March 26, 2007

The Honorable Henry A. Waxman, Chairman
The Honorable Thomas M. Davis, III, Ranking Member
Committee on Oversight and Government Reform
U.S. House of Representatives
2157 Rayburn House Office Building
Washington, D.C. 20515

Dear Chairman Waxman and Ranking Member Davis:

The Biotechnology Industry Organization (BIO) is writing with respect to your Committee hearing on "Safe and Affordable Biotech Drugs—The Need for a Generic Pathway," to be held March 26, 2007. We respectfully request that this letter be submitted to the record for that proceeding.

We are writing to identify and describe the following key issues related to follow-on biologics: 1) our continued opposition to the "Access to Life-Saving Medicine Act" (H.R. 1038); 2) the importance of ensuring a thoughtful, deliberative process for considering the establishment of any regulatory pathway for follow-on biologics; 3) our analysis of prior studies by Pharmaceutical Care Management Association (PCMA) and Express Scripts that substantially overestimate potential savings in health care costs that might result from the establishment of a pathway for regulatory approval of follow-on biologics; and finally to 4) respond to several points raised in a Dear Colleague letter dated March 22, 2007. We will discuss each of these issues in more detail below.

First, BIO members work on the forefront of medical advancement, developing innovative biological products that have revolutionized the treatment of diseases, including cancer, heart disease, infections, arthritis, and multiple sclerosis. In order to ensure a future of continued innovation by the biotechnology industry, it is essential that Congressional deliberations about developing an approval process for follow-on biological products be driven by responsible science, with a focus on protecting patient safety and preserving incentives to ensure innovative, safe and effective biopharmaceuticals can reach patients in a timely manner. In addition to ensuring patient safety, any follow-on biologics pathway created by the Congress must preserve incentives for research and innovation by ensuring protections for intellectual property and by providing data exclusivity for innovative therapies and cures.

Unfortunately, H.R. 1038, which proposes to create such a pathway, is deeply flawed in all three respects. The bill raises numerous patient safety concerns. It would eviscerate incentives to develop life-saving new medicines through its one-sided alteration of long-standing patent law in ways that favor follow-on biologics' manufacturers, who would be

able to restrict and infringe the intellectual property rights of various parties including innovative biotechnology companies. And it lacks any data exclusivity for innovative biologics. Data exclusivity provisions have served as an incentive for innovation under Hatch-Waxman and are part of the European system for regulating "biosimilars" (i.e., follow-on biologics). But this legislation contains no prohibition on the FDA approving a follow-on product relying on innovator data immediately following approval of the reference product. Devaluing property rights and the absence of data exclusivity will reduce incentives for the investment needed for a strong, vibrant pioneer biologic industry upon which any follow-on market would wholly depend.

Second, we urge Congress to consider action relating to establishing a statutory pathway for approving follow-on biologics independent of the reauthorization of the Prescription Drug User Fee Act (PDUFA). Before a framework for follow-on biologics can be established, Congress must carefully consider and resolve complex scientific, legal, and economic issues. Meanwhile, it is important that Congress complete the PDUFA reauthorization in a timely manner. Although PDUFA formally expires on September 30, 2007, reauthorization needs to occur earlier this year to avoid potential delays in review of innovative new medicines. We believe that attaching follow-on biologics legislation to PDUFA would jeopardize reauthorization of the user fee program to the detriment of patients waiting for new therapies, FDA's internal scientific capabilities, and biomedical innovation.

Third, based on BIO's analysis of recently conducted studies relating to potential cost savings from follow-on biologics, we believe it is unlikely that follow-on biologics will produce anything close to the savings recently claimed in these studies published by PCMA and Express Scripts. These reports contain serious flaws including assumptions that raise serious questions about their validity. These flaws include:

- Assumptions about patent expirations that are inconsistent with credible analyst reports seriously call into question more than $40 billion of the alleged savings cited by the Express Scripts study;
- Calculation errors in the PCMA study result in an overestimation of savings of 40 percent, even before examining its other assumptions;
- Internally inconsistent allegations of interchangeability in the Express Scripts study call into question an additional $13.8 billion in alleged potential savings;
- Presuming that a pathway under one law would generate savings for products approved under another law calls into question over $17 billion in additional alleged savings in the Express Scripts study;
- Market penetration rates for follow-on biologics incorrectly modeled on generic drug experience are inconsistent with credible published analyses;
- Calculations based on determinations of interchangeability that include presumption of savings beginning in 2007 are unsupported in both studies.

As a result of numerous flawed assumptions and lack of any credible evidence to support these alleged savings, we believe these studies should be rejected as unreliable. In addition, a recent study from the consulting firm Avalere Health projects that federal

health care programs would save 95% percent less over the next decade from follow-on biologics than the projected savings of $71 billion cited by Express Scripts. BIO's detailed analysis of these studies is available at: http://www.bio.org/healthcare/followon/20070222.pdf

Finally, the attachment to the Dear Colleague dated March 22, 2007, made six assertions, which BIO wishes to correct:

Assertion 1: *Under H.R. 1083, follow-on biologics "must not only be safe, pure, and potent, but also safe, pure and potent to exactly the same degree as the brand name product."*

BIO wholeheartedly agrees that this is the right standard for FDA approval of follow-on biologics—unfortunately, the proposed bill lacks any such requirement. The bill instead provides that:

> "Any person … may submit an application under this paragraph for a biological product that differs from, or incorporates a change to, the reference product … *including a difference in safety, purity, or potency*, so long as the application contains sufficient information to establish the safety, purity, and potency of the biological product *relative to* the reference product…" (New proposed Section 351(k)(2) of the Public Health Service Act (PHSA)) (emphases added)

Further, while the bill defines "comparability" in a way that purportedly requires the "absence of clinically meaningful differences between the two products," it adds language that ties this absence of differences to only those differences that can be detected based upon a statutorily limited pool of data: non-clinical studies, and—only if "necessary"—clinical studies that must "avoid duplicative or unethical clinical testing." Similarly, the "Dear Colleague" attachment asserts that, with respect to meeting approval standards, "if the only way to show this is to do as many, or more, studies than were done on the brand name product, the Access to Life-Saving Medicine Act authorizes FDA to require them." Again, the proposed bill does not include any language to this effect, and instead attempts to limit FDA's ability to require clinical testing. BIO also disagrees with the notion that FDA should be permitted to require these studies only if they are "the only way" to establish safety and effectiveness. BIO believes that FDA should be able to require clinical studies or trials if they are *a better way* to ensure patient safety.

Assertion 2: *"[T]he current statute gives the FDA complete discretion to decide whether clinical trials are necessary at all for the approval of a brand-name biotech drug—and in some cases has not required them."*

To the contrary, the Federal Food, Drug and Cosmetic Act (FFDCA) states that a new drug application shall include "full reports of investigations" which have been made to show whether or not such drug is safe for use and whether such drug is effective in use, and that an application shall not be approved without "adequate and well-controlled investigations, including clinical investigations" supporting the application. (FFDCA Sections 505(b)(1) and (d)). These same standards have been applied to biologics approved under the FFDCA or the PHSA. In fact, it is FDA's longstanding and

consistent policy to require clinical trials for approval of all new drugs and biologics, and we do not know of examples of new biologics that have been or would be approved without results of clinical trials, except in those extraordinarily rare cases where it may be unethical or not feasible to conduct them (*i.e.*, with certain bioterrorism countermeasures).

Assertion 3: *H.R. 1038 "authorizes the FDA to impose exactly the same post-market study conditions on a copy of a biological product as on the brand-name product."*

To the contrary, H.R. 1038 does not impose the same post-marketing study conditions on the follow-on sponsor; in fact, the standard is narrower:

> "If the Secretary has agreed with the sponsor of the reference product that the sponsor shall conduct one or more postmarketing safety studies, the applicant *may agree* with the Secretary to conduct a similar post marketing safety study or studies *upon a reasonable showing that such study or studies would provide relevant information not available from the studies on the reference product*. The Secretary shall not, as a condition of approval, propose any additional postmarketing studies." (New proposed Section 351(k)(wrong cite??) of the PHSA) (emphases added)

Rather than imposing a narrower standard for the follow-on product, BIO believes that reasonable protection of public health would, in fact, demand that the requirements be broader, given that, under this bill, a follow-on biologic that is merely comparable or even non-comparable to an innovator product could be approved for marketing utilizing an abbreviated approval process.

Assertion 4: *"Thus, using the [FDA] Comparability Protocol policy, the industry has demonstrated that, for many biotech drugs… it is possible to manufacture an interchangeable product in multiple different ways, on multiple different sites and/or using multiple different sources of raw materials."*

FDA's comparability guidance has little or no relevance to follow-on biologics. It applies to changes in an already approved product (which was approved based on a full set of investigations and data), and as to which the sponsor has full details of the manufacturing process – and thus can evaluate the potential effects of a specific, discrete change in the process. As FDA's Comparability Guidance states: "Knowledge of the process involved in the manufacture of the product is an integral component in determining the design of an appropriate comparability assessment program." The experience of a biological products manufacturer with manufacturing a particular product provides the context within which "comparability protocols"—as that term is currently used by FDA—can legitimately be used.

The follow-on manufacturer, in contrast, proposes to use a different master cell line, different manufacturing facility, and different manufacturing process, and importantly does not even know how big the differences are. In these circumstances, a "comparability" determination, as contemplated by the FDA guidance, cannot be made. Indeed, clinical trials likely would be required for changes of such a magnitude, even in situations where a manufacturer was making a different version of its own product..

Assertion 5: *"The FDA has approved abbreviated applications (with no or limited clinical studies) for copies of these products despite the fact that the new manufacturers use different manufacturing processes than are used to make the brand name products."*

The products listed in the "Dear Colleague" attachment were all approved under Section 505 of the FFDCA, not under the PHSA, and H.R. 1038 would apply only to the latter category of biologics. Furthermore, all of them did require clinical studies prior to marketing. In the case of Omnitrope, and as FDA has made clear in public documents, Sandoz submitted extensive original clinical trial data supporting approval of Omnitrope. In fact, Sandoz submitted the results from three sequential, multicenter, phase 3 pivotal trials, and also submitted the results from a separate multicenter phase 3 clinical trial with its safety update to the application.

Assertion 6: *The U.S. should not adopt the European practice of requiring an open and transparent public process for establishing the scientific requirements for approval of follow-on biologics.*

As Europe has recognized, the scientifically complex field of follow-on biologics demands a deliberative and thorough public process by which the scientific community and relevant experts can weigh in on the appropriate requirements for approval of such products. And as European regulators also have recognized, the complexities of reviewing biosimilars require a process for establishing data requirements that is different from, and more extensive then, what would be necessary for review of innovator products. In contrast, H.R. 1083 would permit FDA and follow-on manufacturers to determine these requirements behind closed doors and without needed transparency.

BIO represents more than 1,100 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and 31 other nations. On behalf our members, we appreciate your consideration of our views and look forward to a continuing dialogue on this important topic.

Sincerely,

James C. Greenwood
President and CEO