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PRESIDENT AND CHIEF EXECUTIVE OFFICER

PhRMA

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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—Public Workshops and Request for Comments, Project No. P083901

Dear Chairman Kovacic:

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to submit additional comments following the November 21, 2008 roundtable "Follow-on Biologics: Framework for Competition and Continued Innovation." These comments supplement the response we submitted September 30, 2008, in response to questions on emerging health care competition and consumer issues. We are pleased to provide additional comments and views.

Our comments focus on three areas:

- The centrality of considering the state of the science in developing assumptions about the potential competitive effects of follow-on biologics (FOBs).
- Elaboration of our perspective on data exclusivity, patents, and related concepts.
- Discussion of key assumptions and issues in determining an appropriate period of data exclusivity for biologics.

As we have previously shared with the Federal Trade Commission, the U.S. biotechnology sector makes important health and economic contributions to the United States, contributions likely to grow if the underpinnings for large-scale investment in the sector remain intact. Any regulatory 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 establishment of an abbreviated pathway for the approval of FOBs that is developed through transparent processes, is science-based, puts patient safety first, and promotes incentives for innovation. A regulatory approval pathway for FOBs must include adequate quality standards, as well as pre-clinical and clinical testing requirements to ensure patient safety. The regulatory approval pathway for FOBs must also recognize that data exclusivity and patents work in a complementary fashion and are both essential to ensuring continued investment leading to critical medical breakthroughs from biologics. A data exclusivity period of at least 14 years and a significant period of exclusivity for new indications balances the desire for increased competition with the need to maintain incentives for innovation.

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.

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

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to submit additional comments following the Federal Trade Commission's (FTC) November 21, 2008, roundtable on "Follow-on Biologics: Framework for Competition and Continued Innovation." These comments supplement the response we submitted September 30, 2008, in response to questions on emerging health care competition and consumer issues. Our supplemental comments focus on three areas:

- The state of the science, which should be the foundation for any assumptions about the potential competitive effects of follow-on biologics (FOBs).
- Elaboration of our perspective on data exclusivity, patents, and related concepts.
- Discussion of key assumptions and issues in determining an appropriate period of data exclusivity for biologics.

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The State of the Science and Promotion of Patient Safety Should Inform any Hypothetical Competition Scenarios for FOBs

The FTC roundtable on FOBs did not seek to address the scientific concepts associated with establishing an abbreviated regulatory approval pathway for FOBs. However, it is impossible to divorce discussion of biologics marketplace issues from assumptions about the regulatory pathway that may be adopted for approval of FOBs. The regulatory approval pathway and its data requirements would likely influence both the innovator and FOB markets.

Participants at the FTC roundtable recognized that the regulatory aspects of any new approval pathway and, in particular the data requirements for FOB approval, will be based on science and implemented by the Food and Drug Administration (FDA). However, the FTC postulated a scientific framework for discussion purposes only, and thus, the FTC workshop was premised on some underlying assumptions and explicit definitions related to the science surrounding FOBs that are not recognized by the FDA or other scientific experts to be consistent with current science.

The FTC discussion framework defined two types of FOBs: non-interchangeable "biosimilars" and interchangeable "biogenerics." However, Dr. Rachel Behrman, Associate Commissioner for Clinical Programs and Director of the Office of Critical Path Programs, FDA explained at the roundtable that FDA does not recognize these definitions and that the agency does not believe there is currently a scientific basis for determining interchangeability of biologics from different, unrelated manufacturers. Importantly, the FDA noted that interchangeability determinations are unlikely for the foreseeable future and may never be possible for some products.

PhRMA is confident that FOB manufacturers, like innovators, will be subject to high scientific standards in order to ensure that patients receive safe and effective medicines. It would be imprudent to get too far ahead of current scientific understanding in envisioning an FOB pathway and any resulting marketplace effects. The FTC should ground its examination of competition issues in realistic views of the current and reasonably foreseeable state of the science as articulated by the FDA at the roundtable.

The best incentives for competition cannot create a market for FOBs without a regulatory approval pathway grounded in sound science to ensure patient safety, and therefore, generate the confidence needed to foster adoption and use of FOBs.

Reliance on Innovator Data Would Allow the FOB Manufacturer to Benefit from Innovator Investment of Time and Resources and Avoid Risk

Data reliance was discussed at the roundtable in the context of establishment of an abbreviated regulatory approval pathway. The discussion may have left an incomplete picture of the full extent to which FOB manufacturers would rely on innovator data in their abbreviated application for FDA approval. This section elaborates on data reliance and the additional benefits that an FOB manufacturer would gain from the innovator's research and development (R&D), regulatory approval, and market experience.

The premise of an abbreviated regulatory approval is that the FOB manufacturer would rely on the previous FDA determination of safety and efficacy (or purity and potency) for the innovator biologic. The innovator's pre-clinical and clinical data form the basis on which the FOB applicant is able to submit its abbreviated data package. This means that the safety and efficacy data package for the innovator biologic would provide support for the FOB application—this is "reliance." Without the benefit of the innovator data (which can take between 10 to 15 years and cost more than $1.2 billion on average to generate[1]), an FOB manufacturer would have to make the substantial investment needed to generate a complete data package.

In addition to relying on the innovator data showing safety and efficacy, the FOB manufacturer would benefit from the innovator's investment of time and resources in the discovery and development of its innovative biologic. The overall clinical approval success rate for biologics is 30 percent, and the success of any given molecule rides atop the R&D of the many molecules that fail.[2] An innovator bears the full costs and risks of this development, including the cost and risk of failed development programs. The FOB manufacturer would not repeat these failures and would only invest in the development of biologics that are known due to innovators' efforts to be successful. Therefore, the FOB manufacturer would face much less risk than did the innovator that its effort to develop and gain regulatory approval of a biologic will fail.

In summary, reliance on innovator data would allow an FOB manufacturer to submit an abbreviated application—that is, an application that does not contain all of the elements of a full biologics license application (BLA) and/or contains fewer data. The FOB manufacturer also would enjoy the benefit of the innovator's R&D and establishment of

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[1] DiMasi, J.A., and Grabowski, H.G. "The Cost of Biopharmaceutical R&D: Is Biotech Different?" *Managerial and Decision Economics* 469-79 (Jun. 2007).

[2] *Id.*

the market. Thus, under an abbreviated approval pathway the FOB manufacturer would shoulder significantly less risk and uncertainty than innovative manufacturers.

Data Exclusivity is Distinct From, and Complementary to, Patents

The FTC roundtable discussion of the role of data exclusivity and patents in promoting innovation was wide ranging and at times did not fully distinguish the different roles, purposes and effects of patents and data exclusivity.

Data exclusivity and patent protection are separate forms of intellectual property. As discussed in our September 30, 2008, comments to the FTC, data exclusivity recognizes the substantial investment that innovators make to develop the data and information necessary 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 undertake the uncertain and costly R&D and FDA approval processes the opportunity to earn a positive rate of return. *Data exclusivity does not prevent any company from seeking FDA approval based solely on its own data, does not provide protection for a biological or chemical invention itself (only the data generated to support regulatory approval of the product), and does not extend the life of any patent.*

Patents, by way of contrast, provide the owner with the exclusive right, among other things, to make, use, or sell an invention, and thus to exclude an unauthorized person from conducting those activities with respect to the claimed invention. Patent protection does not, in itself, constitute authorization to sell the invention or a product made with the invention. In the context of innovator drugs, including biological products, FDA provides this authorization -- on the basis of submitted data demonstrating safety and efficacy. It is these data that are protected by data exclusivity, which is therefore an incentive to generate and submit the data to the FDA.

The term of data exclusivity runs from the grant of marketing approval for the relevant product. Although data exclusivity runs independently of (and can be concurrent with) patent protection, it is a particularly important incentive for those biological products that would have little or no patent life remaining at the time of market approval. In such cases, data exclusivity may be the only protection that can be relied upon by the innovator to potentially recoup the investment costs incurred in generating the extensive data required to obtain marketing authorization or approval.

Data Exclusivity Provides Certainty

Data exclusivity is a regulatory restriction on when a follow-on product can be approved on the basis of the innovator's data. It is expressed in terms of a defined time period, rather than a specific grant of a right. As such, it is operational automatically as a result of approval of the innovative product. This has many benefits. Perhaps the most significant is that it provides certainty in the marketplace: Data exclusivity would provide an innovator biologic manufacturer with a certain number of years on the market to recoup R&D costs independent of the patent status of the product (although competition from other innovator molecules may of course be immediate). A substantial data exclusivity period may also provides certainty that may allow business planning and support investment in the research program and clinical trials needed to develop new indications over time. The development of such new indications plays a key role in advancing patient care.

Data exclusivity may provide more certainty in the biologics context than will patent protection. Patent litigation generates uncertainty. Although a patent grants exclusive rights to the innovator during its term, those rights are only as effective as the ability to enforce the patent. That, in turn, depends on the nature of the alleged infringer's product, the scope of the patent claims, and the validity and enforceability of the patent claims. Given the inherent unpredictability of the court system, and the fact that the regulatory system developed for FOBs could provide leeway to allow follow-on applicants to attempt to avoid patents, the patent system provides far less certainty for planning than does data exclusivity. Moreover, if one assumes from the FTC's definition of a "biosimilar" that an FOB could be an improved product, i.e., different from the innovator biologic in ways intended to avoid patent protection, data exclusivity would be even more important. During the November 21, 2008, FTC roundtable, participants in Panel III commented that the scope of the claims of biotechnology patents may have changed over time, along with interpretation of the written description and enablement requirements. Any such changes to the interpretation of patent claims for biotechnology patents underscore the uncertain nature of patent protection compared to data exclusivity.

A "Sue or Lose" Mechanism For Participation in Patent Litigation Would Raise Significant Legal and Policy Concerns

During the November 21, 2008, roundtable, there was a robust discussion of the framework for patent dispute resolution that could be implemented prior to marketing of an FOB. One issue raised was enforcement of participation in the patent dispute resolution process. One option that was noted was the concept of "sue or lose", which we understand from the discussion to mean that an innovator (or other patent owner) could lose its right to enforce its patent against the follow-on applicant unless it participated in a pre-approval patent dispute resolution process or enforced the patent precisely as dictated by the regulatory or statutory framework.

Such a concept raises numerous legal and policy problems, and should not be supported. First, it would likely be an unconstitutional taking of property, i.e., patent rights. Second,

a "sue or lose" system could lead to "gamesmanship" on the part of a follow-on applicant. Under such a regime, the patent owner would be forced to decide whether to sue based on the information it obtained from the follow-on applicant. That applicant, in turn, would have an incentive to convince the patent owner not to bring a suit. The dynamic created by such a process could lead to unfair results that reduce incentives for innovation. Third, a "sue or lose" proposal could create artificial incentives to litigate, which would waste time and money and impose burdens that would not be beneficial for the patent or the judicial system. Finally, it would appear unnecessary. For example, the law already provides penalties that could be applicable for not asserting patents early (such as statutes of limitation, laches or estoppel).

A regulatory framework can create strong incentives for patent dispute resolution without a "sue or lose" policy. For example, under the Hatch-Waxman Amendments, an innovator cannot obtain a 30-month stay if it brings suit more than 45 days after receiving notice of a paragraph IV certification from a generic applicant – a significant penalty. However, the innovator can still enforce its patent rights if it sues later, but without the opportunity for a 30-month stay.

Discussion of Key Assumptions and Issues in Determining an Appropriate Period of Data Exclusivity for Biologics

As discussed at the November 21, 2008, FTC roundtable, Grabowski's work established 12.9 to 16.2 years as an appropriate base period of data exclusivity for biologics.[3] The roundtable participants, including Alex Brill, a consultant for Teva Pharmaceuticals, indicated acceptance of Grabowski's overall framework.[4] However, Brill recently has suggested changes to the values of key assumptions, among other changes, to suggest that a shorter data exclusivity period would be appropriate.[5] Grabowski has examined these changes, and the conclusions derived from them are not well-founded.[6]

Alternative Assumptions Posited at the FTC Roundtable Reflect a Computational Error and a Lack of Understanding of Key Aspects of Biologics

At the FTC roundtable, Brill suggested that altering the assumptions in Grabowski's model would result in differing estimates of the expected break-even period. Brill claims that based on his revised assumptions an exclusivity period that permitted FOB entry after 7 years would allow innovators to break even in about 10 years. Grabowski et al. (2008) have since critically reviewed Brill's research and find major flaws in Brill's analysis. Among those that PhRMA believes are relevant to the consideration of competition issues and biologics are the following:

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[3] Grabowski, H. "Follow-On Biologics: Data Exclusivity and the Balance Between Innovation and Competition," *Nature Reviews Drug Discovery*, 2008(7):479-88.
[4] Brill, A. "Proper Duration of Data Exclusivity for Generic Biologics: A Critique," November 2008.
[5] *Id.*
[6] Grabowski, H., Long, G., and Mortimer, R. Data Exclusivity Periods for Biologics: An Update of Prior Analysis and Response to Recent Critiques. Duke University, Department of Economics Working Paper, No. 2008-10, December 22, 2008.

- **A computational error in incorporating the Congressional Budget Office's (CBO's) scoring assumptions, which when corrected does not support the 7-year data exclusivity period that Brill recommends.** Brill assumes that based on FOB entry the innovator biologic will be priced at a discount, but fails to reduce the level of assumed innovator biologic sales to take account of this expected discount. Correcting the mathematical error would mean that a break-even period would not be achieved in the first 50 years that a biologic is on the market, based on a 11.5% cost of capital and a base data exclusivity period of 7 years.[7] Brill also excludes sales for the biologics comprising the bottom quintile as measured by sales—Grabowski et al. state that this arbitrary exclusion serves to bias break-even lifetimes downward.

- **Unrealistic costs of capital and inaccurate average contribution margins.**[8] Brill bases his result on an unrealistically low cost of capital of 10%. The current literature, together with accepted published industry metrics, find real costs of capital range between 13.25% and 15% (Golec and Vernon, 2007; Ibbotston's Annual Cost of Capital Yearbook, 2008).[9] Brill also fails to acknowledge that a large sub-sample of private and public biotechnology firms do not yet have marketed products. These firms, which rely on venture funding and financial instruments, are likely to face even higher costs of capital, particularly given the current economic situation. For both of these reasons, Brill's calculation of an appropriate data exclusivity period is unrealistically low.

  Brill suggests a contribution margin of 60%. According to Grabowski et al., this does not accurately reflect publicly available information on the experience of firms in this sector. Brill states that he relies on results from six of the most successful biotech firms, yet even among those firms, margins can range from 43.4% to 63.7%. As discussed by Grabowski et al. (2008) adding data on two additional firms to Brill's estimate further increases the variability in contribution margins. Moreover, this small, upwardly biased sample puts inordinate weight on two of the more successful biotech firms.

[7] Grabowski, H., Long, G., and Mortimer, R. Data Exclusivity Periods for Biologics: An Update of Prior Analysis and Response to Recent Critiques. Duke University, Department of Economics Working Paper, No. 2008-10, December 22, 2008.

[8] As defined in Grabowski et al. (2008): Cost of capital is the annual rate of return that an investor would require on average in order to make a given investment. In the case of biologics, this accounts for the risks associated with potential failure to develop or market the biologic candidate product successfully. Contribution margin is a measure of how much a company earns in gross sales, after subtracting costs for labor and materials (cost of goods sold), and selling, general and administrative expenses.

[9] Golec, J., and Vernon, J. "Financial Risk in the Biotechnology Industry," *Journal of Applied Economics and Health Policy*, forthcoming; also NBER Working Paper # 13604, November 2007. Ibbotston, *Cost of Capital Yearbook*, Morningstar, 2008.

FTC Graph and Discussion of "Cash-Flow Curves for Branded Biologic" Does Not Reflect Grabowski's Framework or Current Analysis Regarding FOB Entry

We also would like to call the FTC's attention to Grabowski's review of the chart presented by the FTC and the assumptions underlying the chart. The FTC shared a graph modeled on Figure 6 of Grabowski's *Nature* article, which the FTC entitled "Cash-Flow Curves for Branded Biologic." The representation does not accurately portray competition in the biologics sector and should not be relied upon in framing recommendations.

As noted in the appendix to Grabowski's letter to the FTC dated December 22, 2008, this graph does not accurately reflect Grabowski's model. First, the Grabowski model did not envision an outcome corresponding to the line representing "w/o competition." This is because he states brand biologics currently face and will continue to face significant competition from other branded biologics as well as other forms of treatment. Innovator-to-innovator competition has a material effect in the marketplace and needs to be recognized in the FTC's analysis, including analysis related to FOBs.

Second, Grabowski's model did not include the line corresponding to the term used by the FTC of "w/biogeneric FOBs." Based on adjustments for these issues, Grabowski concludes in his letter to the FTC "at the time of 'FOB entry,' the line in Figure 1 corresponding to 'w/biosimilar FOBs' should meet with the 'w/branded competition' line, not the 'w/o competition' line. This would result in a substantial shift down in the line representing biosimilar entry in the FTC graph."[10]

Conclusion

Given the novel therapies that have been developed that address some of the most pressing diseases and conditions, the potential of the robust biologics pipeline, the potential for post-approval research to yield new indications for biologics in vastly different diseases and conditions, and the more uncertain application of patent protection to biologics that are similar to (rather than the same as) the innovator, it is critical that a base period of data exclusivity be established of at least 14 years with significant exclusivity for new indications.

[10] Grabowski, H. Letter to the FTC Re: Emerging Health Care Competition and Consumer Issues – Comment, Project No. P083901, December 22, 2008.