May 2, 2008

The Honorable Frank Pallone, Jr.
Chairman, Committee on Energy & Commerce, Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Nathan Deal
Ranking Member, Committee on Energy & Commerce, Subcommittee on Health
2133 Rayburn House Office Building
Washington, DC 20515

Dear Chairman Pallone and Ranking Member Deal:

The National Venture Capital Association (NVCA) appreciates the opportunity to respond to the questions put forth in your April 3, 2008 letter regarding follow-on biologics (FOBs). NVCA is the premier trade association that represents the U.S. venture capital industry. It is a member-based organization, consisting of venture capital firms that manage pools of risk equity capital dedicated to be invested in high growth, entrepreneurial companies.

NVCA's mission is to foster greater understanding of the importance of venture capital to the U.S. economy and support entrepreneurial activity and innovation. Given the nature of our membership, NVCA has responded to the questions related to the impact a follow-on biologics pathway would have on venture capital investing in innovative biotechnology companies.

Please find enclosed our responses to the relevant April 3, 2008 questions.

Sincerely,

Mark G. Heesen
President
National Venture Capital Association
1655 North Fort Meyer Drive, Suite 850
Arlington, VA 22209

cc: The Honorable John D. Dingell, Chairman, Committee on Energy & Commerce
The Honorable Joe Barton, Ranking Member, Committee on Energy & Commerce

Incentives/Exclusivity/Investment

1. *Should reference product manufacturers be given a period of exclusive marketing in addition to the patent-term restoration already provided to them in Hatch-Waxman? If yes, how much is necessary to provide adequate incentives for innovation without unnecessarily delaying competition?*

   It is critical for innovator companies to be afforded an adequate period of data exclusivity in addition to patent-term restoration provided under Hatch-Waxman. It is also important to distinguish between market exclusivity and data exclusivity. During a period of data exclusivity, a follow-on biologic (FOB) competitor may not rely on the data from the reference innovator product to show the safety and efficacy of the FOB. Competitor products may, however, generate their own safety and efficacy data and receive FDA approval on the basis of that data during this timeframe. Market exclusivity, in contrast, is a period during which the FDA may not approve an FOB similar to the reference listed product for the same indication as the reference innovator product.

   Relying upon this distinction, NVCA and others, including the Biotechnology Industry Organization (BIO) have determined that at least 14 years is an appropriate period of data exclusivity (not market exclusivity) which will ensure continued incentives for innovation without unnecessarily delaying competition. As explained more thoroughly below, data exclusivity in addition to patent-term restoration is essential, because under the current suggested approval frameworks, FOBs are required to be "similar" to innovator products, but not identical. It is thus possible for an FOB manufacturer to develop a product that is similar enough for approval purposes but at the same time cleverly designed to avoid infringing the innovator's patents.

2. *What types of assessments have been conducted to determine the minimum term of exclusivity that will enable a robust industry for discovery and development of biologics?*

   Several studies have been conducted which discuss the required minimum term of data exclusivity to secure a robust innovator biotech industry, including:

   - Henry Grabowski, *Data Exclusivity for New Biological Entities,* Duke University Department of Economics Working Paper, June 2007 (suggesting a "substantial period" of data exclusivity is required of between 12-16 years for innovator biologics).[1]

   - Bruce Manheim, Patricia Granaham, and Kenneth Dow, *Follow-On Biologics: Ensuring Continued Innovation in the Biotechnology Industry*, Health Affairs,

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

March/April 2006 (discussing the inability of patents to protect innovator biologics, and suggesting at least a 12 year period of data exclusivity is necessary).[2]

- The European Union system provides up to 11 years of exclusivity for innovator compounds.

The Grabowski and Manheim *et al.* studies both conclude that data exclusivity is an important form of intellectual property protection for innovators and is critical in addition to patent protection. "Without an…exclusivity period, there would be little incentive to invest in developing and marketing new product candidates with few remaining years of patent protection or with uncertain forms of protection. In addition, newly approved products with substantial commercial sales would be exposed immediately to legal risks associated with patent challenges and early generic entry."[3]

3. *How should exclusivity modifications to approved products be addressed?*

Under the Hatch-Waxman Act of 1984, 21 U.S.C. 355(j)(5), innovator pharmaceuticals receive an additional 3 years of exclusivity for an approved new indication if the NDA holder files an NDA supplement for a new indication with new clinical investigations conducted (or sponsored) by the NDA holder which are "essential for approval." Similarly, approval of new indications for innovator biologics (in the form of supplemental BLAs) should receive an additional period of data exclusivity.

In addition, second-generation and modified innovative biotechnology products must go through the same rigorous FDA approval standards as apply to the approval of the initial innovator product. Accordingly, these second-generation and modified products should receive the full period of data exclusivity upon approval.

4. *What benefits do innovator firms obtain from data exclusivity, and how is this protection different from patent protection?*

Data exclusivity and patent protection are complementary forms of intellectual property protection. The patent system provides a framework for reward based on novelty, utility, and non-obviousness. The patent is generally applied for and received in pre-clinical stages, before the most costly and riskiest investments in the product have been made. The patent therefore protects the earliest forms of the compound and manufacturing processes. The patent protection may expire before, or shortly after, approval for marketing of the product and thus may not afford the patent holder adequate exclusive market time to achieve a return on investment. Furthermore,

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[2] Bruce Manheim, Patricia Granaham, and Kenneth Dow, *Follow-On Biologics: Ensuring Continued Innovation in the Biotechnology Industry*, Health Affairs (March/April 2006) *available at* http://content.healthaffairs.org/cgi/content/abstract/25/2/394.

[3] Grabowski at 3.

securing patent rights may require litigation. Data exclusivity, on the other hand, is designed to reward innovators for the expensive, high risk, long-term investment the innovator must make in proving safety and efficacy of the product to win FDA approval which can often add up to $1 billion. The data exclusivity provides the innovator an opportunity to earn a return on investment in the product, and thus encourages continued investment in innovative biologics. Data exclusivity is automatic and not subject to litigation.

It is again important at this point to distinguish between market and data exclusivity. Data exclusivity, in contrast to market exclusivity, does not prevent competition to innovator biologics. During the period of data exclusivity, a competitor is free to develop a similar product and gain FDA approval of that product based on rigorous clinical studies and safety and efficacy data. Data exclusivity only protects against the competitor relying upon the proprietary safety and efficacy data developed to gain FDA approval of the innovator product, which can cost up to $1 billion dollars to generate, as noted above. Again, the period of data exclusivity is intended to provide the innovator with the opportunity to earn a return on investment in the product, not to stifle legitimate competition for those that choose to engage in the full complement of clinical trials to gain approval of a product.

5. *Do you think biologics should receive a different period of data exclusivity than drugs? Why or why not?*

Under the 1984 Hatch-Waxman Act, Congress established a period of data exclusivity for new drugs, in addition to provisions for patent restoration (which apply to both drugs and biologics) to make up for patent time lost during the FDA approval process. The patent restoration term may not be more than five years under Hatch-Waxman, but can result in total patent life after approval of up to 14 years. Congress has thus previously determined that a period of up to 14 years of market protection, whether in the form of data exclusivity or patent protection is appropriate for new drugs and biologics. In addition, in 1998, CBO found that new molecular entities, on average, are marketed for 13 ½ years before the entry of generic competition.[4] As discussed above, the patent system is inadequate to protect innovator biologics, accordingly, and consistent with the Congressional determinations in 1984, NVCA believes that 14 years of data exclusivity is necessary to protect innovator biologics in the same manner that innovator small molecule drugs are afforded exclusivity to achieve a return on investment. This is especially true because it has been found that the "break even" point for a biologic occurs only after it has been on the market for 12.9-16.2 years, thus necessitating a substantial period of data exclusivity.[5]

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[4] CBO, How Increased Competition from Generic Drugs Has Affected Prices and Returns in the Pharmaceutical Industry (July 1998), *available at* http://www.cbo.gov/ftpdocs/6xx/doc655/pharm.pdf.

[5] Grabowski at 3.

When creating a pathway for approval of FOBs, it is important to remember the significant differences between small molecule drugs and the biotech industry. When the Hatch-Waxman Act was passed in 1984, virtually all small molecule drugs were discovered and produced by large pharmaceutical companies which had been in existence for years and had significant portfolios of existing products which generated large quantities of stable cash flow. It was this cash flow which was the primary, if not the exclusive, source of capital for research for new drug discovery.

The biotech industry, in contrast, is still an emerging industry which was largely created by the venture capital (VC) community within the last 20 years. Virtually all major discovery and innovation in biologics is still funded today by the venture capital industry, in the form of research and development startup companies with no existing products and no stable cash flow. Venture capital funding is extremely unstable and risk averse for many reasons: it is diversified, and under the control of the VC fund manager who is accountable to his investors, pension funds and endowment fund managers who provide VCs with funding. At the slightest hint of lost return on investment, VCs will redirect their dollars to assure the best risk adjusted returns. FOB legislation without a minimum of 14 years of data exclusivity will adversely affect this risk/reward equation and drive VCs away from funding development of biotechnology. Without VC funding, the biotechnology industry will collapse.

For example, if FOB competitors may rely on the innovator data immediately after approval of the innovator product, and therefore the FOB may come to market essentially at the same time as the innovator product, the value of the innovator product is so reduced during the years in which it is intended to generate a return on the initial investment, that it will drive away initial VC investment. A 14 year period of data exclusivity, however, prevents this devaluation and protects VC investment in the biotech industry. This is especially important when one considers that VCs invest in an entire portfolio of early stage companies, many of whom are developing products which will never make it to market. Thus the successful products must generate a sufficient return on investment to cover the costs of investing in those products which are never commercialized.

6. *What policy considerations justify that patent protections be the principal form of intellectual property protection for biologics and drugs?*

NVCA does not believe that patent protection should be the principal form of intellectual property protection for biologics and drugs. As we discussed above, data exclusivity periods are equally important as an incentive to encourage continued investment in innovative biotechnology companies. Patents reward the initial discovery, data exclusivity protects the enormous investment in proving the product is safe and effective to gain FDA approval and bring the product to clinical fruition and patients in need.

7. *If a follow-on biologics pathway was created without additional incentives—beyond existing patent protections—for continued innovation, how would innovation be affected*

either positively or negatively? What additional incentives, if any, would be necessary to support continued research and innovation, including at American universities?

As we noted above, the patent system is inadequate in the protection it affords innovator biologics. In fact, it creates incentives for follow on biologic manufacturers to cleverly design around innovator patents such that the product will be similar enough to gain approval based on the safety and efficacy data of the innovator product, but will not infringe on the innovator patents. If a follow-on biologics pathway without additional incentives beyond current patent protections were enacted, this would have serious negative consequences for research and development of innovative biotechnology products. To ensure a regulatory framework which supports the development of life-saving new innovative biological products, Congress must provide innovators a period of data exclusivity sufficient to achieve an adequate, risk-adjusted return on their investments in drug development. This period must account for the nearly $1 billion invested in bringing a new biologic to market, as well as the reality that the majority of approved drugs do not yield a return on investment sufficient to cover research and development costs, not to mention the investment in biologics that never make it to market.

Without the certainty of a risk adjusted return on investment provided by an adequate period of data exclusivity, large companies will be reluctant to invest in biotechnology inventions, and the bulk of the biotech industry—smaller biotech companies—will find themselves unable to raise sufficient capital from NVCA members and in the public markets to support the cost, and justify the risk, of attempting to commercialize cutting edge biotech therapies. Patients, physicians, and industry will all suffer alike.

Economic Impact

1. *How much savings would a generic biologics pathway create and in what period (taking into account the time it will take to implement any new law, and the time needed by manufacturers to develop products and submit applications?) Please describe the evidence on which you base your answer.*

   It has been very difficult to estimate the cost savings from implementation of a follow on biologics pathway for several reasons, including difficulty in estimating the "market penetration" of follow on biologics in light of uncertainty as to whether a follow on product will be interchangeable with the innovator reference product. Furthermore, the clinical requirements necessary for approval of a follow on biologic have not been fully identified, and thus the cost-savings in developing and securing approval of a follow on biologic are not clear. In addition, the Congressional Budget Office has not scored any of the current legislative proposals. A 2007 study by Express Scripts and PCMA estimated approximately $71 billion in savings over 10 years post-enactment of an FOB

pathway.[6] A study by Robert Shapiro, former Under Secretary of Commerce in the Clinton Administration suggested $67 billion to $108 billion in savings over 10 years.[7]

However, BIO has identified serious flaws with the methodology and assumptions of the Express Scripts Study, including false assumptions about patent expiration dates, calculation errors which could overestimate savings by as much as 40%, inconsistent allegations related to interchangeability, and questionable estimation of market penetration rates for follow-on biologics. These flaws undermine the savings suggested by the Express Scripts Study.[8]

In short, it is almost impossible to estimate true cost savings which will be realized by creation and implementation of an FOB pathway. We do know that production costs for a biological product can be between $250-$450 million and that the costs of materials used to produce a biologic are 20 to 100 times more expensive than materials used to produce a small molecule compound. We can infer that the savings from FOBs will not be as dramatic as the savings realized from Hatch-Waxman permitted generic small molecule competition.[9]

2. *Can you provide an estimate of the amount of money your agency/company will spend on biological products over the next 10 years, in absolute dollars, and as a percentage of total program/plan spending? If FOBs, approved by FDA as comparable to the brand name product were available, what is your estimate for the cost of the reference product and the follow-on product?*

   Venture capital investment in the life science space continues to grow and is 31% of all venture capital investment. In 2007, over $5 billion was invested in biotech start up companies which is an all time record for annual venture capital investment.

3. *What implications would a follow-on biologics pathway have on U.S. economic competitiveness and leadership in protection of intellectual property rights?*

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[6] Engel and Novitt, Potential Savings That Might Be Realized, A Report to PCMA (Jan. 2, 2007), *available at* http://www.pcmanet.org; Express Scripts, Potential Savings of Biogenerics in the United States (Feb. 2007), *available at* http://www.express-scripts.com.

[7] Robert J. Shapiro, The Potential American Market for Generic Biological Treatments and the Associated Cost Savings (Feb. 2008), *available at* http://www.insmed.com/PDF/Biogeneric_Savings.pdf.

[8] BIO, The Inflated Projections of Potential Cost Savings from Follow-On Biologics: An Analysis of the Express Scripts and Engel & Novitt Reports (May 207), *available at* http://www.howrey.com/files/News/6efa58d8-75a8-49e0-ac0f-512f45769c77/Presentation/NewsAttachment/13ce02b8-b57f-4f2f-b682-4d79c22d578a/Biologics%20White%20Paper%205-2-07.pdf.

[9] For more information, *see* Henry Grabowski et al., *The Effect on Federal Spending of Legislation Creating a Regulatory Framework for Follow-on Biologics: Key Issues and Assumption*, White Paper (August 2007), *available at* http://bio.org/healthcare/followonbkg/Federal_Spending_of_followonbkg200709.pdf; *see also* Avalere Health Modeling Federal Cost Savings from Follow-on Biologics, *available at* http://www.avalerehealth.net/research/docs/Follow_on_Biologic_Modeling_Framework.pdf.

Failure to enact a follow-on biologics pathway without adequate protection for innovator biotech companies, including both patent protection and adequate data exclusivity would be devastating for U.S. economic competitiveness and leadership in protection of IP rights. The U.S. has traditionally been a leader in protecting innovator companies, which has contributed to our status as a global leader in biomedical research. For example, under the 1984 Hatch-Waxman Act, a fair compromise between generic reliance on innovator data (to allow generics to more quickly reach the market) in exchange for reasonable patent restoration and innovator data exclusivity was brokered. This compromise fostered continued investment in innovative pharmaceutical research and development, while still allowing patients access to generic versions of pharmaceuticals. Without patent protections and data exclusivity to incentivize continued investment in the innovative pharmaceutical research, the U.S. would not have remained globally competitive in pharmaceutical research and development. Similarly, we must afford innovative biotechnology companies with same patent and data exclusivity protections to allow the U.S. to remain economically competitive in biomedical research. A great deal of the generic industry is located offshore. Without these incentives, the creation of an FOB pathway will shift a substantial number of biotech jobs from the VC backed U.S. innovators to these offshore based generic companies, dampening the U.S. industry and our leadership in biomedical research.

4. *What implication does the treatment of patents in the context of a follow-on biologics approval pathway have for the future of biotechnological innovation?*

Adequate patent protection and a clear framework for resolution of patent disputes is critical for the future of biotechnological innovation. Venture capital investing hit an all time high in 2007 with $29.4 billion invested. The Life Sciences sector, which includes biotechnology and medical devices, accounted for 31% of VC money invested, the largest investment sector in 2007. Historically, venture capital investment has been the backbone of the biotechnology industry and the industry has continued to be dependent on VC funding given the significant risk and cost it takes to bring a biotech drug to market (see also Incentives/Exclusivity/Investment question 5). This is particularly true for start-up companies who cannot rely on revenue from marketed biologics to fund their research and development pipeline, but instead must seek out VC funding.

Given the high failure rates and enormous costs of bringing a biologic to market, companies and their investors look to successful drugs to reap sufficient revenue to compensate for both the research and development costs of the successful drug and the expense of failed biologics. In this landscape, intellectual property protection is critical to the start-up biotech company and to its VC investors — without assurance that there exists adequate market exclusivity to allow a successful biologic product to earn adequate profits, VC investors have no guarantee of a return on investment, and will be hesitant to direct their funds to the Life Sciences sector. For many early stage biotech companies, intellectual property is the only asset of value to the company. Thus, to ensure continued biotechnology innovation, adequate patent protections and a clear

framework for resolving patent disputes is essential to ensuring continued VC investment in the industry.

5. *If a follow-on biologics pathway was created without ample incentives for innovators to continue to innovate, what would the effect be for future research, current clinical programs, and universities?*

   If an FOB pathway was created without ample incentives for innovators to continue to innovate, the effect on research, clinical programs, universities and patient care would be disastrous. As we have noted above, adequate, well-defined incentives for innovation, in the form of a substantial period of data exclusivity for innovator products and a clear framework for resolving patent disputes, are critical for ensuring continued investment in the biotech sector. Failure to invest in the biotech sector destroys the capacity for research and development of life-saving new biologics, which negatively impacts clinical patient care. Furthermore, if there is no funding available for the biotechnology industry, via technology transfer programs and other licensing arrangements, to build on basic discoveries made by university based researchers, there is reduced incentive for these university based academics to invest the time and energy in the initial, basic research.

European Model

2. *Legislation passed by the European Parliament encourages innovation by providing 10 years of market exclusivity, extendable to 11 years for select new indications of use, for innovator biologics, thereby preventing the introduction of FOBs during that period. Should the U.S. be guided by treatment of drugs and biologics in the EU with respect to exclusivity periods?*

   The European Union model is a start with regard to data exclusivity periods. However, at least 14 years of data exclusivity is a more appropriate time frame for U.S. innovator biologics, given the differences between the U.S. and European markets. For example, the U.S. per capita biotech R&D expenditures are 574% higher than the EU's per capita biotech R&D expenditures. The U.S. is the global leader in biomedical research. To maintain that status, and to continue to attract high quality researchers to U.S. academic and industry institutions, it is critical to maintain incentives to engage in innovative biotechnology research. As we noted above, prominent U.S. economists have found that between 12-16 years of data exclusivity is necessary to ensure continued investment in the innovative biotechnology industry. To ensure an adequate return on the nearly $1 billion investment required to bring a new biologic to market, it is critical that Congress include appropriate periods of data exclusivity. The European time period of 11 years will not suffice in the U.S. market.

3. *If the U.S. adopts incentives for innovation in biologics that are substantially less than those afforded in Europe, what could the potential effect be on U.S competitiveness?*

As we addressed above, enacting a follow-on biologics pathway without adequate protection for innovator biotech companies, including both patent protection and adequate data exclusivity would be devastating for U.S. economic competitiveness.

A PriceWaterHouseCoopers/NVCA study from 2006 estimated that VCs invested $25.5 billion in 2006, 28% of which was invested in the Life Sciences Sector (the largest investment sector that year).[10] The U.S. has been a leader in biomedical research, due to both NIH funding and VC investing in Life Sciences. Without adequate data exclusivity, robust patent protection, and a clear framework for resolving patent disputes, VCs will not be willing to risk continued investment in biotechnology. These incentives are essential to ensuring a risk adjusted return on investment. With a decline in VC investing, the biotech industry will flounder, and the U.S. will lose its competitive edge as the global leader in biomedical research. We are already losing a generation of talented scientists in academia due to chronic underfunding of the NIH—the loss of VC investing in the biotech industry will only worsen this problem as highly qualified researchers move overseas or abandon science altogether and choose different careers.

[10] PriceWaterhouseCoopers/NVCA Study, *available at* http://www.nvca.org/pdf/06Q4MTPRnewsFINAL.pdf.