, it is the identicality of the generic drug and the brand drug that allows for substitution. Even then, there are certain generic drugs for which the FDA has recommended against a determination of therapeutic equivalence, a determination on which the current system of generic drug substitution is based. In contrast, a biosimilar can only be similar (not identical) to the innovator, so the competition dynamic will be more akin to therapeutic alternative competition, or competition between two branded products.

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 referenced drug product manufacturers and follow-on biologic applicants be filed with the FTC and the Department of Justice Antitrust Division?**

A rigorous examination of any "competitive concerns" must take into consideration the benefit consumers reap from a stable marketplace and innovation incentives. The ability of companies to enter into research and development, licensing, and other agreements is critical to the advancement of any research-intensive, innovation-driven industry. This is particularly true in the biotechnology industry, which is characterized by a diverse array of small companies that often lack the manufacturing, distribution, or other capabilities required to commercialize products independently. A greater concern than any potential anticompetitive impacts would be the chilling effect on innovation if the ability of companies to enter into such agreements was curtailed.

Biotechnology holds the most promising possibility of treatment and cure for patients with the most deadly, devastating, and recalcitrant diseases. Any requirement that agreements between referenced biologic manufacturers and biosimilar applicants be filed with regulators should be narrowly tailored to address competitive concerns, if any, involving the specific products that are the subject of a biosimilar application. As explained in the response to question #1, economic factors suggest that the biotechnology industry is unlikely to develop in the same way as the pharmaceutical industry, which is made up of relatively discrete groups of research-based and generic companies. Some biotechnology companies may rely on joint ventures and cooperative research, development, source material, and manufacturing relationships with other companies and institutions that develop potentially competitive products. A requirement that such agreements be filed with regulators may prove unduly burdensome, put sensitive information at risk, and may discourage the collaboration critical to biotechnology innovation. If a requirement to file such agreements with FTC and Department of Justice (DOJ) is instituted, it would be essential that any information filed with those agencies be treated as confidential and competitors should not have the opportunity to access this proprietary business information.

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?

The balance between competition and innovation is a delicate one. The impact of prospective competition from biosimilar drugs on research and development clearly will depend upon the provisions of the biosimilar legislation. However, the ability of the biotechnology industry to research and develop new cures, and to deliver them to patients, will be greatly diminished if Congress fails to put in any biosimilar legislation adequate incentives to innovate.

Strong protection of intellectual property – both patents and data – is the cornerstone of any research-intensive, innovation-driven industry. Failure to provide adequate intellectual property protection will undermine investment in biotech innovation. Venture capital that is the lifeblood of startup companies will divert resources to investments with more certain returns, regardless of their social value. Investment decisions by more mature biotech companies that are self-funding are necessarily driven by the possibility of recovering the cost of bringing a product to market because this funds the next discovery. Without adequate intellectual property protection, research and development will be greatly diminished. This is a very expensive proposition for patients waiting for cures. We know that incentives to invest can be successful. Both pediatric studies and orphan drug development have been significantly stimulated by intellectual property protections put in place by Congress. Moreover, partnerships with American universities on high-risk, early-stage research would be severely hindered if the necessary innovation incentives are not preserved.

The biotech industry is very resource-intensive and companies must choose how to invest limited R&D resources. It takes, on average, 12 years and $1.2 billion to bring a biotech medicine to patients.[16] Success is the exception rather than the rule: 40% to 50% of candidates fail in Phase III studies.[17] The vast majority of biotechnology companies are not profitable today and are highly dependent on the flow of venture and investment capital to complete the research and development needed to bring their first product to the marketplace over a decade later.

Companies must make investment decisions on a regular basis, but so do venture capitalists, who fund a great part of the research and development done by most biotech companies. Venture capitalists weigh the opportunity available to recover their investment with the already unlikely odds that a biotech company will be able to get a biologic product through the rigorous FDA approval process. Intellectual property is the primary way innovators are assured an opportunity to try to recover the resources that they invested in research and development. If intellectual property protection is inadequate to ensure an opportunity to recover the investment, venture capitalists will go elsewhere.

Without capital investment, universities will be unable to license their basic research discoveries to cash-strapped biotech companies, which, in turn, will not be able to invest in the long research and development process needed to convert that basic research into meaningful and useable treatments for patients.

One way to encourage innovation is to allow those who invest in research to benefit from that research. Data exclusivity, a form of intellectual property protection, allows an innovator a period of time after FDA approval during which no one else may rely on the valuable data developed by the innovator to gain FDA approval. Generating the data for approval through the development process can cost more than a billion dollars. Without a data exclusivity period, other companies would be allowed to piggyback on the

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[16] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), *available at* http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008).

[17] *See* "Deconstructing De-risking," *BioCentury* (June 7, 2004) (discussing risks associated with biotechnology research and development).

innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved. The purpose of data exclusivity is to encourage companies to embark on the lengthy, complicated, and risky clinical development program required for FDA approval.

According to economist Henry Grabowski of Duke University:

> Proposed [biosimilar] legislation without any provisions for a data exclusivity period or only very nominal periods of exclusivity would have adverse effects for these biological innovation activities. Under these legislative scenarios, there would likely be an explosion in patent challenges shortly after a new product is introduced. The resulting uncertainty and litigation costs would increase risks and diminish R&D investment funding sources for this sector, especially for early-stage R&D in companies without any profitable products (the majority of biotech firms). As a consequence, the future introduction of important new medicines could be delayed significantly or deterred altogether. This would not be a desirable outcome for policymakers who must balance the terms of competition between innovators and imitators. It is important to avoid these unintended consequences for an industry with strong entrepreneurial roots and important expected benefits for human health and welfare.[18]

The need to encourage research and development of new therapies, however, does not suddenly cease with the initial approval of a biologic. Indeed, data exclusivity is also critical to providing the necessary incentive to research, develop, test and obtain FDA approval for new indications and other important developments emerging from existing biologics. For example, data exclusivity for new indications is critical in areas such as cancer research, where the initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies typically occur much later in time. In fact, on average, a biologic that has been on the market for six years is expected to have another two additional indications approved after those first six years.[19] Data exclusivity provides companies with the incentive to incur the significant additional time and expense required for this later research and development. In order for this innovation to thrive, and for researchers to discover future generations of existing products, robust data exclusivity must be provided. Without this incentive to continue to discover, patients may ultimately be left only with attempted copies of older medicines, rather than more advanced, targeted ones. A well-considered biosimilar regime should ensure more therapeutic options for patients, not fewer.

Second-generation products represent important advancements for patients and must go through the same rigorous FDA approval process as the first generation product, including development and submission of full safety and efficacy data to support approval of the application. This is why data exclusivity for second-generation products is very important in the context of a biosimilar approval pathway; it is necessary to ensure that these types of advancements occur and patients have the opportunity to benefit from them.

For these reasons, we strongly suggest that a comprehensive biosimilar system should incentivize not only the discovery and development of new substances, but also improvements to existing therapies. Failure by Congress to support evolutionary developments in products will deny patients the valuable advances that may be the foundation for the next life-saving cure.

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[18] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), at p. 30, *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007).

[19] The Boston Consulting Group, "Continued Development of Approved Biological Drugs" (Dec. 2007).

It should also be noted that data exclusivity for innovators in any biosimilar regime would not, as some may have suggested, operate as an extension of patent protection. Rather, the period of data exclusivity would run concurrently with the patent term for the product.

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 referenced 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?**

Amgen believes that many of the questions regarding Medicare reimbursement for biologic products would be best answered by the Centers for Medicare and Medicaid Services (CMS), which is responsible for establishing those reimbursement rates consistent with the pertinent Medicare statutes. It is important to note that there are a number of different reimbursement methodologies depending on the type of product. For example, infused products furnished through an item of durable medical equipment are paid under a different methodology than inhaled products furnished through an item of durable medical equipment.

The methodology applicable to payment for most biologic products covered under Medicare Part B is the average sales price (ASP) methodology. ASP is designed to reflect the average cost of purchasing a specific drug across purchasers. While Amgen is supportive of the market-based pricing that occurs under the ASP methodology, we believe that CMS is better suited to respond to the detailed questions about the mechanics of the ASP methodology.

6. **How are 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)?**

In general, there are many similarities and differences between the typical patent portfolio covering a biotech product and a chemical drug but the implications of these similarities and differences depend upon the context in which they are considered. In many cases, both patent portfolios would include patents on the products themselves, although for some biotech products that are the recombinant version of a known naturally occurring product only limited patent protection, or none, may be available on the product itself. In contrast, small molecule drugs are typically patented in both generic (broadly claimed) and species (narrowly claimed) chemical structure-based patents. Biotech product patent portfolios are more likely to include patents on the process for making the product and other types of non-product patent protection that may or may not impact biosimilars.

For most biotech patent applications, the examination process by the Patent and Trademark Office (PTO) lasts much longer and the hurdles for obtaining biotech patents are much higher as compared to small molecule patents. One contributing factor is the relatively common occurrence of more than one company filing patent applications that overlap in subject matter and the PTO has to sort out who was the first to invent and thus entitled to a patent on what subject matter. Our own experience has been that our biologic products are typically in late stage clinical trials, or even on the market (some for several years), before the PTO issues the patent(s) that protect the product. Also, from our perspective, biotech patents

are scrutinized much more closely by both the PTO and the courts and held to a higher standard for all aspects of patentability than small molecule patents. The combination of these factors leads to greater uncertainty for some biotech companies about their ability to rely on patents to protect both their investment in innovation and their risk taking in product development.

In our view, in addition to the factors discussed above, there are several other factors related to biotech patent portfolios that should be considered in formulating legislation on biosimilars, and particularly, the aspects of patent litigation and data exclusivity. First, the number of patents that cover a biotech or small molecule drug portfolio is far fewer than for other technologies -- about five (compared to the hundreds that may be involved in a computer, for instance). For this reason, a litigation structure should permit the resolution of all relevant patent disputes in a single litigation. Phasing the litigation based on different types of patents is inefficient and only delays resolution of the patent dispute. All stakeholders have spoken to the importance of certainty when making the massive investments required for developing biotech medicines. A dual track litigation scheme, as proposed in H.R. 1038 and S. 1695, would undermine rather than foster certainty.

Second, due to the potential of different types of biotech patents, a patent listing process such as the Orange Book regime used for small molecules would not capture all the relevant patents; instead, we view an information exchange modeled on the process patents provisions of the patent statute to be an adequate vehicle to inform the potential biosimilar competitor of the relevant patents on a biotech product. Biotech patent portfolios often contain certain kinds of patent claims – such as process claims and claims that confer indirect protection – that are less frequently seen in small molecule product patent portfolios. It is impractical to require listing because the innovator will have many platform process patents and will not know which apply to the biosimilar until the biosimilar discloses its process to innovator and is far enough into its development and clinical trials to be confident that the process will not change. Listing these patent types would be impractical and not be the most effective way to achieve the objective of alerting the biosimilar manufacturer to the risk of infringement.

Third, the length of time it will take to resolve a patent litigation case involving either a biotech or chemical drug will vary widely and is generally not dependent upon differences between small and large molecule patent portfolios. Most cases will be resolved within three years. If there is to be a litigation trigger in the biosimilars legislation, it should be within about three years of the end of data exclusivity. Consistent with this, H.R. 5629 appropriately makes it possible for the biosimilar to initiate a declaratory judgment action three years before the end of the data exclusivity period. Allowing for a declaratory judgment significantly prior to that, as proposed in S. 1695, is counterproductive. It creates an opportunity to harass legitimate business owners throughout the life of the patent and often years before a product could come to market as a biosimilar relying on the safety and efficacy data of another product.

Finally, the regulatory standard proposed for biosimilars, i.e., similarity rather than sameness, will have significant implications for the extent to which patents provide effective incentives for innovation. Hatch-Waxman (the generic drug law) requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents that claim the chemical structure of the drug. However, the assumption of patent infringement that is inherent in the generic drug model does not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness."

Put simply, because biotech products are exponentially more complicated in size and structure than small molecule products, to date, it has proven to be technically impossible to make an identical copy of a biologic medicine. Thus, we are addressing "biosimilars" rather than generic copies of biotech products. Biosimilar manufacturers can be expected to leverage this difference in standards and claim that they

have "designed around" the innovator's patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections for innovators of biotechnology products. The standard for approval of biosimilar products has not been established so it is unknown whether the breadth of patent claims will line up with the scope of the regulatory standard. For this reason, the regulatory standard could increase the uncertainty surrounding biotech patents. This uncertainty can be resolved by establishing that statutory infringement occurs when a product is referenced for purposes of securing FDA marketing approval.

Any pathway for abbreviated approval of biosimilars must consider both patents and data exclusivity. As discussed elsewhere in Amgen's responses to the FTC, patents protect the invention, i.e., the product or the process, but do not protect the intellectual property that is embodied in the preclinical and clinical data submitted to the FDA for product approval. This data is very expensive to create and has significant value separate and apart from the product itself and the patent rights. Data exclusivity protects the information gathered by the innovator to demonstrate the safety and effectiveness of the product and is intended to encourage companies to embark on the lengthy, complicated, and risky development program required for FDA approval. Without an adequate period of data exclusivity, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved. The data exclusivity period runs concurrent with the patent term, beginning at the point the product is approved for marketing. Together, patents and data exclusivity provide a limited period of protection for the innovator to attempt to recover the cost of product discovery and development. Without this opportunity, investment in biotechnology would be significantly diminished.

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?**

Data exclusivity for innovative products – including for significant new indications, as well as for continued research and development advances that necessitate the filing of a new BLA – is an essential component of any abbreviated approval pathway for biosimilar products, however, the exclusivity period provided in the Hatch-Waxman generic drug model is insufficient to encourage ongoing biotech innovation.

The Hatch-Waxman generic drug law uses two different "exclusivity" mechanisms: data exclusivity for innovator products and market exclusivity for generic products. The first, as its name implies, has a limited reach because it only protects the data from use by others. Market exclusivity, on the other hand, provides a broad protection from competition in the market. Under Hatch-Waxman, 180 days of market exclusivity is provided to the first[20] generic to challenge an innovator patent by prohibiting the FDA from approving another generic drug for a limited period of time. The implications of market exclusivity for biosimilars and generics are discussed in the answer to question 10.

Data exclusivity ensures innovators have exclusive use of the data they developed for purposes of securing FDA marketing approval of their product. This exclusivity is implemented by prohibiting FDA from accepting a generic drug application that references that data for four or five years from the date the innovator product was approved for marketing.

[20] More than one generic can be considered "first" and, thus, share the 180 days of market exclusivity.

The purpose of data exclusivity is to encourage companies to embark on the lengthy, complicated, and risky clinical development program required for FDA approval. The average cost of developing a biologic product through FDA approval has been estimated to be about $1.2 billion.[21] If a biosimilar pathway is established, a generic will be able to rely upon that valuable data developed by the innovator to gain FDA approval. To compensate the innovator and encourage development of innovative products, data exclusivity for the innovative biologic is necessary. Without such a period in a biosimilar pathway, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved.

Data exclusivity is particularly important in the context of biosimilars because of the scientific differences between biologics and traditional small molecules. The Hatch-Waxman model requires a generic drug (an "Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents. The assumption of patent infringement that is inherent in the generic drug model may not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness." Put simply, because of the complexity of biotechnology products and the differences that can arise in a product made by different manufacturers, it will be nearly impossible for a biosimilar manufacturer to make an identical copy of an innovator's biologic medicine. Indeed, the label of "biosimilar" assumes that it is not identical to the innovator's product. With these differences, biosimilar manufacturers can be expected to claim they have "designed around" the innovator's patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections – namely longer data exclusivity – for innovators of biotechnology products.

The Hatch-Waxman period of five years of data exclusivity for small molecule products is not adequate to support robust investment in biotech innovation. A 14 year period of data exclusivity is justified for the following reasons:

- The break-even point for a biologic is 12.9 to 16.2 years on the market.[22] Currently, the cost to develop a new biological therapy is estimated at $1.2 billion, an increase of three times what it cost to develop a drug back in 1984.[23] Only 10% of potential drug candidates reach the human trial phase.[24] Only a small portion of that 10% actually reach the market[25] and only two out of ten marketed drugs ever produce revenues that match or exceed R&D costs.[26] The "break-even" point for biologics has been found to occur after it has been on the market somewhere between 12.9 and 16.2 years. Therefore a 14 year period of data exclusivity is appropriate to recognize

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[21] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), *available at* http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008).

[22] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007).

[23] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), *available at* http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008). Hatch-Waxman preserved 5 years of data exclusivity for innovative small molecule drugs to recoup the $397 million (adjusted to 2005 dollars) it cost then to develop a new drug.

[24] Conaway, Carrie, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, *Regional Review*, Vol. 13, No. 1 (Q1 2003), at p. 12.

[25] C. Conaway, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, Regional Review, Vol. 13, No. 1 (Q1 2003).

[26] Vernon, J. *et al.*, "Drug Development Costs when Financial Risk is Measured Using the Fama-French Three Factor Model," Unpublished Working Paper, January 2008.

this increased cost and to provide the proper incentives to invest in products which may fail at any stage in the research and development process.

- New uses for existing therapies. The most important use of a new medicine may not be apparent for years. Many biotechnology companies continue to research additional uses for their medicines. Indeed, many companies get original approval of their products for one indication and then discover new uses and indications for their therapies, sometimes in different diseases years later. An example of this is a biologic called Herceptin®, developed by Genentech, which gained approval in the adjuvant cancer setting eight years after its original approval in the metastatic setting.[27] Without a substantial period of data exclusivity, the incentive to find new and novel uses for therapies will be significantly diminished.

- The biotechnology industry is young and susceptible to disruption. The biotechnology industry is very new compared to the pharmaceutical industry at the time a generic drug pathway was established. The biotechnology industry is less than 30 years old and few biotech companies have products on the market. Out of the more than 1400 biotechnology companies, only 20 of them are currently profitable. Small companies account for two-thirds of the industry's clinical pipeline and these companies rely on venture capital funding to finance their research and development. Without data exclusivity, the hope for a return on investment would be greatly diminished and therefore so would venture capital funding. The biotech industry is vulnerable to market instabilities and maintaining an incentive structure that promotes investment in uncertain research and development is essential to the future of this U.S. industry and finding cures for patients.

- The potential cost in terms of human suffering as a result of inadequate incentives for biotech is huge. Many devastating diseases lack effective treatments or cures. The impact on human lives and the national economy are enormous. If just one medicine is approved that can delay the onset or slow the progression of Alzheimer's disease by five years, Medicare and Medicaid could save $100B in annual costs by 2020.[28] In 2006, biopharmaceutical companies had 42 drug candidates for Alzheimer's in their pipelines.[29] Cancer is another example. The National Institutes of Health estimated that, in 2006, $78.2B was spent on total direct medical costs for cancer.[30] In 2004, the national cost burden for patients with metastatic bone disease (MBD) was estimated at $12.6B.[31] This means that, even if a cure is found for no other cancer except MBD, 17% of the total direct medical cost for cancer could be eliminated. There are currently fourteen industry-sponsored studies actively recruiting patients with metastatic bone disease.[32] Four of

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[27] "The approval for Herceptin in the adjuvant setting occurred eight years after the original approval in the metastatic setting and involved more than 3,500 women in multiple randomized clinical trials. These trials can take easily more than five years from inception to completion, at huge cost, without any assurance of clinical success. Herceptin in the adjuvant setting reduced the risk of cancer recurrence by 50 percent, and if the cancer doesn't recur, these women cannot die from it." Testimony of Dr. David Schenkein, Vice President, Clinical Hematology/Oncology, Genentech, before the House Committee on Energy and Commerce, May 2, 2007.

[28] The Lewin Group, "Saving Lives, Saving Money: Dividends for Americans Investing in Alzheimer's Research" (2004).

[29] Pharmaceutical Research and Manufacturers of America, 2006 Survey, "Medicines in Development for Neurological Disorders: Pharmaceutical Companies Developing 241 Medicines for Neurological Disorders."

[30] American Cancer Society, "Cancer Facts and Figures 2007," *available at* http://www.cancer.org/downloads/STT/CAFF2007f4PWSecured.pdf (last visited May 2, 2008).

[31] Schulman, K.L. & Joseph Kohles, "Economic Burden of Metastatic Bone Disease in the U.S.," *Cancer* vol. 109, no. 11 (June 1, 2007).

[32] *See* Clinical Trials.gov, *available at* http://clinicaltrials.gov/ct2/results?flds=Xe&flds=a&flds=b&flds=c&recr=Open&cond=metastatic+bone+disease&fund=2&show_flds=Y (last visited April 30, 2008).

these trials are already in phase III, which is the final stage before approval. The Human Genome Project was just completed in 2003 and we are on the leading edge of the biotech revolution that will produce treatments for scores of illnesses. It would be a mistake at this exciting time in biotechnology research to do anything to inhibit innovation in this young and promising industry.

- Congress has already recognized the need for up to 14 years to recover R&D costs. In 1984, Congress determined that providing patent term restoration up to 14 years of effective patent life was appropriate to give innovator companies the proper incentives to spend the hundreds of millions of dollars on R&D that it takes to bring a new therapy to market.[33] The cost of bringing a biotech medicine to market is three times more expensive than in 1984 when adjusted for inflation. Medical discovery has become more difficult, more complex and more expensive since the Hatch-Waxman scheme was adopted. Many patients are still waiting for cures. Reducing the incentive to innovate now is akin to paying for short term savings at the expense of future cures.

- Europe recognizes the need for data exclusivity: European law appropriately recognizes the importance of data exclusivity, providing ten years of exclusivity to innovative biologics, and an additional year of exclusivity for the product if the manufacturer develops a new medically significant indication. Biotech is a uniquely American industry and we lead the world in biotech employment and R&D investment. It remains to be seen if the data exclusivity provided by Europe is adequate to foster biotech innovation but it is instructive that the data exclusivity offered by this competitor is more than double that provided under the Hatch-Waxman generic drug scheme.

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?

The regulatory exclusivity provided to biotech medicines should be determined by the best interests of patients. Factors to consider include (1) patient need for biotech medicine, (2) the economic breakeven time for biotech products that come to market, and (3) the state of the regulated industry. These apply without regard to the type of biotech product, the competition facing the product, or the patent portfolios covering the product.

When discussing regulatory exclusivity, it is important to distinguish between the two kinds of exclusivity employed by the Hatch-Waxman generic drug model: data exclusivity for innovative products and market exclusivity for generic drugs. Data exclusivity provides those who invested in the development of data the exclusive right – for a limited time – to use that data for the purpose of securing FDA approval to market the medicine. Data exclusivity does not prevent other products from being approved – so long as the other manufacturer conducts its own studies rather than relies on the studies of the reference product. Without a period of data exclusivity, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved and thus discourage investment in the expensive clinical data necessary for approval of innovative biotech medicines.

[33] The House Report accompanying the Hatch-Waxman amendments noted that "by providing up to fourteen years of market exclusivity, the Committee expects that research intensive companies will have the necessary incentive to increase their research and development activities." H.R. Rep. No. 98-857, at 41 (1984).

Market exclusivity is very different. Under Hatch-Waxman, it prevents FDA from approving another generic drug for a limited period of time and is not related to data. The implications of market exclusivity for biosimilars and generics are discussed in question 10.

Factors to consider: #1 Patient Need for the Biotech Medicine

Many devastating diseases lack effective treatments or cures. The impact of incurable and untreatable disease on human lives and the national economy are enormous. Biotechnology is widely recognized as the likely source of treatments and cures for many of these conditions. The needs of patients waiting for cures must not be second to the interests of those for whom cures and treatments are already on the market. Biosimilar medicines do not address unmet medical needs. Without incentives to invest in innovation, the R&D pipeline of breakthrough therapies will be diminished and patient outcomes will be affected. Data exclusivity encourages biotech innovation by making it possible for those who invest in research and development to, for a limited period of time, exclusively use the data they spent hundreds of millions of dollars and more than a decade developing.

Factors to consider: #2 Breakeven Times for Biotech Medicines

The ability of a company to fund research and development is constrained by the funding available – either from venture capitalists or from revenue generated from the sale of other medicines. A recent study conducted at Duke University examined the "breakeven" times of new biologic drugs. The breakeven time is defined as the time necessary for a biologic to earn a positive and risk-adjusted return on the upfront investment made in its research and development. The study in question analyzed a model portfolio of biotech products with sales that are representative of the actual historical distribution.

The study found that breakeven lifetimes were between 12.9 and 16.2 years.[34] Any data exclusivity period proposed for innovative biologics should reflect this range of breakeven times. Based on these findings, the study's author asserted that providing only nominal data exclusivity periods would have "adverse effects" on biological innovation.

According to the study, providing little or no data exclusivity would encourage premature patent challenges by biosimilar applicants shortly after introduction of the innovative product.[35] This would add more uncertainty to the already uncertain venture of innovative drug development. Only 10% of potential drug candidates reach the human trial phase.[36] Only a small portion of that 10% actually reach the market[37] and only two out of ten marketed drugs ever produce revenues that match or exceed R&D costs.[38] If those revenues are diverted because the law fails to protect the underlying intellectual property (patents and data) by allowing others to free ride on the innovators' investments, biotech R&D will suffer irreparable harm.

Partnerships with American universities on critical early-stage research would be severely hindered without adequate innovation incentives. In addition, venture capitalists that provide the lifeblood of startup companies will divert resources to investments with more certain returns, regardless of their social value. Investment decisions by more mature biotech companies that are self-funding are necessarily driven by the possibility of recovering the cost of bringing a product to market, because this

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[34] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007).

[35] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007) at p. 30.

[36] Conaway, Carrie, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, *Regional Review*, Vol. 13, No. 1 (Q1 2003), at p. 12.

[37] C. Conaway, "The Pros and Cons of Pharmaceutical Patents," Federal Reserve Bank of Boston, Regional Review, Vol. 13, No. 1 (Q1 2003).

[38] Vernon, J. *et al.*, "Drug Development Costs when Financial Risk is Measured Using the Fama-French Three Factor Model," Unpublished Working Paper, January 2008.

funds the next discovery. Without adequate intellectual property protection, research and development will be greatly diminished. This is a very expensive proposition for patients waiting for cures. We have proof that incentives to invest can be successful. Both pediatric studies and orphan drug development have been significantly stimulated by intellectual property protections put in place by Congress.

According to economist Henry Grabowski of Duke University:

> Proposed [biosimilar] legislation without any provisions for a data exclusivity period or only very nominal periods of exclusivity would have adverse effects for these biological innovation activities. Under these legislative scenarios, there would likely be an explosion in patent challenges shortly after a new product is introduced. The resulting uncertainty and litigation costs would increase risks and diminish R&D investment funding sources for this sector, especially for early-stage R&D in companies without any profitable products (the majority of biotech firms). As a consequence, the future introduction of important new medicines could be delayed significantly or deterred altogether. This would not be a desirable outcome for policymakers who must balance the terms of competition between innovators and imitators. It is important to avoid these unintended consequences for an industry with strong entrepreneurial roots and important expected benefits for human health and welfare.[39]

It is important to note that the need to encourage research and development of new therapies does not suddenly cease with the initial approval of a biologic. Indeed, data exclusivity is also critical to providing the necessary incentive to research, develop, test and obtain FDA approval for new indications and other important developments emerging from existing biologics. For example, data exclusivity for new indications is critical in areas such as cancer research, where the initial marketing approval generally focuses on late-stage disease, and research and development activities for early-stage or adjuvant therapies typically occur much later in time. Data exclusivity provides companies with the incentive to incur the significant additional time and expense required for this later research and development. In order for this innovation to thrive, and for researchers to discover future generations of existing products, robust data exclusivity must be provided. Without this incentive to continue to discover, patients may ultimately be left only with attempted copies of older medicines, rather than more advanced, targeted ones. A well-considered biosimilar regime should ensure more therapeutic options for patients, not fewer.

Data exclusivity for second-generation products is very important in the context of a biosimilar approval pathway. These products represent important advancements for patients and must go through the same rigorous FDA approval process as the first generation product, including development and submission of full safety and efficacy data to support approval of the application. Accordingly, data exclusivity for second generation products is necessary to ensure that these types of advancements are developed and allow patients to benefit from them.

Thus, a comprehensive biosimilar system should incentivize not only the discovery and development of new substances, but also meaningful improvements to existing therapies.

Factors to consider: #3 The State of the Industry

The field of biotechnology is immature compared to the traditional small-molecule drug market at the time of the Hatch-Waxman legislation and thus is more vulnerable to disruption. In 1984, when the Hatch-Waxman amendments were passed, there were tens of thousands of marketed drug products, many

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[39] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), at p. 30, *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007).

of which had been safely used for dozens of years. FDA, the medical community, and the public had decades of experience with these products. By contrast, today there are only about 155 approved biotechnology products, most of which were approved very recently.[40] Additionally, only 20 or 30 of the 1400 U.S. biotech companies have turned a profit. Moreover, the cost to develop a new biological therapy today is estimated at $1.2 billion, an increase of three times what it cost to develop a drug back in 1984.[41] The biotech industry is vulnerable to market instabilities and maintaining an incentive structure that promotes investment in uncertain research and development is essential to the future of this U.S. industry, and finding treatments for patients.

The majority of biotechnology companies are not profitable. In fact, as of 2006, the publicly traded U.S. biotechnology industry as a whole had not once been profitable in its 31-year history.[42] Early-stage biotechnology companies without any products on the market are wholly dependent on investors' willingness to take a risk on an uncertain promise of return. It would be imprudent to insert into legislation any provisions that would reduce this willingness.

It should also be noted that data exclusivity for innovators in any biosimilar regimen would not, as some may have suggested, operate as an extension of patent protection. Rather, the period of data exclusivity would generally run concurrently with the patent term for the product.

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?

European law appropriately recognizes the importance of data exclusivity, providing ten years of exclusivity to innovative biologics, and an additional year of exclusivity for the product if the manufacturer develops a new medically significant indication. While the European system's approach may provide one early example of regulatory exclusivities, several factors suggest that a more robust approach should be taken in the U.S.

Specifically, we agree with the Duke University economist, Henry Grabowski, that,

> "U.S. policy should be guided by the recognition around the world that data exclusivity is an important form of intellectual property protection. It remains to be seen whether the 11 years of data protection provided by Europe will be adequate to foster continued investment in research and development in biotechnology. Economic studies in the United States suggest that 11 years falls short of the time needed for many products to recover the cost of development."[43]

The United States should adopt a data exclusivity period for innovative biotech products of at least fourteen years. The period of data exclusivity under a U.S. biosimilar scheme should be guided by an analysis of the amount of time it takes for a successful product to "break-even" on research and

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[40] Biotechnology Industry Organization, "Biotechnology Industry Statistics," *available at* http://www.bio.org (last visited April 18, 2008).

[41] Tufts Center for the Study of Drug Development, "Average Cost to Develop a New Biotechnology Product is $1.2 Billion" (Nov. 9, 2006), *available at* http://csdd.tufts.edu/NewsEvents/NewsArticle.asp?newsid=69 (last visited April 14, 2008). Hatch-Waxman preserved 5 years of data exclusivity for innovative small molecule drugs to recoup the $397 million (adjusted to 2005 dollars) it cost then to develop a new drug.

[42] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007" (2007), at p. 17.

[43] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007).

development resources invested in order to ensure there is adequate incentive for future innovation. Grabowski found that number to be between 12.9 and 16.2 years.[44] Consequently, a data exclusivity period of 14 years would be appropriate for a biosimilar regime in the United States.

Undermining biotech innovation will have a direct impact on the development of new biotech medicines, as well as on United States competitiveness. The U.S. leads the world in biotechnology research and development. In 2006, the U.S. biotech industry invested in R&D nearly four times what the next largest market spent.[45] That translates into U.S. jobs. Economic research makes clear that data exclusivity is important to foster future biotech innovation. If biotech innovation is stunted because intellectual property is not adequately protected, our economy will be negatively affected. At a time when countries around the world are courting clean industries that bring with them high-skilled and well-paying jobs, it would be very short sighted of the U.S. to do the opposite. Failure to provide adequate innovation incentives could diminish what is now a vibrant U.S.-based industry.

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?

It appears from the number of biosimilar products under development in Europe, where no market exclusivity is provided for biosimilar products, that market exclusivity for biosimilars in the United States may not be necessary. The generics industry is in a very different place today than it was at the time the Hatch-Waxman pathway for approval of generic drugs was adopted. In 1984, the industry was not yet established and success of the generic business model was uncertain. Today, generics constitute more than 53% of all prescriptions written[46] and the industry is highly profitable[47]. These same companies have demonstrated their intent to pursue the manufacture of biosimilar products in the United States and some are already doing so in Europe – without market exclusivity. For this reason, marketing exclusivity should play a very different role in a biosimilars approval regime than they played in the early years of generic drugs under the Hatch-Waxman regime.

If Congress does choose to provide exclusivity for biosimilars, it should be based on product approval rather than patent challenge. The Hatch-Waxman Act 180 days of exclusivity to the first generic[48] product to successfully challenge the relevant innovator patent(s) created a perverse incentive to challenge the innovator's patents early and often, regardless of the merit of the challenge. This has forced innovators to divert much-needed R&D funds to litigation. A similar framework for biosimilars would add unnecessary expense to the health care system.

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[44] Grabowski, Henry, "Data Exclusivity for New Biological Entities," Duke University Department of Economics Working Paper (June 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf (last visited April 17, 2007). (emphasis added).

[45] Ernst & Young, "Beyond Borders: The Global Biotechnology Report 2007," *available at:* http://www.ey.com/Global/assets.nsf/International/Industry_Biotechnology_Beyond_Borders_2007_Full/$file/BeyondBorders2007.pdf (last visited May 2, 2008), at p. 7.

[46] "Generic Drugs Hit Backlog at FDA", Marc Kaufman, *The Washington Post* (February 4, 2006).

[47] "As Patents on Popular Drugs End, Costs for Generics Show a Surge", Milt Freudenheim, *The New York Times* (December 27, 2002).

[48] More than one generic can be considered "first" and, thus, share the 180 days of market exclusivity.

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?**

A biosimilar approval pathway should include a mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market. This is in the best interest of patients as well as both the innovator and biosimilar industries. No two biosimilar products are identical and the differences between two similar products could have therapeutic implications for patients. Therefore, switching from one product to another during treatment may be inadvisable. (The medical explanation for this appears to be beyond the scope of FTC's inquiry; however, we would be happy to provide more detail on this point.) This risk can be minimized by resolving patent disputes prior to biosimilar market entry. It will also increase the confidence in physicians making prescribing decisions that the product will remain available should they choose to direct the patient to a biosimilar product. Early resolution also offers a level of certainty for investors in both innovative and biosimilar products and thus fosters the development of both industries.

The litigation provisions must be designed in a way that encourages timely resolution of patent disputes but avoids costly and unnecessary litigation. The framework should effectively balance the interests of the patent holder and the patent challenger and, if a patent is found to be valid and infringed, the infringing product should be kept off the market until the relevant patents expire.

The dispute resolution framework should avoid encouraging premature patent challenges. A biosimilar will need to be sufficiently far along in its development for both parties to be able to determine whether patent litigation is warranted. The Hatch-Waxman Act had the unintended consequence of encouraging early patent challenges, whether or not the challenge had any merit. This is because the current generic framework grants 180 days of exclusivity to the first generic product that challenges the innovator's patent(s), and allows those challenges only four years after approval of the innovator's product. Four years after approval is much too early in a biologic product life cycle to disrupt and divert the innovator's attention from fully developing its product for the approved and new uses for the product to a posture of defending itself in patent litigation with the prospect of competition if it loses the litigation. Hatch-Waxman actually creates a disincentive to innovators to make further investments in developing its product once the generic companies challenge the patent rights.

Instead of duplicating this system, a biosimilar regime should include a simplified mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market. Such a mechanism should ensure notification of the innovator of possible infringement, notification of the biosimilar manufacturer of patents that may be infringed, and an opportunity to bring an infringement suit early enough before the end of the data exclusivity period in order to ensure resolution before the biosimilar goes to market. This certainty benefits all parties by limiting unnecessary litigation and reducing the infringement risk faced by the biosimilar manufacturer.

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

According to Avalere Health, approval time for innovative biologics vary by "therapy area, geography, and time period, but [] typical review times are around one year."[49] It is reasonable to anticipate that review of biosimilar applications will initially take longer than one year because of lack of agency experience with the application process and the development of the protocol for determining similarity. The review and approval process will presumably get more efficient as the agency accumulates experience. It is also likely that publication of product class guidances will enable manufacturers to submit higher quality applications upon initial submission and thus limit review time.

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?**

In general, there are many similarities and differences between the typical patent portfolio covering a biotech product and a chemical drug but the implications of these similarities and differences depend upon the context in which they are considered. In many cases, both patent portfolios would include patents on the products themselves, although for some biotech products that are the recombinant version of a known naturally occurring product only limited patent protection, or none, may be available on the product itself. In contrast, small molecule drugs are typically patented in both generic (broadly claimed) and species (narrowly claimed) chemical structure-based patents. Biotech product patent portfolios are more likely to include patents on the process for making the product and other types of non-product patent protection that may or may not impact biosimilars.

For most biotech patent applications, the examination process by the PTO lasts much longer and the hurdles for obtaining biotech patents are much higher as compared to small molecule patents. One contributing factor is the relatively common occurrence of more than one company filing patent applications that overlap in subject matter and the PTO has to sort out who was the first to invent and thus entitled to a patent on what subject matter. Our own experience has been that our biologic products are typically in late stage clinical trials, or even on the market (some for several years), before the PTO issues the patent(s) that protect the product. Also, from our perspective, biotech patents are scrutinized much more closely by both the PTO and the courts and held to a higher standard for all aspects of patentability than small molecule patents. The combination of these factors leads to greater uncertainty for some biotech companies about their ability to rely on patents to protect both their investment in innovation and their risk taking in product development.

In our view, in addition to the factors discussed above, there are several other factors related to biotech patent portfolios that should be considered in formulating legislation on biosimilars, and particularly, the aspects of patent litigation and data exclusivity. First, the number of patents that cover a biotech or small molecule drug portfolio is far fewer than for other technologies -- about five (compared to the hundreds that may be involved in a computer, for instance). For this reason, a litigation structure should permit the resolution of all relevant patent disputes in a single litigation. Phasing the litigation based on different types of patents is inefficient and only delays resolution of the patent dispute. All stakeholders have spoken to the importance of certainty when making the massive investments required for developing biotech medicines. A dual track litigation scheme, as proposed in H.R. 1038 and S. 1695, would undermine rather than foster certainty.

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[49] Avalere Health, LLC, "Modeling Federal Cost Savings from Follow-on Biologics," (April 2007), at p. 5.

Second, due to the potential of different types of biotech patents, a patent listing process such as the Orange Book regime used for small molecules would not capture all the relevant patents; instead, we view an information exchange modeled on the process patents provisions of the patent statute to be an adequate vehicle to inform the potential biosimilar competitor of the relevant patents on a biotech product. Biotech patent portfolios often contain certain kinds of patent claims – such as process claims and claims that confer indirect protection – that are less frequently seen in small molecule product patent portfolios. It is impractical to require listing because the innovator will have many platform process patents and won't know which apply to the biosimilar until the biosimilar discloses its process to innovator and is far enough into its development and clinical trials to be confident that the process will not change. Listing these patent types would be impractical and not be the most effective way to achieve the objective of alerting the biosimilar manufacturer to the risk of infringement.

Third, the length of time it will take to resolve a patent litigation case involving either a biotech or chemical drug will vary widely and is generally not dependent upon differences between small and large molecule patent portfolios. Most cases will be resolved within three years. If there is to be a litigation trigger in the biosimilars legislation, it should be within about three years of the end of data exclusivity. Consistent with this, H.R. 5629 appropriately makes it possible for the biosimilar to initiate a declaratory judgment action three years before the end of the data exclusivity period. Allowing for a declaratory judgment significantly prior to that, as proposed in S. 1695, is counterproductive. It creates an opportunity to harass legitimate business owners throughout the life of the patent and often years before a product could come to market as a biosimilar relying on the safety and efficacy data of another product.

Finally, the regulatory standard proposed for biosimilars, i.e., similarity rather than sameness, will have significant implications for the extent to which patents provide effective incentives for innovation. Hatch-Waxman (the generic drug law) requires a generic drug (an Abbreviated New Drug Application," or ANDA) applicant to provide evidence to the FDA that the proposed generic drug is "the same as" the innovator drug. In making this statement or "admission" to FDA, the ANDA sponsor would have difficulty claiming that its product does not infringe the innovator's patents that claim the chemical structure of the drug. However, the assumption of patent infringement that is inherent in the generic drug model does not automatically apply in biotechnology because the standard for biosimilar approval will be "similarity" not "sameness."

Put simply, because biotech products are exponentially more complicated in size and structure than small molecule products, to date, it has proven to be technically impossible to make an identical copy of a biologic medicine. Thus, we are addressing "biosimilars" rather than generic copies of biotech products. Biosimilar manufacturers can be expected to leverage this difference in standards and claim that they have "designed around" the innovator's patent and thus challenge any claim of infringement that would be assumed – even admitted – in the small-molecule context. Requiring biosimilars to be only "similar" to the reference product causes an increased burden on the patent owner, as compared to the Hatch-Waxman context, to show infringement and thus necessitates additional protections for innovators of biotechnology products. The standard for approval of biosimilar products has not been established so it is unknown whether the breadth of patent claims will line up with the scope of the regulatory standard. For this reason, the regulatory standard could increase the uncertainty surrounding biotech patents. This uncertainty can be resolved by establishing that statutory infringement occurs when a product is referenced for purposes of securing FDA marketing approval.

Any pathway for abbreviated approval of biosimilars must consider both patents and data exclusivity. As discussed elsewhere in Amgen's responses to the FTC, patents protect the invention, i.e., the product or the process, but do not protect the intellectual property that is embodied in the preclinical and clinical data submitted to the FDA for product approval. This data is very expensive to create and has significant value separate and apart from the product itself and the patent rights. Data exclusivity protects the information gathered by the innovator to demonstrate the safety and effectiveness of the product and is

intended to encourage companies to embark on the lengthy, complicated, and risky development program required for FDA approval. Without an adequate period of data exclusivity, other companies would be allowed to piggyback on the innovator's pre-clinical and clinical data "for free" as the basis for approval of their biosimilar product as soon as the innovative drug was approved. The data exclusivity period runs concurrent with the patent term, beginning at the point the product is approved for marketing. Together, patents and data exclusivity provide a limited period of protection for the innovator to attempt to recover the cost of product discovery and development. Without this opportunity, investment in biotechnology would be significantly diminished.

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?**

First and foremost, it is in the best interests of patients to resolve patent issues prior to marketing by a biosimilar applicant. Abrupt changes in product availability could come about in the context of patent litigation. As explained above, no two biotech medicines from different manufacturers are identical. The differences between two similar products could have therapeutic implications for patients. Therefore, switching from one product to another during treatment may be inadvisable. (The medical explanation for this appears to be beyond the scope of FTC's inquiry; however, we would be happy to provide more detail on this point.) Resolution of patent disputes before a biosimilar comes to market will help ensure that products that make it to market will continue to be available and thus avoid disruption of a course of treatment. It will also increase the confidence of prescribing health care providers in the stability of the biotech medicines industry – an important factor in facilitating adoption of new treatments.

Resolution of patent disputes before a biosimilar product comes to market will also foster the development of both innovative and biosimilar industries by providing a level of certainty for investors. Innovators rely on investors to fund the very expensive and risky research and development required to bring biotech medicines to patients. The ability to enforce patents, as well as have an adequate period of data exclusivity is essential; without it, investors cannot be confident of getting a return on their investment and will turn to other industries. Early resolution of patent disputes will also enable biosimilar manufacturers to enter the market without the risk resulting from unresolved litigation.

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?**

Since the founding of the nation, the U.S. Constitution has prohibited courts from providing advisory opinions. Article III of the U.S. Constitution requires there to be an actual dispute or at least some dispute clearly brewing between two parties before a federal court can get involved. The threshold question is when a controversy exists such that the court can make a decision on the facts.

Any biosimilar litigation process must learn from experience with the existing Hatch-Waxman litigation process. Providing clarity surrounding patent rights is beneficial for all stakeholders, but declaratory judgments cannot be available before a true "case or controversy" exists. Three years prior to the end of data exclusivity, when the timing of possible biosimilar market entry creates a real dispute about the relevant innovator's patents, is an appropriate time for the court to consider whether a case or controversy exists. Any time significantly prior to that and a biosimilar product will likely be too early in the development process for either party to determine with confidence whether infringement litigation is

warranted. Frivolous and unnecessary litigation increase the cost of medicines and thus should be discouraged.

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

Regulatory exclusivities are not necessary to encourage patent challenges. The opportunity for a biosimilar manufacturer to bring a product to market by relying on the research of the innovator, rather than conducting its own extensive safety and efficacy trials, is the only incentive necessary to encourage a biosimilar to challenge an innovator patent.

Instead of duplicating Hatch-Waxman, a biosimilar regime should include a simplified mechanism for facilitating resolution of patent disputes before a biosimilar product comes to market. Such a mechanism should ensure notification of the innovator of possible infringement and an opportunity to bring an infringement suit early enough before the end of the data exclusivity period in order to ensure resolution before the biosimilar goes to market. This certainty benefits all parties by limiting unnecessary litigation and reducing the infringement risk faced by the biosimilar manufacturer.

Experience with Hatch-Waxman has shown that an exclusivity period tied to patent challenges is counterproductive. It effectively requires the biosimilar to initiate litigation simply to secure the exclusivity, whether or not the manufacturer believes the patent challenge has merit. This patent litigation model adds unnecessary expense to the health care system.

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?**

The first few years of experience with the Hatch-Waxman's generic drug approval mechanism demonstrated that complex laws often have unintended consequences and require modification. Several provisions of the generic drug authorization bill were applied in ways not anticipated and Congress subsequently amended the law. The modified Hatch-Waxman law limits the way that certain provisions – such as marketing exclusivity – work. Congress should take into consideration the changes that were needed in the past as well as the undesirable side effects of current law when crafting biosimilar legislation.

Of primary concern to the innovative biotech industry is the excessive patent litigation spawned by the 180 day exclusivity provided by the Hatch-Waxman Act to generics that are first to challenge innovator patents. The legal harassment of legitimate patent owners has the net effect of increasing the cost of producing new treatments and cures. Resources that would be better spent on research and development have to be directed to patent infringement law suits. We recommend that Congress avoid basing an incentive system on patent challenges because it rewards behavior that increases costs and hinders the delivery of new and improved medicines to patients.

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?

Amgen believes it is premature to speculate how patent settlement agreements between referenced biologic product manufacturers and biosimilar applicants might be structured. Similar agreements in the pharmaceutical industry generally reflect case-specific assessments by the parties in the context of litigation. Patent settlement agreements also may include various supply arrangements and intellectual property licensing arrangements.

Amgen would not object to a requirement that patent settlement agreements be filed with the antitrust agencies. However, it would be essential that any information filed with the FTC or DOJ be treated as confidential and competitors should not have the opportunity to access this proprietary business information.