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The Honorable William E. Kovacic
Chairman, Federal Trade Commission
Office of the Secretary
Room H-135 (Annex F)
600 Pennsylvania Ave., NW
Washington, DC 20580

Re: Emerging Health Care Competition and Consumer Issues—Comment, Project No. P083901

Dear Chairman Kovacic:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to respond to the Federal Trade Commission's questions regarding competition and consumer protection policy implications from developing an abbreviated regulatory approval pathway for follow-on biologics (FOBs) and from competition among health care providers based on quality information. We are pleased to provide our responses to these questions.

PhRMA represents the country's leading pharmaceutical research and biotechnology companies, which are devoted to inventing medicines that allow patients to live longer, healthier, and more productive lives. PhRMA companies are leading the way in the search for new cures. PhRMA members alone invested an estimated $44.5 billion in 2007 in discovering and developing new medicines. Industry-wide research and investment reached a record $58.8 billion in 2007.

The U.S. biotechnology sector makes important economic contributions to the United States, contributions likely to grow if the underpinnings for large-scale investment in the sector remain intact. Any pathway for FOBs must recognize the importance of assuring patient safety and maintaining strong incentives for the investment needed to seize the extraordinary opportunities for medical advances and economic growth offered by this 21st Century knowledge-based sector. PhRMA supports the development of an abbreviated pathway for the approval of FOBs that is science-based, open, transparent, puts safety first, and promotes incentives for innovation.

PhRMA also supports efforts to improve the quality of healthcare provided to all Americans. Quality measurement is one tool that holds promise in achieving improved quality and health outcomes. Additionally, the output of quality measures has the potential to be a powerful driver of competition in healthcare, provided that the measures are created to provide appropriate incentives within the healthcare system. PhRMA supports the use of sound, evidence-based quality measures that are grounded in stakeholder consensus.

We appreciate your engagement in these important areas and the thoughtful approach in which you are soliciting views from key stakeholders on these issues. We look forward to continuing to work with you, your colleagues at the Federal Trade Commission, and other stakeholders, as you continue consideration of these important topics.

Sincerely,

Billy Tauzin

I. Competition Issues Involving Follow-on Biologic Drugs

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to respond to the Federal Trade Commission's (FTC's) questions regarding competition and consumer protection policy implications in the development of an abbreviated regulatory approval pathway for follow-on biologics (FOBs). Any pathway for FOBs must recognize the importance of assuring patient safety and maintaining strong incentives for investment in innovation.

The FTC questions focus almost exclusively on how an abbreviated regulatory pathway for FOBs would affect marketplace competition. Because the specifics of the potential pathway are not known, comments on the competitive effects necessarily are speculative.

Notwithstanding some uncertainty around the impact of FOBs in the marketplace, it is clear that the effect of FOBs in the biologics market will not be the same as the effect of generic small molecule drugs in the pharmaceutical market. It is agreed by nearly all stakeholders that the scientific basis for an abbreviated FOB approval pathway would be different from the scientific basis for generic small molecule drug approval due to fundamental scientific differences. Unlike generic small molecule drugs, which are approved based on a demonstration that the active ingredient is the same as the active ingredient of the reference product, FOBs would be approved based on a demonstration of similarity to a reference product.

The FTC's missions of competition and consumer protection are both important considerations in the discussion surrounding establishment of an FOB approval pathway. PhRMA urges the FTC to begin its discussions with the premise that patient safety is paramount. A well-reasoned FOB approval pathway would protect the consumers who need it most — patients taking biologic medicines — and seek to achieve a balance between ensuring incentives for innovation and encouraging the entry of FOBs. PhRMA supports the development of an abbreviated pathway for the approval of FOBs that is science-based, open, transparent, puts safety first, and promotes incentives for innovation.

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

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?

This response addresses Questions A.1 and A.4.

Biotechnology has emerged as an engine of innovation, with benefits for patients and the economy. With scientific knowledge about the molecular basis of disease developing rapidly, the opportunities to maintain and expand this engine of innovation are strong. In fact, the biologics sector is widely regarded today as highly innovative and one of the most research-intensive industries in the U.S.[1] American Enterprise Institute scholar John Calfee has written that "medicine today is actually in a new golden era of innovation."[2]

Biologics created under the current system of incentives have been characterized as revolutionizing health care through effective targeted therapies. For example, biologics have produced dramatic progress against many cancers, multiple sclerosis, and rheumatoid arthritis, and biologic medicines being researched today provide hope for needed advances against such diseases as Alzheimer's and Parkinson's. Fortunately, there is opportunity for further innovation and treatment advances that can change the course of diseases that have been without effective treatments, based on the growing scientific understanding of disease at the molecular level.

Some observers may believe that the biotechnology sector is so economically strong that it could easily weather weakened incentives for innovation while maintaining its innovative capacity and the exceptional scale of its research and development enterprise. However, this conclusion does not reflect the inherently diverse and risk-filled nature of R&D in this sector, nor does it consider how particular approaches to an abbreviated pathway for FOBs may affect this sector. It is true that some biologics have achieved

[1] Congressional Budget Office. "Research and Development in the Pharmaceutical Industry." Washington, DC: CBO (Oct. 2006), *available at* http://www.cbo.gov/doc.cfm?index=7615.

[2] Calfee, J. "The Golden Age of Innovation." *The American* (Mar./Apr. 2007), *available at* http://www.american.com/archive/2007/march-april-magazine-contents/the-golden-age-of-medical-innovation/.

significant clinical successes and earned a return, reflecting the opportunity to beat the odds by having a valuable product progress through clinical trials (where the large majority of products fail), receive FDA approval, and become widely accepted in the market. But the biologics sector also has had many failures, with companies investing venture capital and publicly raised funds for decades without achieving an approved drug let alone a blockbuster. Biotechnology has been characterized as "one of the biggest money-losing industries in the history of mankind…," losing nearly $100 billion since 1976.[3] In fact, *The New York Times* reports that only 54 of the 342 publicly traded biotechnology U.S. companies were profitable in 2006.[4]

According to the National Venture Capital Association, "[l]arge successful companies such as Genentech, Amgen, and countless smaller innovative life sciences companies may never have gotten off the ground if not for the venture capital support received in the early stages of their development."[5] Due to the uncertainty, high-risk nature, and costs associated with biologics development, venture capital investment is often the only funding option for small firms. In fact, 70% of small biotechnology firms never become profitable, even after more than 20 years in business.[6]

This is not to suggest that the sector should be viewed negatively — again, it has had real successes — but rather that incentives matter to its continued ability to attract the resources needed for a large-scale biomedical research enterprise that can deliver the medical advances society needs and desires. Absent a public policy environment that rewards innovation, venture capitalists could shift funding to other sectors as their investment is based on the rationale that whereas the "majority of their high risk early stage investments will fail … strong returns on a few successful projects are often enough to justify investments in high risk endeavors that entail many losses" (Grabowski 2007).[7] Ernst & Young (2006) reports that since 2002, venture capitalists have become more risk averse and have shifted to later-stage, product-focused alliances. This reflects an investment focus on expected returns within their investment horizons, and may negatively impact the biotechnology sector's long-term viability.[8] This trend would likely be exacerbated if an abbreviated pathway for FOBs provided insufficient incentives for innovation. It is critical that an appropriate balance be struck between

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[3] Pisano, G. *Science Business: the Promise, the Reality, and the Future of Biotech*. Cambridge: Harvard Business School Press. (2006).

[4] Pollack, A. "It's Alive! Meet One of Biotech's Zombies." *The New York Times* (Feb. 11, 2007).

[5] National Venture Capital Association. "Patient Capital: How Venture Capital Investment Drives Revolutionary Medical Innovation" (2007), *available at* http://www nvca.org/pdf/NVCAPatientCapital.pdf.

[6] Pollack, A. "It's Alive! Meet One of Biotech's Zombies." *The New York Times* (Feb. 11, 2007).

[7] Grabowski, HG. "Data Exclusivity for New Biological Entities." Duke University Department of Economics working paper (Jun. 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

[8] Ernst & Young. "Beyond Borders: A Global Perspective." (2006).

making room for additional competition and maintaining incentives for continued innovation.

In assessing the biologics market, it is important to recognize that there is currently significant competition among innovator biologics. As noted by Calfee and DuPre,[9] multiple biologics may focus on the same therapeutic target, resulting in robust direct competition among multiple innovators. As of July 2008, there were 633 biotechnology medicines in development for more than 100 diseases.[10] Up to 10 biologics are in clinical trials targeting the same protein.[11] Thus, the presence of innovator-to-innovator competition needs to be considered in assessing the potential competitive effect of FOB market entry.

Another factor that needs to be considered in striking a balance between the desire for additional competition and the maintenance of incentives for continued innovation is the extensive biologics research that occurs post-approval, leading to new indications for an already approved medicine.[12] Research and development, including clinical trials, to achieve such new indications undoubtedly advances patient treatment. Such research could be jeopardized should the incentives for post-approval innovation be inadequate. In a recent study, 47 percent of biologics regulated by FDA's Center for Drug Evaluation and Research were found to have at least one new FDA-approved indication after the initial approval.[13] Calfee cites the record of advances achieved by post-approval research on biologics, concluding that "[t]he dominant role of post-approval research extends to many other drugs used as what are called 'targeted therapies'…. Some of these targeted therapies find value in treating a completely different illness. More successes are, no doubt, on the way."[14]

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[9] Calfee, J and DuPre, E. "The Emerging Market Dynamics of Targeted Therapeutics." *Health Affairs* (Sept./Oct. 2006):1302-1308.

[10] PhRMA. "2008 Report on Biotechnology Medicines in Development: Biotechnology Research Continues to Bolster Arsenal Against Disease with 633 Medicines in Development." (Sept. 2008), *available at* http://www.phrma.org/files/Biotech%202008.pdf.

[11] Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488.

[12] *See, for example,* PhRMA. "Post Approval Research on Biotech Medicines Leads to Key Medical Advances." (Oct. 2007), *available at* http://www.innovation.org/documents/File/PhRMA_Post-Approval_Research_FINAL.pdf.

[13] Boston Consulting Group. "How Biological Drugs Continue to be Developed Long After Their First Approval: Quantitative Study of New Indications Approved in the U.S." (Dec. 2007), *available at* http://www.bcg.com/impact_expertise/publications/files/Biologics_Dec07_final.pdf.

[14] Calfee, J. "The Golden Age of Innovation." *The American* (Mar./Apr. 2007), *available at* http://www.american.com/archive/2007/march-april-magazine-contents/the-golden-age-of-medical-innovation/.

There are uncertainties regarding how the potential market for FOBs may evolve, in large part, because there are substantial uncertainties regarding the specifics of the eventual FOB regulatory framework and the incentives for continued innovation. As discussed in more detail in our response to Questions A.7 and A.8, the degree to which the development of new biologics and research into new indications is affected positively or negatively will depend on the length and certainty of data exclusivity granted for innovative biologics as well as on the patent provisions in an FOB framework.

While there is some degree of uncertainty regarding how the market will develop, a number of factors have been identified that will impact competition between innovator biologics and FOBs. Research suggests that the FOB market would not mirror the market for small molecule generic drugs.[15] The Congressional Budget Office (CBO) recently concluded that "the process of designing and manufacturing FOBs is complex and more costly than typical generic drugs approved under the Federal Food, Drug and Cosmetic Act," which will influence the number of FOB entrants.[16] Another factor is that some level of clinical testing would be necessary to establish the safety and efficacy of FOBs. Research by the CBO and others indicates that FOBs will not have the high-level of price discount characteristic of generic small molecule drugs.[17]

Additionally, experts project a lower market penetration rate for FOBs compared to small molecule generics because of the fact that FOBs would not be identical to the innovator biologic.[18] The uncertainty inherent in using FOBs that will not be the same as the innovator medicine is projected to result in a slower uptake among physicians, which will be compounded by safety concerns around switching patients between medicines that may be similar but not identical. Many patients with chronic disease have been treated

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[15] *See, for example,* Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488 and Avalere Health LLC, "Modeling Federal Cost Savings from Follow-On Biologics" (Apr. 2007), *available at* http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf.

[16] CBO. "S. 1695, Biologics Price Competition and Innovation Act of 2007 (as ordered reported by the Senate Committee on Health, Education, Labor, and Pensions on June 27, 2007)." (June 25, 2008) at 6, a*vailable at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf. Note, *for example*, CBO also estimates that it "would be more typical for an innovator biologic to face competition from between one and three competitors." *See also,* Grabowski, HG, et al. "The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumptions." (Aug. 2007), *available at* http://www.bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf.

[17] Examining Safe and Affordable Generic Biotech Drugs: Hearing before the House Committee on Oversight and Government Reform, 110th Cong. (Mar. 26, 2007) (statement of Henry Grabowski, Ph.D., Duke University) at 8-9, *available at* http://oversight.house.gov/story.asp?ID=1223; and CBO. "S. 1695, Biologics Price Competition and Innovation Act of 2007 (as ordered reported by the Senate Committee on Health, Education, Labor, and Pensions on June 27, 2007(June 25, 2008) at 6, a*vailable at* http://www.cbo.gov/ftpdocs/94xx/doc9496/s1695.pdf.

[18] Examining Safe and Affordable Generic Biotech Drugs: Hearing before the House Committee on Oversight and Government Reform, 110th Cong. (Mar. 26, 2007) (statement of Henry Grabowski, Ph.D., Duke University) at 8-9, *available at* http://oversight.house.gov/story.asp?ID=1223.

with biologic medicines under stable conditions for relatively long periods of time, and some physicians and patients would likely be reluctant to allow substitution of FOBs for the innovator biologic compared to substitution of generic small molecule drugs for innovator drugs. [19]

As a trade association, PhRMA does not have information on the marketplace experience of specific biopharmaceuticals or on the business decisions of our member companies, and therefore cannot speculate on the specific business strategies or marketing activities that companies may employ in response to any FOB entry. Nor are we aware of any empirical models that can reliably predict in any detail the nature of this potential competition from FOBs based on existing biologic drug product competition, particularly given that this sector is relatively new. However, as discussed previously, the degree to which innovation is positively or negatively impacted will depend in large part on the length and certainty of data exclusivity for innovative biologics as well as on the patent provisions.

We believe that there is insufficient experience with biosimilars in Europe to adequately assess their influence on competition. In addition, there are significant differences between the U.S. and European markets. For example, in Europe each national authority can promulgate its own regulations that impact competition within individual countries — making generalizations about the competitive effect within and across European markets difficult. The market dynamics in Europe include variations in pricing and reimbursement systems across European countries. In Europe, the combination of regulation and economic disincentives, chief among them government price controls, have resulted in fewer biopharmaceuticals coming to the market (see Calfee 2008).[20]

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?

An abbreviated regulatory pathway for approval of FOBs is intended to result in approval of products that are similar to, not the same as, their reference product. We are not aware of data available in the scientific literature that establish how interchangeability would be determined for products that are not the same, produced by different, unrelated manufacturers. Nor does there seem to be scientific consensus for how an adequate scientific model could be established to determine such interchangeability.[21] In the

[19] *Id.*

[20] Calfee, J. "White Paper on Pharmaceutical Market Competition Issues." (Jun. 2008), *available at* http://www.efpia.org/content/default.asp?PageID=559&DocID=4894.

[21] *See, e.g.*, Department of Health and Human Services, Food and Drug Administration. "U.S. FDA Considerations: Discussion by National Regulatory Authorities with World Health Organization (WHO) On Possible International Non-proprietary Name (INN) Policies for Biosimilars." (Sept. 1, 2006), *available*

absence of a clear scientific basis for establishing interchangeability between products that are similar, there could be a risk to patients from such a determination.

Different biological products affect individuals differently. Using one biologic product in place of another creates significant concerns about the potential for immunogenicity[22] and serious adverse events. The FDA would not make a determination of interchangeability until and unless there were a scientific basis supporting the determination and upon concluding that such an interchangeability determination would not compromise patient safety. While FDA is confident in its ability to approve safe and effective FOBs, it also has stated that its ability to determine interchangeability for FOBs would be limited.[23]

It would be speculative to project how payers or insurers would choose to cover innovator biologics and FOBs that may not be interchangeable. As a result, we are unable to project with certainty how the market for biologics ultimately may be affected in terms of competition, costs, and reimbursement for innovator biologics or FOBs

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

Any competitive concerns arising from the types of agreements listed will necessarily depend on the particular factual circumstances and marketplace conditions. Antitrust law's well-developed rule of reason provides a tested analytical framework for evaluating the competitive impact of such agreements. There is insufficient experience with FOBs to support any sweeping statements about the likely competitive impact of these types of agreements in this particular sector.

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at http://www fda.gov/cder/news/biosimilars.htm. *See also*, Letter from Michael Leavitt, Secretary, United States Department of Health and Human Services to Edward Kennedy, Senator, United States Senate. (June 26, 2007), *available at* http://www.thepinksheet.com/nr/FDC/SupportingDocs/pink/2007/070702_Leavitt_biogenerics_letter.pdf.

[22] Immunogenicity is the ability or propensity of something to cause an immune response. Immunogenicity is not desired for most biologics (with vaccines being an exception). Biologics frequently elicit an immune response, and the consequences of an immune response to a biologic vary greatly. There may be no noticeable clinical effect. There may be reduced efficacy because the immune response inactivates the therapeutic molecule—reduced efficacy can pose safety risks due to the resulting disease progression. In some cases, the immune response may inactivate and destroy the naturally occurring protein as well as the therapeutic protein. This kind of autoimmunity is rare but can be life-threatening.

[23] Examining Safe and Affordable Generic Biotech Drugs: Hearing before the House Committee on Oversight and Government Reform, 110th Cong. (Mar. 26, 2007) (statement of Janet Woodcock, Deputy Commissioner and Chief Medical Officer, U.S. Food and Drug Administration) at 9, *available at* http://oversight.house.gov/story.asp?ID=1223.

Fact-specific, rule of reason analysis. The areas of "joint research and development, supply, licensing, marketing, and distribution" encompass a wide range of agreements. These types of agreements are typically analyzed under a rule of reason that takes into account the marketplace conditions and other factual circumstances bearing on the competitive impact of the agreement. Accounting for the particular factual conditions, the rule of reason distinguishes between agreements with anticompetitive effect that are harmful to consumers and efficiency-enhancing agreements that are in the consumer's best interest.[24] While antitrust law may quickly condemn some agreements in these fields as per se illegal (e.g., a joint marketing arrangement that is merely horizontal price fixing), the overwhelming majority of these types of agreements involve some legitimate benefit and thus must be considered under a more fact-intensive rule of reason.

As such, any generalization about the competitive effect of these types of agreements is inherently questionable. By their very nature, these types of agreements are not subject to blanket generalization or categorization. Instead, the evaluation of such agreements requires fact-specific inquiry.

In addition, antitrust law and competition law do not categorize these types of agreements by sector. Indeed, the antitrust authorities have disfavored such a sector-specific approach.[25] Antitrust analysis accommodates differences in the particular marketplace conditions across sectors. These types of agreements are common in other sectors including those characterized as high technology or those undergoing rapid change. Agreements in the biotechnology sector cannot be subject to any particular generalization warranting application of unique antitrust or competition law. These types of biotechnology agreements, like those in other high-technology sectors, should be subject to a rule of reason analysis that is designed to account for the particular marketplace conditions.

[24] *See Leegin Creative Leather Products, Inc. v. PSKS, Inc*., 127 S. Ct. 2705, 2712-13 (2007).

[25] U.S. Department of Justice. Statement Regarding Release of the Antitrust Modernization Commission Report. (Apr. 3, 2007) at 1, *available at* http://www.usdoj.gov/atr ("New or different rules are not needed for industries in which innovation, intellectual property, and technological innovation are central features. Unlike some other areas of the law, the core antitrust laws are general in nature and have been applied to many different industries to protect free-market competition successfully over a long period of time despite changes in the economy and the increasing pace of technological advancement."); Antitrust Modernization Commission. "Report and Recommendation." (Apr. 2007) at 32, *available at* http://govinfo.library.unt.edu/amc/report_recommendation/toc.htm ("The economic principles that guide antitrust law remain relevant to and appropriate for the antitrust analysis of industries in which innovation, intellectual property, and technological change are central features. Antitrust analysis, as refined to incorporate new economic learning, is sufficiently flexible to provide a sound competitive assessment in such industries.").

Limited marketplace experience. Any departure from well-developed antitrust analysis must be grounded in actual U.S. marketplace conditions and in experience evaluating the competitive effect of agreements in the marketplace.[26] There is no such experience with FOBs. Both innovative and FOB manufacturers would likely have extensive technical capabilities and intellectual property, and therefore, there might be many kinds of licenses and other contractual relationships between them that are normal, legitimate and pro-competitive. Any learning about how U.S. marketplace participants might actually structure and implement these types of agreements must await regulatory and marketplace developments. Moreover, any consideration of a per se rule could only be appropriate after there are marketplace developments and case law interpreting those developments.

There is insufficient experience with FOBs in the U.S. and elsewhere to draw any conclusions about the likely short-term or long-term impact on consumers of these types of agreements. Thus, it would be premature to draw any conclusions about unique competitive concerns that might arise from these types of agreements concerning biologics.

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

There is no rule of thumb as to the contents of patent portfolios for small molecule or biologic drugs. As general background, the Patent Code provides that "[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore…."[27] The Supreme Court correspondingly has interpreted the Patent Code broadly, and specifically includes as patentable subject matter biotechnology inventions.[28]

The Hatch-Waxman Act and FDA implementing regulations[29] recognize the existence of a number of different kinds of patent claims that can be part of the small molecule drug patent portfolio: patents directed to the drug substance (active ingredient); drug product (formulation and composition); methods of using drugs; and methods of manufacturing drugs (process patents). These, as well as other types of patent claims, are also available for biologic drugs. For example, one can have patent claims covering the protein that is

[26] *See, e.g., Leegin*, 127 S. Ct. at 2714 ("the per se rule is appropriate only after courts have had considerable experience with the type of restraint at issue . . . and only if courts can predict with confidence that it would be invalidated in all or almost all instances").

[27] 35 U.S.C. § 101.

[28] *Diamond v. Chakrabarty*, 447 US 303 (1980).

[29] 21 C.F.R. § 314.53.

the active substance, compositions including the protein (formulations), and methods of using that protein to treat patients. [30]

There are additional considerations. Many biologics are versions of naturally occurring substances, which can affect the nature of their patent protection. In addition, given the nature of manufacturing processes in the biotechnology field, there can be a broad variety of methods of manufacture that are protected, and patents covering the method of manufacture could represent a more important part of the patent portfolio than for small molecule drugs. Finally, a wider array of technology, including platform technology, may apply to some biological products. Such technology may be more likely to be owned by third parties.

7-8. 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?

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?

This response addresses both Questions A.7 and A.8.

Due to the research-intensive nature of the biopharmaceutical sector, both patents and data exclusivity are critical forms of intellectual property essential to ensuring continued investment leading to critical medical breakthroughs. Data exclusivity for innovator companies associated with an FOB pathway should be at least 14 years, with additional exclusivity available for clinical investigations critical to obtaining a supplemental Biologic License Application (BLA).

Patents and data exclusivity work in complementary fashion to provide incentives for investment in innovation. Patents reward an invention by providing the innovator with the right to prevent anyone else from making, using or selling the patented invention for a defined period of time. Data exclusivity recognizes the large-scale investment required to develop the safety and efficacy data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and efficacy of its product. (Data exclusivity differs from market exclusivity because data exclusivity does not prevent an applicant from submitting an application and obtaining approval based solely on its own data. Market exclusivity would prevent approval of an application within the exclusivity period even if the applicant used its own data). Neither patents nor data exclusivity bar other innovators with competing, non-infringing drugs.

[30] Linda R. Judge, *Biotechnology: Highlights of the Science and Law Shaping the Industry*, 20 Santa Clara Computer & High Tech. L.J. 79, 85 (2003).

As the Hatch-Waxman compromise for drugs reflects, patent protection is necessary but not alone sufficient to provide adequate incentives for medical innovation. Some of the patent life necessarily is lost during the time consumed by the extensive development and FDA approval process that is required to bring a new medicine to market, and patent term restoration provides only partial compensation for this lost time. Further, in the case of biologics, a product patent might provide insufficient protection if an FOB applicant could circumvent the patent under the similarity standard for FOB approval. Moreover, patents nearly always have a measure of uncertainty, but investments in the testing and clinical trials needed to obtain FDA approval must be made long before an innovator knows whether a patent may someday be successfully challenged. Data exclusivity provides a measure of certainty, allowing investments in clinical trials to be supported. Because patents are filed relatively early in the clinical development process, by the time a drug receives FDA approval and is launched it may have a short patent life remaining. Data exclusivity, which is independent of patents, runs from the time of FDA approval. Thus, patent terms and data exclusivity often run concurrently.

The uncertainty of patent protection, which emphasizes the need for data exclusivity, is evident in the research of Grabowski and Kyle (2007).[31] They found that the number of patent lawsuits associated with Paragraph IV filings has grown in recent years and that these legal challenges are occurring much earlier in the drug's lifecycle. Grabowski and Kyle (2007) conclude that these trends are shortening the average time that innovators have to attempt to recoup their research and development investment. According to Grabowski (2007), "[m]ost of these patent challenges now occur four years after market approval which is the earliest point in time that a generic firm can submit an abbreviated new drug application (ANDA) filing with a paragraph IV certification."[32] Grabowski (2007) concludes that these challenges and the accompanying uncertainty adversely impact biopharmaceutical R&D resulting in firms abandoning R&D projects on future drug candidates with uncertain patent prospects. "Early patent challenges also can have a chilling effect on the development of new indications and formulations, given the uncertain time horizon concerning generic entry and the fact that new indications are developed and approved several years after the original approval."[33]

New medicine development is a lengthy process, and total development time has grown significantly. The average development time has increased from approximately eight years as of 1960, to between 10 and 15 years.[34] The research and development process is

[31] Grabowski, HG and Kyle, M. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals," *Managerial and Decision Economics* 492 (2007).

[32] Grabowski, HG. "Data Exclusivity for New Biological Entities." Duke University Department of Economics working paper (Jun. 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

[33] Grabowski, HG. "Data Exclusivity for New Biological Entities." Duke University Department of Economics working paper (Jun. 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

[34] DiMasi, JA and Grabowski, HG. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 469-79 (Jun. 2007).

also very risky, with few drugs or biologics surviving the rigorous development process. For every 5,000 to 10,000 compounds tested, just five will make it to clinical trials and, of those, and only one will eventually receive FDA approval.[35] Further, for those drugs or biologics that do reach human clinical trials, clinical trial protocols have become far more demanding and complex. In addition to increases in the number of clinical studies performed, the number of unique procedures per protocol has increased, as have the criteria for enrollment and the time to conduct clinical trials.[36]

Accordingly, the average cost to develop a new medicine is now estimated to be more than $1.2 billion.[37] Despite popular misconceptions about the invariable profitability of biopharmaceutical companies, only two in 10 approved medicines bring in enough revenue to recoup the average cost of development. [38] These dynamics reinforce the importance of strong intellectual property protection and appropriate incentives to ensuring a vital, innovative biopharmaceutical sector. In the absence of strong intellectual property protections, Kaitin (2008) suggests that research programs focused on developing biologics for more chronic and complex diseases could be discontinued, as these areas of research are particularly challenging, costly, and uncertain. Similarly, Grabowski (2007) asserts that neither innovator companies nor generic drug nor FOB manufacturers would be able to grow and prosper, as the rate of new product introductions would decline dramatically.[39] If a pathway were created without substantial data exclusivity, innovators would be less likely to invest in developing and marketing new biologics with few remaining years of patent protection or with uncertain forms of protection.

Data exclusivity periods are a recognition of the substantial investment that innovators have to make to demonstrate safety and efficacy for FDA approval. To advance the discovery of new biologics, the exclusivity period must be long enough to allow innovators, who undergo costly R&D and the FDA approval process, to earn a positive rate of return.

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[35] PhRMA. "Drug Discovery and Development: Understanding the R&D Process." (2007), *available at* http://www.innovation.org/drug_discovery/objects/pdf/RD_Brochure.pdf.

[36] Tufts University Center for the Study of Drug Development. "Growing Protocol Design Complexity Stresses Investigators, Volunteers." *Tufts Impact Report* (Jan./Feb. 2008), *available at* http://csdd.tufts.edu/_documents/www/Doc_309_65_893.pdf.

[37] DiMasi, JA and Grabowski, HG. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 469-79 (Jun. 2007).

[38] Vernon, J, Golec, R, and DiMasi, J. "Drug Development Costs When Financial Risk is Measured Using the FAMA-French Three Factor Model." (Jan. 2008) (submitted to the Journal of Health Economics).

[39] Grabowski, HG. "Data Exclusivity for New Biological Entities." Duke University Department of Economics working paper (Jun. 2007), *available at* http://www.econ.duke.edu/Papers/PDF/DataExclusivityWorkingPaper.pdf.

Currently available exclusivity periods for small molecule drugs are inadequate for biologics. Based on the economic analysis conducted by Grabowski (2008),[40] a base period of at least 14 years is needed to balance the incentives needed to develop new medicines with the interest in additional competition through the entry of FOBs. As a result, the exclusivity period for small molecule drugs (five years) is clearly insufficient for biologics. In fact, 5 years is now insufficient for small molecule drugs.[41]

While conceptual models of optimal exclusivity periods have been developed by other economists,[42] most modeling efforts have not resulted in a specific value for the data exclusivity period for biologics. However, Grabowski (2008)[43] has developed economic modeling that supports a minimum of 14 years of data exclusivity to provide companies with approved biologics the potential to earn a return on their investment and to continue to finance their operations.[44] Grabowski's analysis provides a carefully reasoned assessment of the average period of data exclusivity necessary to encourage the development of new medicines without unduly delaying the entry of FOBs. The break-even analysis for a representative portfolio of biologics provides support for a data exclusivity period of between 12.9 and 16.2 years (with the variance based on differing costs of capital). This work supports a base period of at least 14 years of data exclusivity for biologics. Additional exclusivity should be available for new clinical investigations essential to obtaining a supplemental BLA, such as post-approval indications, in light of the R&D investment required.

The exclusivity period should not vary based on the extent of competition facing the referenced product or the patent portfolios claimed by the referenced product. Data exclusivity recognizes the large-scale investment required to develop safety and efficacy data needed to support an application for FDA approval and bars another company from relying on the innovator's data for a period of time to demonstrate the safety and efficacy of its product. Neither patents nor data exclusivity bar other innovators from introducing competing, non-infringing products into the market based on their own safety and efficacy data rather than reliance (during a fixed period) on the innovator's data. Data

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[40] Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488.

[41] *See, e.g.*, Grabowski, HG and Kyle, M. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals." *Managerial and Decision Economics* 491-502 (28: 2007). *See also* DiMasi, JA, and Paquette, C. "The Economics of Follow-on Drug Research and Development: Trends in Entry Rates and Timing of Development." *Pharmacoeconomics* 1-14 (22 Supp 2:2004).

[42] *See, e.g.*, Nordhaus, W. *Invention, Growth and Welfare: A Theoretical Treatment of Technological Change*. Cambridge: MIT Press (1969).

[43] Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488.

[44] Biotechnology Industry Organization. "A Follow-On Biologics Regime Without Strong Data Exclusivity Will Stifle The Development Of New Medicines." (Sept. 2007) at 1, *available at* http://www.bio.org/healthcare/followonbkg/FOBSMarket_exclusivity_20070926.pdf.

exclusivity simply provides a measure of certainty, allowing investments in clinical trials to be supported. Data exclusivity also provides an incentive for continued research leading to new indications post-approval and after patents (often issued years before FDA approval) have expired.

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?

The European Union (EU) has recognized the importance of providing incentives for innovation by establishing exclusivity periods for new drugs and biologics and by recognizing the need for additional exclusivity for a significant new indication. However, as noted previously in our response to Questions A.1 and A.4, the market dynamics in the U.S. differ from those in Europe. For example, in Europe each national authority can promulgate its own regulations (e.g., on pricing and reimbursement) that would impact competition within individual countries, which makes generalizations about the competitive effect within and across European markets difficult. Additionally, the U.S. market differs from these varying market systems in terms of pricing and reimbursement systems and parallel trade. Because of these factors we must be cautious not to extrapolate too much from the EU experience, as the U.S. market is unique. The market experience with FOBs under the EU system is relatively short making it difficult to assess whether the exclusivities establish appropriate balance in Europe. Economic analysis by Grabowski (2008)[45] found that based on the market dynamics in the U.S., a minimum data exclusivity period of 14 years is warranted, which differs from the exclusivities provided in Europe.

[45] Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488.

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?

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?

This response addresses Questions B.1 and B.4.

It is important for litigation of any patent disputes to proceed during the approval process for FOBs.[46] Litigation under the Hatch-Waxman Act is resource intensive and risky. However, it would be even more resource intensive if the system encouraged allowing the marketing of an infringing generic drug product prior to patent expiration and thus led to more patent litigation over damages.

If patent litigation concerning an FOB takes place during the approval process, litigation can be resolved before the FOB is marketed. This could avoid altogether the potential marketplace disruption and confusion to patients and physicians caused by the marketing of a product at risk followed by the removal of that product from the market due to an infringement finding. Resolving litigation before marketing the FOB increases certainty and facilitates rational business planning for both the innovator and the FOB applicant. Litigation concurrent with the FDA approval process would ensure the opportunity to protect granted patent rights. Finally, it would avoid the need to seek preliminary injunctive relief to cease marketing of infringing products and expensive litigation over damages caused by the marketing of an infringing product.

Such a concurrent litigation process reflects a balanced approach. Follow-on applicants may use certain patented technology under 35 U.S.C. 271(e)(1) for purposes of developing information to submit to FDA without being liable for patent infringement. However, that provision fosters the application process — it does not permit the marketing of an infringing product.

To achieve the goal of resolving patent disputes prior to marketing an FOB, the law can provide incentives for expediting litigation. In the context of small molecule generic drugs, the incentives include (1) the 45-day period for determining whether to bring suit

[46] Note, however, that, depending on the timing of an follow-on application and approval in any approval pathway created by Congress, it could be potentially inefficient for courts and the parties to initiate patent litigation too early.

and then a 30-month stay following suit and (2) the potential for courts to lengthen or shorten the 30-month stay based on conduct during the litigation. Litigation involving FOB applicants could be even more efficient if there were a procedural mechanism and incentive for the FOB applicant to provide information about its proposed FOB, the process for making it, and samples of it to the patent holder as soon as litigation could arise.

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

Multiple factors are likely to affect the time required for the actual review of applications. Such processes and reviews are likely to evolve over time. The review time for individual applications will be influenced by the resources available to the FDA, the quality of the guidances governing FOB submissions, and the quality of the data and the submissions. Thus, it is difficult to predict with certainty when the first FOB would be approved following enactment of legislation and what the average routine review times might be after the first few FOB approvals.

However, Avalere estimates an average application review time of two years for the first applications FDA reviews after creating an FOB pathway.[47] This estimate is predicated on application submissions and data packages that meet regulatory expectations as described in FDA regulation and existing guidance. Avalere projects that, for the first set of FOB applications received by the FDA, the agency's review process would take longer than one year because of a lack of experience with the application process and the complexity of the products.

FDA resources. Significant resources would be required to review the FOB application package. Even though an FOB application would rely in part on innovator safety and efficacy data, and the quantity of data needed to support an FOB application may be less than what would be needed to support an innovator BLA, the full range of scientific, medical, and statistical expertise that must be brought to bear to review FOB applications would be comparable to what is currently needed for FDA's review of innovator biologics. As a result, the resources available to the FDA for the proper consideration of safety and efficacy of any FOB may significantly affect the timing of review and approval.

Guidance—Improving FDA review efficiency. While potentially time consuming, the development of effective regulations and guidances through a transparent process may ultimately conserve applicant and FDA resources and increase the speed with which the FDA reviews and approves FOB applications. If the FDA issues guidance that makes its expectations and approval considerations explicit and clear, FOB manufacturers may be able to concentrate their resources more effectively and may be more likely to submit applications acceptable for review.

[47] Avalere Health LLC. "Modeling Federal Cost Savings from Follow-On Biologics." (Apr. 2007), *available at* http://www.avalerehealth.net/research/docs/Modeling_Budgetary_Impact_of_FOBs.pdf.

FDA can review applications more efficiently if it receives applications ready for review and encounters fewer delay-causing issues during the review. Well-developed and clear standards will also advance consistency in the FDA's review of applications within a given product class. This could help reduce risk and uncertainty for future FOB applicants. As the Secretary of Health and Human Services has stated, a requirement that FDA issue product-specific guidance before acting on FOB applications will help "ensure the agency has optimum information regarding safety and efficacy considerations for FOBs; enhance transparency of decision making; establish a level-playing field for all FOB applicants; and encourage FOB applications by describing Agency expectations for application content."[48]

Quality of FOB data and submission. As noted in Avalere's estimate of FOB application review time, this period of time is in part predicated on FOB application submissions and data packages that meet regulatory expectations. Findings from a recent Department of Health and Human Services Office of Inspector General (OIG) report,[49] although specific to ANDA filings, suggest that low quality applications may prolong FDA review and approval times. One of the recommendations offered by the OIG to solve this problem is for FDA to offer more guidance to the sector in order to decrease the percentage disapproved ANDA applications. This example suggests quality applications may expedite FDA reviews, and guidance to the sector may improve the application quality.

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?

As noted in the response to Question A.6, there could be more types of patents involved in patent litigation concerning biologics than small molecule generic drugs. It is possible that the litigation could involve more method of manufacture (process) patents, potentially more complex scientific arguments, and potentially more third parties. Regardless of any differences, it would be inefficient for the court system and the parties if there were a requirement to litigate patents relating to the same product at different times.

[48] Letter from Michael Leavitt, Secretary, United States Department of Health and Human Services to Edward Kennedy, Senator, United States Senate. (June 26, 2007), *available at* http://www.thepinksheet.com/nr/FDC/SupportingDocs/pink/2007/070702_Leavitt_biogenerics_letter.pdf.

[49] U.S. Department of Health and Human Services Office of Inspector General. "The Food and Drug Administration's Generic Drug Review Process." OEI-04-07-00280 (Jun. 2008), *available at* http://www.oig hhs.gov/oei/reports/oei-04-07-00280.pdf . (The OIG found that the FDA approved or tentatively approved only 4 percent of original ANDAs under review in 2006 based on the initial ANDA application packages. The remaining 96 percent were not approved because they contained deficiencies as determined by the Chemistry division. To correct the deficiencies, applicants submit major or minor amendments. A large number of amendments were received – over 4,100 amendments for 828 applications – and resulted in an increased review burden. One outcome of this increased burden was the failure of FDA to meet its 180-day review requirement in nearly half of the cases).

In addition, the dynamics of the litigation could be different in the context of FOBs. If the regulatory pathway developed by Congress is focused on "similarity" of the FOB to the reference product, rather than "sameness" (as would be the case for a small molecule generic drug), there could be less certainty as to whether an FOB would infringe a patent. This is because in the generic drug context, companies must show that a generic drug is the same, and patent coverage (at least as to patents for drug substances) is not generally an issue. However, if differences are allowed, then whether a product infringes may depend on narrow issues of claim interpretation by the court in the infringement case,[50] and, potentially, on applicability of the patent law doctrine of equivalents.[51]

With respect to the length of patent litigation, there is no general rule. In existing patent litigation, there is a range of lengths of litigation in different district courts. Similarly, it is likely that the length of patent litigation concerning an FOB would also be influenced largely by the docket and case management rules of the particular courts in which cases are pending, and the particular judge before whom the case is pending. As with other kinds of litigation, other factors affecting the length of litigation could include the number of patent claims at issue in the case, and the defenses raised in the particular case.

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?

Whether and when declaratory judgments on patent infringement or invalidity issues would be available for an FOB applicant could be influenced by, among other things, the nature of any patent litigation procedure enacted as part of a regulatory approval pathway for FOBs. In addition, the availability of declaratory judgments is limited by Article III of the Constitution. Under Article III, federal court jurisdiction can only exist if there is a "case or controversy." As the Supreme Court has stated, Article III jurisdiction for a declaratory judgment action can only lie if there is a "substantial controversy, between parties having adverse legal interests, of sufficient immediacy and reality to warrant the issuance of a declaratory judgment." [52] Thus, in addition to satisfying any procedures concerning declaratory judgments specified in applicable legislation, an FOB applicant that has not been sued for patent infringement would need to be able to meet this constitutional test for there to be declaratory judgment jurisdiction.

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[50] *See* Manheim, B, Granahan, P, and Dow, K. "'Follow-On Biologics': Ensuring Continued Innovation In The Biotechnology Industry." *Health Affairs*, 25(2): 394- 398 (March/April 2006); *see also,* Grabowski, HG. "Follow-on Biologics: Data Exclusivity and the Balance Between Innovation and Competition." *Nature Reviews Drug Discovery* 7 doi:10.1038/nrd2532 (June 2008): 479-488.

[51] The doctrine of equivalents may permit a patent owner to prove infringement where the defendant's product does not literally infringe the patent, but nevertheless performs substantially the same function in substantially the same way to achieve substantially the same result. This complex doctrine has evolved in recent years with Supreme Court and Federal Circuit precedent. *See* Manheim at 400, discussing *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722 (2002). *See also Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 344 F.3d 1359, 1367 (Fed. Cir. 2003).

[52] See *MedImmune, Inc. v. Genentech, Inc.,* 127 S. Ct. 764, 771 (2007) (internal quotations omitted).

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

It is not clear that regulatory exclusivity would be needed to encourage patent challenges under an FOB regulatory pathway.

The Hatch-Waxman Act contains a regulatory exclusivity — a 180-day exclusivity period — for which the first generic applicant(s) to challenge patents for a small molecule drug is eligible. Over the years, with this exclusivity available, generic companies have been filing challenges to patents earlier in the product life of the innovator product and more frequently.[53] This has created a burdensome situation in which uncertainty is created with respect to patents and resources of innovator companies are tied up in the litigation process for years, beginning relatively early in the product life.

Furthermore, it is not clear that the incentive is needed for there to be patent challenges for small molecule drugs. As noted by the FDA,[54] 180-day exclusivity is not the sole incentive to challenge patents, which is demonstrated by patent challenges submitted even though companies know they were not the first generic applicant to challenge the patents, and thus would not be eligible for 180-day exclusivity. More importantly, exclusivity incentivizes early litigation, without regard to merit.

In any event, as noted in response to Questions A.1 and A.4, experts predict that the biologics marketplace following establishment of a regulatory approval pathway for FOBs would be different from the marketplace for small molecule drugs.

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?

Biopharmaceutical companies operate in a highly regulated environment, and our member companies are committed to following the law. If a situation arises in which an enforcement agency believes a company may have violated the law, the agency can take a wide range of actions to investigate and address the particular situation, as appropriate.

Citizen petitions, which are public filings, are an important First Amendment-protected element of open, transparent government proceedings that provide members of the public

[53] Grabowski, HG, and Kyle, M. "Generic Competition and Market Exclusivity Periods in Pharmaceuticals." *Managerial and Decision Economics* 491-502 (28: 2007).

[54] U.S. Department of Health and Human Services, Food and Drug Administration. "FDA Response to Citizen Petitions submitted by Mylan and Teva Pharmaceuticals." (Jul. 2, 2004), *available at* http://www fda.gov/ohrms/dockets/dailys/04/july04/070704/04p-0261-pdn0001.pdf.

the ability to be involved in the regulatory process and permit public vetting of important scientific and policy issues. It is important that all interested persons and other stakeholders, including biopharmaceutical companies, have the ability to submit citizen petitions to FDA, in order to provide them with an avenue to raise important scientific and regulatory issues. FDA regulations permitting the submission of citizen petitions have been in place since the 1970s, and Congress added new procedures addressing these submissions in the Food and Drug Administration Amendments Act of 2007. Citizen petitions have sparked important public dialogues and have been the catalyst for many important steps taken by the FDA to protect the public health.

As in the case of generic drugs, any regulatory approval pathway for FOBs would involve complex scientific and legal considerations that can and should be raised through appropriate mechanisms, such as citizen petitions. Innovator companies have extensive knowledge about their products, and are often in the best position to bring to FDA's attention complex regulatory and scientific issues regarding appropriate approval standards. Limiting or otherwise constraining the right of interested persons to submit citizen petitions to the FDA would potentially put consumers at risk by closing a key procedural mechanism to raise important issues before FDA, and could undermine the legitimate economic interests of innovators and other competitors.

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?

As a trade association, PhRMA is not privy to how individual patent settlement agreements would be structured, or whether the dynamics with respect to FOBs would impact such agreements. As noted in the January 17, 2007 statement of Billy Tauzin, President and Chief Executive Officer of PhRMA,[55] courts and experts recognize that public policy strongly favors settlement of disputes without litigation and that settlement of patent litigation often benefits consumers. Patent settlement agreements can be pro-competitive and can be an important part of maintaining the incentives for innovation created by the patent system.

In the case of future patent infringement litigation relating to an FOB regulatory pathway, courts and enforcement agencies should evaluate patent settlements on a case-by-case basis. Given the nascent nature of FOBs and the absence of a mature regulatory approval pathway, there is no empirical basis or marketplace experience supporting any conclusion about the incentives to enter into patent settlement agreements. It is premature to generalize about whether companies in the biologics sector will have unique incentives to enter into pro-competitive or anticompetitive patent settlements.

[55] Paying Off Generics to Prevent Competition with Brand Name Drugs: Should It Be Prohibited: Hearing before the Senate Committee on the Judiciary. (Jan. 17, 2007) (statement of Billy Tauzin, President and CEO, PhRMA). http://judiciary.senate.gov/hearings/testimony.cfm?id=2472&wit_id=5982.

PhRMA believes that the rule of reason analysis developed by the courts strikes the right balance between the policy encouraging patent settlements against any claim that a patent settlement unreasonably restrains trade and would therefore harm consumers. Ultimately, this is a fact-specific determination as to whether any particular agreement excludes competition beyond the scope of the patent's protection. This rule-of-reason approach or case-by-case approach can account for any difference in incentives to settle patent litigation that might potentially arise in the future after FOBs are approved and commercialized.

II. Competitive Significance of Health Care Quality Information

Healthcare quality has been defined by the Institute of Medicine (IOM) as, "The degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[1] In 2001, the IOM published a landmark report, "Crossing the Quality Chasm: A New Health System for the 21st century," which further defined quality care as aiming to be safe, effective, patient-centered, timely, efficient, and equitable. In order to provide better care and thereby improve quality, patients must have access to care, available treatments for their condition, and a healthcare delivery system that can meet their needs.

Quality measurement has been identified as a tool to help achieve improved quality of care and improved health outcomes. Through measurement, healthcare quality can be assessed, analyzed, and improved. Results of such measurement can identify areas for improvement, as well as areas of strength, for a given healthcare professional, plan, or system. Those identified areas needing improvement can be evaluated and analyzed to isolate processes or practices that, with change, can lead to better care. Performance evaluation can help lead to improvements in quality of care by ensuring that patients are receiving appropriate care, which can include appropriately ordering and monitoring results of lab tests, imaging studies, medical and surgical procedures, counseling, or medication use. Likewise, performance evaluation can help lead to improvements in the structuring of systems that organize, manage and deliver care, and that play a key role in determining the care that patients receive. Measurement also provides a means of accountability, ensuring that there is a responsible party for a patient's care.

By providing additional information on healthcare performance (including both clinical interventions and the systems of delivering care), quality measurement holds potential as a powerful driver of competition in healthcare. It is important for measurement to create incentives for the right kind of competition – that is, competition centered on patient care and patient value. This type of measurement will help achieve a shift from misaligned incentives.

To support quality-focused competition in healthcare, measurement should overcome, and not reinforce, fragmentation in care delivery and narrow silo budgeting. Measures should support the overall goal of improved long-term patient outcomes, accommodate patient preferences, and give physicians and patients flexibility to choose the optimal treatment to achieve high quality outcomes for the individual.

Sound measures must be applied for meaningful quality measurement to occur. Measures should be: grounded in science and well-defined; reliable, thereby providing the same results when used in the same population; valid, meaning that they accurately represent the concept being evaluated; evaluate areas of care that are a priority and have been shown to display variation in the quality of care provided; feasible to use and implement; and reportable and provide meaningful information about the area of care being evaluated. To ensure that measures meet these qualifications, they should be

[1] Institute of Medicine, http://www.iom.edu/CMS/8089.aspx, accessed 17 September 2008.

rigorously reviewed by consensus-based bodies, such as the National Quality Forum (NQF), prior to widespread dissemination and use.

Further, reporting of the results of performance measurement holds promise of improving healthcare quality. For instance, reporting results back to providers gives them an opportunity to see the facts about the quality of care that they give and to change their practices for the better.

Experts agree that appropriate use of medicines plays a central role in both the quality of healthcare patients receive as well as the quality of the lives they lead. Appropriate use encompasses addressing underuse, overuse, and misuse of medicines (RAND research on vulnerable elders showed underuse outweighed overuse as a quality problem by a ratio of 17 to 1[2]). It also includes adherence by the patient to the therapy prescribed. Numerous studies have reported that appropriate prescribing of medication therapy and adherence to that therapy improve quality and outcomes, while often reducing total costs and use of other, often more expensive, health services.[3]

In future quality measure development efforts, adherence and persistence to medication therapy should be addressed. This could be done by measuring a patient's medication use; for example, a common measurement is medication possession ratio which calculates the number of days a patient has medication within the evaluation period. The prescriber or pharmacist's efforts to encourage medication adherence could also be evaluated.

For many purchasers and consumers, a key choice about healthcare is which health plan to purchase. Plan-level measures of quality have been developed by organizations such as the National Committee for Quality Assurance. Given the centrality of choice among health plans to quality of care and effective functioning of markets, it will be important to continue development of quality measures at the plan-level, in parallel with ongoing efforts to develop and promote quality measures at the level of providers and interventions.

While measure use, quality data collection and analysis, and reporting have potential to improve quality, it is important to consider the costs to the healthcare system that these efforts consume. Various stakeholders must supply resources, time, and money in order to provide quality data that can be meaningful.

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[2] Higashi T et al., "The Quality of Pharmacologic Care for Vulnerable Older Elders," Annals of Internal Medicine, 2004(140):714-720.

[3] M. Sokol et al., "Impact of Medication Adherence on Hospitalization Risk and Healthcare Cost," *Medical Care*, June 2005. ; D. Goldman, "Pharmacy Benefits and Use of Drugs by the Chronically Ill," *Journal of the American Medical Association*, 19 May 2004. See also M. Gaynor et al., "Is Drug Coverage a Free Lunch? Cross-Price Elasticities and the Design of Prescription Drug Benefits," *NBER Working Paper 12758*, December 2006.; D. Cutler, et al., "The Value of Antihypertensive Drugs: A Perspective on Medical Innovation," *Health Affairs*, January/ February 2007.; M. Cloutier, et al., "Asthma Guidleine Use by Pediatricians in Private Practices and Asthma Morbidity," *Pediatrics*, November 2006.; E. McGlynn et al., "The Quality of Health Care Delivered to Adults in the United States," *New England Journal of Medicine*, 348 (2003): 26, 2635-45.

Finally, in considering the role of information about quality in the effective functioning of markets and efforts to improve value, it is important to recognize the disparate regulatory requirements governing different participants in the health system. For instance, pharmaceutical manufacturers marketing to physicians and consumers are governed by strict FDA regulation. Manufacturers may promote their products only in terms that are consistent with the FDA-approved labeling, which itself is backed by rigorous research required by the FDA. Many other participants in the healthcare community are not subject to such a rigorous level of regulation or standards. Such disparate standards may have important effects on the quality of information available to consumers.

Responses to Specific Questions

A. Purchaser Decision Making and Quality Information

5. What information is needed to measure the efficiency of a provider? What is the proper weighting of quality and resource use in an efficiency measure?

Measures focused on cost must always be considered in the context of quality improvement and overall outcomes and value of care. Otherwise, such measures could have unintended detrimental effects on the care provided to a patient and even add to total costs. As RAND researcher Elizabeth McGlynn has stated, "If we want to improve quality and reduce costs, we should focus on quality improvement rather than cost reductions."[4] We believe assessing quality and resource use requires considering the full range of resources used, including, for example, physician office visits, hospitalizations, procedure costs, and pharmacy costs, and the full range of outcomes, including, for example, health, disability, and productivity, over a period of time rather than as a snapshot in time. At the same time, quality improvement is consistent with more efficient, higher value care. For instance, there are large well-documented gaps between care known to be effective and the care patients receive[5]; a focus on closing these known gaps would enhance value.

Measures should also account, as appropriate, for potential differences in populations being treated, such that physicians who treat and plans that cover the sickest patients are not penalized. Risk or severity adjustment is important to providing consumers with information that accurately informs their choices.

C. Federal Policies to Facilitate Quality Information Collection and Reporting

3. What are the costs and benefits of a single entity developing the quality measures, collecting and analyzing the data, and reporting the results? What are the costs and benefits of governmental involvement in these activities?

[4] E. McGlynn, "There is No Perfect Health System," Health Affairs, 2004;23(3):100-102.
[5] Institute of Medicine, Committee on Quality Health Care in America, "Crossing the Quality Chasm: A New Health System for the 21st Century," National Academy Press, Washington, DC, 2001.

Developing sound quality measures is a lengthy process involving many experts and stakeholders. By having multiple developers, the burden of the work is distributed so that multiple measure development projects can be undertaken at the same time. Moreover, some developers focus their efforts on specific aspects of the healthcare system. For example, one developer may focus its work on developing measures for physicians versus another developer that may focus its work on measures targeted at health plans. Developers may also have differing expertise allowing them to focus on different types of measures. Having multiple measure developers also creates an environment that allows innovation in the quality measurement field to thrive. Developers compete to derive new ways and concepts of evaluating care.

Government is currently participating in measure development and making positive contributions. Measure development should continue to occur in a balanced fashion involving the public and private sectors, patients, and other stakeholders. Private and public sector work in this area should continue to support development of measures and new thinking about evaluating quality.

4. How should federal, state, and private sector efforts to measure and report on healthcare quality be harmonized so that purchasers obtain the benefits of cost and quality information?

CMS has implemented a variety of quality initiatives for its various programs that impact numerous areas of the healthcare system. Within these various quality initiatives, CMS has selected for use many measures whose purpose is nearly the same. Having multiple measures targeted at the same process to yield the same outcome but with slightly different specifications applied to different care settings can be confusing and burdensome. Harmonization of the measures across care settings could result in simplification of the many measures such that they are easier to implement, report, and compare. To that end, PhRMA supports measure harmonization across the various CMS quality initiatives.

A work group of the Quality Alliance Steering Committee (QASC) is focused on measure harmonization, and its plan is to develop a strategy to harmonize measures across care settings. We encourage support of the efforts of the QASC in this measure harmonization endeavor.

Conclusion

As the Federal Trade Commission (FTC) continues to examine the role of competition in healthcare quality improvement, PhRMA encourages the FTC to view healthcare in its totality, viewing all sites of care, treatment regimens, and aspects of care as part of the healthcare realm, rather than dissecting healthcare into small silos. All sites of care, treatment options, and other aspects of care impact one another and the ultimate healthcare outcome. As such, they should be taken together instead of in sections.

PhRMA appreciates the opportunity to respond to the FTC on the matter of healthcare quality.