PhRMA

November 12, 2004

VIA HAND DELIVERY

Division of Dockets Management
U.S. Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments of the Pharmaceutical Research and Manufacturers of America in Support of Citizen Petition Submitted by Genentech Inc. (Docket No. 2004P-0171)

Ladies and Gentlemen:

The Pharmaceutical Research and Manufacturers of America (PhRMA) submits these comments in support of the Citizen Petition submitted by Genentech Inc. The petition requests, in part, that FDA refrain from approving a biotechnology-derived biologic product based on agency findings of safety and effectiveness for a product that relies on trade secret and confidential commercial data and information, and that FDA refrain from issuing a draft guidance document on similarity or sameness of proteins that relies on trade secret and confidential commercial data and information. For the reasons that follow, PhRMA supports the petition and urges FDA to enhance and expand the dialogue with stakeholders begun with the September public stakeholder workshop in order to work through the fundamental issues of patient safety, science, law and public policy that are raised by follow-on biologic products.[1]

In testimony before the Senate Judiciary Committee, Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of FDA, stated that the agency intended to open a dialogue with the public on the issues presented by follow-on biologics.[2] Specifically, Dr. Crawford indicated that the agency would conduct "a public process to examine the scientific, and related issues regarding follow-on biologics," to ensure that "scientific considerations and issues related to [FDA] authority are fully examined and that all interested parties have an opportunity for

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[1] As used in this document, the term "follow-on biologic" means a biological product for which FDA approval would rely in part on the safety and effectiveness of similar already-approved products developed by other, unrelated manufacturers.

[2] *The Law of Biologic Medicine, 2004: Hearing Before the Senate Comm. on the Judiciary*, 108th Cong., 2d Sess. at 135 (June 23, 2004)(hereinafter referred to as "Senate Comm. Tr.") (prepared statement of Lester M. Crawford, D.V.M., Ph.D., Acting Commissioner of Food and Drugs) (hereinafter referred to as "Statement of Dr. Crawford").

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input."[3] PhRMA strongly supports this proposed approach, but believes that FDA also needs to consider additional relevant issues.

PhRMA is a voluntary, nonprofit association representing the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, healthier and more productive lives. This year alone, PhRMA's member companies invested more than $30 billion in discovering and developing new medicines, including complex therapeutic proteins and other biotechnology products. These companies are the source of nearly all new drugs and biologics that are discovered, made and used throughout the world.

Summary Of Argument

The creation of a new or different pathway for the approval of follow-on biologics raises fundamental questions of patient safety, science, law, and policy that have yet to be resolved by FDA and interested stakeholders.

As an initial matter, it is clear that FDA lacks legal authority to approve follow-on versions of any biological product approved under section 351 of the Public Health Service Act (PHSA).[4] Section 351 of the PHSA contains no provisions for approval of an abbreviated biologic license application (BLA). For nearly three decades FDA has taken the position that a BLA is a product-specific license that cannot be relied upon by another manufacturer, and the agency has never indicated that it intends to establish a pathway for follow-on versions of section 351 products. Accordingly, no action can be taken by FDA to establish a mechanism for approval of follow-on biologics under the PHSA without statutory and regulatory changes that address the approval mechanism, as well as the other legal and scientific issues raised in this document.

Thus, the only products that could conceivably be eligible for a follow-on process under the current legal framework are the small subset of biologic products that have historically been approved as drugs under section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA). Although two pathways exist under section 505 for the approval of drugs without full product-specific safety and effectiveness data, neither can be used for biologic products. Section 505(j) of the FDCA permits FDA to approve an abbreviated new drug application (ANDA) upon a showing that the generic product is the "same as" and bioequivalent to a reference listed drug. Due to the complexity and inherent variability of biologics, however, few if any of these

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[3] *Id.* Dr. Crawford also stated in his oral testimony that FDA would hold a "scientific workshop" on follow-on biologics, but that FDA was "still considering a separate process to address the legal and regulatory issues," Senate Comm. Tr. at 8, and would "have ... to get the science first," Senate Comm. Tr. at 13.

[4] Of course, a company may always submit a full application for a second version of a biologic product.

products would be eligible for ANDAs because they cannot be shown to be identical to the innovator product. Section 505(b)(2) is properly limited to "paper NDAs" based on published studies, and does not authorize FDA to rely on safety and efficacy data submitted for innovator products.[5] Even if section 505(b)(2) were interpreted to allow reliance on data submitted by innovators, it is not currently scientifically justifiable for a follow-on manufacturer to rely on the safety and effectiveness data from another product made by a different manufacturer.

As FDA has recognized, biologic products are extremely complex and often have inherent molecular heterogeneity. Biologics raise unique concerns due to the close relationship between the product's manufacturing process and its clinical attributes. In general, for biologics, current scientific technology is unable to fully characterize the molecules. Further, because each biologic product is complex, differences in the manufacturing process potentially can alter the clinical profile of the product. It has not yet been demonstrated with current technology that it is possible to ensure that any follow-on biologic product will have the same safety and effectiveness profile as the innovator. Accordingly, any approach to follow-on biologics must ensure that sufficient product-specific data are generated by every sponsor, whether innovator or follow-on manufacturer, to demonstrate the safety and effectiveness of each biologic product.

Finally, strong intellectual property protections are critical to promoting innovation that results in advanced therapies to meet patient needs. These protections – including rights in patents, trade secrets, and confidential commercial information – are well-established in the law and must be respected. Data and information included in an NDA, BLA, or other application are submitted with the expectation that FDA will treat the information as trade secret or confidential commercial information. Any mechanism for the approval of follow-on biologics, therefore, must respect the confidential nature of data submitted by innovators and appropriately preserve incentives for innovation. Additionally, FDA must also ensure that any information or process used to develop a guidance document on these topics is carefully monitored to be certain that trade secrets and other intellectual property are protected.[6]

For these reasons, and consistent with the legal arguments set forth in the Citizen Petition, FDA should allow for adequate substantive input and discussion by key stakeholders before any policy decisions are made regarding follow-on biologics. FDA should expand the

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[5] In the April 10, 1987 "Parkman letter," FDA described circumstances in which it would accept a single application (which, according to the letter, would "be considered an application described in section 505(b)(2)") in lieu of a two-step process involving an ANDA and a separate supplement for approval of certain changes to a listed innovator product. By its own terms, the Parkman-letter procedural vehicle for a single application has no relevance to follow-on biologics because an ANDA could not be approved for these products in the first place.

[6] We are not challenging FDA's general procedures for issuing guidance documents. We note that very few guidance documents would raise the types of issues presented here, where the very purpose of the guidance is to reduce data requirements based on confidential data and trade secret information previously submitted by other manufacturers.

current process begun with the Public Stakeholder Workshop by including hearings and other public proceedings to fully explore all of the complex issues raised by follow-on biologics. PhRMA looks forward to being a constructive and active participant in this process.

Statement of Grounds

I. Background

A. The Complexity Of Biologics

Biologic products constitute a large and diverse class of products generally characterized by a method of manufacture involving a living substrate. These include products such as recombinant DNA-derived therapeutic proteins, which are created by inserting a hybrid DNA sequence into a living organism that synthesizes the desired protein.

There are significant differences between biologic products and chemically synthesized drugs -- in molecular size, complexity, and heterogeneity, among other considerations. Biologically-derived products are generally large and complex molecules derived from living organisms, while chemically synthesized drugs generally have smaller molecular structures. To the extent it is possible to describe a "typical" biologic product, the description would include a complex, three-dimensional molecular structure essential to the product's function; chains of several hundred or thousand amino acids; and possibly additional post-translational modification such as specific glycosylations. Due to product heterogeneity, it is generally impossible to precisely characterize all components which constitute the active ingredient of the product.

In addition, in contrast to chemically synthesized drug products, the manufacturing process for biologics, particularly biotechnology products, involves a series of complicated steps based upon the production and secretion of the biologically active molecule by living cells or organisms. While thorough characterization of the physical, chemical, and bioanalytical properties of the process, drug substance and product is essential, these tests alone cannot ensure the therapeutic equivalence of two biological products produced under different conditions of manufacture.

B. The Current Approval Process For Biologics

Most biologics are approved under section 351 of the PHSA.[7] The approval process under the PHSA, including FDA's regulations implementing the statute, is clear. In order to gain premarket approval under section 351, the manufacturer must submit a biologics license application (BLA) that demonstrates that the biological product that is the subject of the application is safe, pure, and potent.[8] Further, the application must establish that any facility in which the biological product is manufactured, processed, packed, or held meets standards designed to ensure that the product continues to be safe, pure and potent.[9]

Historically, a small number of biologic products have been approved under section 505 of the FDCA.[10] For example, insulin and human growth hormone have been approved under section 505, despite the fact that they meet the definition of "biological product" under the PHSA. The decision to regulate these biological products as drugs was not based on any scientific or chemical distinction between these and other biologics. Like other biologic products, these products are relatively complex substances derived from biological sources. Although these products were approved as drugs, FDA has never indicated that it intended to establish a regulatory framework different from other biologic products. The need for product-specific data for each biologic was fully recognized by FDA. For every biological product approved under section 505, the agency has required a full NDA containing reports of product-specific clinical studies establishing the safety and efficacy of the product.

Yet recent pronouncements by FDA officials indicate that the agency is now considering a new pathway for approval of biologic products, one that may not require product-specific data demonstrating the safety and efficacy of each product. It was reported that former FDA Commissioner Mark B. McClellan, M.D., Ph.D., stated at a conference that "human insulin and growth hormone present opportunities for approving generics under current law."[11] In

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[7] Section 351 of the PHSA defines a biological product as "a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product ... applicable to the prevention, treatment, or cure of a disease or condition of human beings." 42 U.S.C. § 262(i). FDA's regulations contain a near-identical definition. 21 C.F.R. § 600.3(h). Most modern biotechnology products are "analogous" to, or derivative of, live cellular products and therefore fall within the definition of "biological product" as set forth in the PHSA.

[8] 21 C.F.R § 601.2. This requires "submission of complete reports of clinical and animal data to support approval." Senate Comm. Tr. at 7 (testimony of Dr. Crawford) and 131 (Statement of Dr. Crawford).

[9] *See* 21 C.F.R. §§ 601.2, 601.20(c).

[10] *See* Intercenter Agreement Between The Center for Drug Evaluation and Research and The Center for Biologics Evaluation and Research (1991). *See also* Statement of Dr. Crawford, Senate Comm. Tr. at 130 ("Traditionally, some natural source proteins have been regulated as drugs,... while other natural source proteins...are regulated as biological products.") and Senate Comm. Tr. at 7 (testimony of Dr. Crawford).

[11] BioCentury Extra (April 2, 2003). Dr. McClellan acknowledged, however, that there are scientific issues generally with respect to follow-on biologics.

addition, the former Commissioner stated: "I have a vision that includes effective and safe biogenerics potentially being available in the very long-term....We are taking some baby steps now" toward creating an approval mechanism.[12]

Following Dr. McClellan's announcement, several FDA officials have confirmed that the agency is in the process of developing a guidance document that will set forth a framework for how a generic manufacturer might obtain approval of a follow-on biologic.[13] The guidance will purportedly establish standards for demonstrating that a follow-on biologic is similar enough to an innovator to permit the approval of the follow-on product based on reliance, in some way, on the safety and effectiveness data submitted for the innovator (including reliance on FDA's approval of the innovator product).

Were such a guidance document issued, it would reverse decades-old policies established by FDA. During that time, the public has come to rely on a high standard of safety and efficacy for all products, including biological products, and hundreds of manufacturers have submitted applications for approval with the expectation that FDA would strictly protect the trade secret and confidential commercial information contained therein. FDA has only just begun public dialogue about some of the numerous challenges posed by follow-on biologics. PhRMA believes that these challenges, including complex patient safety, legal, scientific, and public policy issues, need to be explored by FDA and interested stakeholders.

II. FDA Lacks Legal Authority To Approve Follow-On Versions Of Biologic Products Licensed Under Section 351 Of The Public Health Service Act.

While there are many difficult legal issues presented by follow-on biologics, FDA's authority under the PHSA is not one of them. Section 351 of the PHSA provides no authority for FDA to grant a biologics license without a product-specific demonstration of safety and efficacy and of compliance with the manufacturing requirements specified in the statute. FDA has acknowledged this point on many occasions over the past three decades.[14] Accordingly, any attempt by the agency to craft a pathway to approval of follow-on biologics under the PHSA would clearly exceed the statutory authority provided by Congress.

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[12] *See id.*

[13] Health News Daily, *FDA Follow-On Biologics Guidance Delayed, Agency Tells BIO* (June 9, 2004). In his oral testimony, Dr. Crawford also referred to a guidance document being prepared. Senate Comm. Tr. at 8.

[14] For example, in his prepared testimony at the Senate Hearing, Dr. Crawford stated that "there is no provision under the PHS Act for an abbreviated application that would permit approval of a 'generic' or 'follow-on' biologic based on the Agency's earlier approval of another manufacturer's application." Senate Comm. Tr. at 133 (Statement of Dr. Crawford.)

Section 351 of the PHSA permits FDA to approve a license to manufacture a biological product only upon a showing by the manufacturer that

(I) the biological product that is the subject of the application is safe, pure, and potent; and
(II) the facility in which the biological product is manufactured, processed, packed or held meets standards designed to assure that the product continues to be safe, pure and potent.[15]

Nowhere in the PHSA is there any alternative mechanism for obtaining a license to manufacture a biological product.

FDA's regulations implementing the PHSA specify that in order to obtain a BLA, the manufacturer "shall submit data derived from nonclinical laboratory and clinical studies which demonstrate that the manufactured product meets prescribed requirements of safety, purity, and potency."[16] Furthermore, shortly after jurisdiction over section 351 was transferred to FDA, the agency stated that every biological product must be independently proven safe and effective:

> Unlike the regulation of human and animal drugs, all biological products are required to undergo clinical testing in order to demonstrate safety, purity, potency, and effectiveness prior to licensing, regardless whether other versions of the same product are already marketed or standards for the product have been adopted by rule making. Indeed, many of the existing standards require specific clinical testing before approval will be granted. This is required because all biological products are to some extent different and thus each must be separately proved safe, pure, potent, and effective. ... There is no such thing as a "me-too" biologic.[17]

Because no follow-on biologic could ever attempt to rely for its approval on the data of an innovator biologic, FDA took the position that "safety and effectiveness data for a biologic regulated under section 351 of the Public Health Service Act is not properly classified

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[15] 42 U.S.C. § 262(a)(2)(C). Prior to the Food and Drug Modernization Act of 1997, manufacturers were required to obtain approval of an Establishment License Application and a Product License Application. This dual requirement reflected the centrality of the manufacturing process to assuring that a biological product is safe, pure and potent. Although these applications have since been combined into a single license, the BLA, approval of a BLA still requires the manufacturer to prove the integrity of both the product and the production process.

[16] 21 C.F.R. § 601.2(a). As noted above, this requires submission of complete reports of clinical data. Senate Comm. Tr. at 7 (testimony of Dr. Crawford) and 131 (Statement of Dr. Crawford).

[17] 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974) (promulgating regulations under the Freedom of Information Act).

as a trade secret. Such data afford no competitive advantage because, unlike the situation with new drugs, no competitor can utilize it to gain approval for his product."[18] FDA, therefore, promulgated regulations that allowed for public disclosure of safety and effectiveness data for biologics licensed under the PHSA.[19]

FDA's position that each biological product must be independently proven safe and effective was confirmed in 1984, when Congress declined to make the approval mechanisms for abbreviated new drug applications (ANDA) and applications under section 505(b)(2) of the Hatch-Waxman Act available to biological products approved under the PHSA. Following Hatch-Waxman, FDA reaffirmed its position that there could be no generic versions of biologics licensed under the PHSA. For example, when promulgating Hatch-Waxman regulations in 1992, FDA reiterated that the ANDA process for generic drugs was "inapplicable to ... biological drug products licensed under [section 351 of the PHSA]."[20]

Thus, the PHSA, FDA's regulations, and FDA's policy statements unambiguously provide that no products licensed under section 351 may be approved without clinical studies demonstrating the safety, purity, potency, and effectiveness of the product to be marketed. FDA has consistently maintained this position. Accordingly, there can be no follow-on versions of biologic products regulated under section 351 absent action by Congress amending the PHSA to provide for such a mechanism (and resolution of the other legal and scientific issues raised in this document), as well as rulemaking by FDA.

III. Section 505 Of The FDCA Provides No Viable Pathways For Approval Of Follow-On Biologics.

Given the lack of any follow-on approval mechanism for biologics approved under the PHSA, the only biological products that FDA could legally consider for follow-on approval under the section 505 pathways are those products that have historically been approved under section 505 of the FDCA. Section 505 provides for two approval mechanisms other than a full NDA: approval of an ANDA under section 505(j) and approval of a "paper NDA" under 505(b)(2). For both legal and scientific reasons, neither is appropriate for follow-on biologics.

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[18] *Id.*

[19] 21 C.F.R. § 601.51(e). In contrast, the safety and effectiveness data contained in an NDA is treated as confidential commercial information and is not subject to disclosure to the public until the product is off-patent. 21 C.F.R. § 314.430(e)(2), (f). However, trade secret information contained in both BLAs and NDAs, including chemistry, manufacturing and controls (CMC) information, remains exempt from disclosure. 21 U.S.C. § 331(j); 21 C.F.R. § 20.61.

[20] 57 Fed. Reg. 17950, 17951 (April 28, 1992). *See also* Letter from H. Meyer, Director, Center for Drugs and Biologics, FDA (Nov. 16, 1984) ("There is no specific provision in Title I [of Hatch-Waxman] that includes ... biologicals.").

A. Section 505(j) Is Not A Pathway For Follow-On Biologics.

Section 505(j) permits FDA to approve an abbreviated new drug application only if the generic manufacturer can demonstrate that the generic product is "the same as" and bioequivalent to the reference listed drug.[21] Assuming these two standards can be met, FDA may rely on the clinical studies submitted by the innovator to establish that the drug product is safe and effective.

Section 505(j) of the FDCA was drafted to allow duplication of small-molecule drugs whose active ingredients can be reliably characterized. In 1984, when Congress passed the Hatch-Waxman amendments establishing an abbreviated application process for generic drugs, the scientific processes for characterizing most small-molecule drugs were already well understood. In drafting section 505(j), Congress expressly relied upon the fact that under then-current science, small-molecule drug products were thoroughly understood and the therapeutic equivalence of two drug products made by different manufacturers generally could be conclusively proven.

Synthetic small-molecule drug products generally have simple chemical structures that can be easily identified and replicated. Even twenty years ago, scientific testing methods were in place to accurately characterize the active ingredients in drug products and to ensure that a generic product would have the same therapeutic effect as the original. Moreover, by 1984, FDA had been approving abbreviated applications for drugs for some time. The Drug Amendments of 1962 permitted FDA to approve generic or "me too" copies of drugs that were approved prior to 1962. This rudimentary ANDA process provided FDA and industry with substantial scientific expertise regarding comparisons between two drug products.

By 1984, the standards for bioequivalence had been established and codified into final regulations. FDA's bioequivalence regulations, 21 C.F.R. Part 320, were originally proposed in 1975[22] and published in final form in early 1977.[23] When promulgating the final rule, FDA stated that:

> Advances in pharmaceutical technology have made bioequivalence a most precise and reproducible method of determining drug product variability. These bioequivalence techniques are not inadequately defined or reckless concepts. They are scientifically valid methods of comparing different drug products as well as different batches of the same drug product. The Commissioner believes that the actions he is taking to assure bioequivalence of marketed drug products will enhance the physician's ability to choose appropriate drug therapy, because the

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[21] 21 U.S.C. § 355(j)(2)(A).

[22] 40 Fed. Reg. 26164 (June 20, 1975).

[23] 42 Fed. Reg. 1624 (Jan. 7, 1977).

> physician will be assured that the product he selects will perform with greater consistency.[24]

The above statements were published by FDA nearly seven years before the statutory ANDA process for generic small-molecule drugs was established. At the present time, by contrast, the state of scientific knowledge regarding biological products in no way approaches the level of certainty required by section 505(j).[25]

As FDA is well aware, the "same as" requirement in section 505(j) demands that the generic applicant demonstrate that the generic product is "identical" to the innovator product "in active ingredient(s), dosage form, strength, route of administration, and conditions of use."[26] Under the current state of science and technology, few if any follow-on biologics would be able to meet this standard. It is critical that approval standards for follow-on biologics be consistent with those for innovator products.

FDA has described biologics as "complex mixtures of molecular species that were difficult to characterize as individual entities. In some cases, the specific active moiety could not be identified, or the active moiety existed in a milieu of other components that had the potential to affect many of its characteristics."[27] Even biological products that have been marketed for decades and rigorously studied generally do not have a fully characterized active ingredient. For the vast majority of biological agents, therefore, it is currently impossible to satisfy the key requirement of section 505(j) -- the comparison of two biologics in order to ensure that they are "identical."[28]

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[24] *Id.*

[25] In addition, because of their inherent product characteristics and their mechanism of action, it may not be possible to apply the concept of bioequivalence as defined under section 505(j)(8) to some follow-on biologics. This presents a further complication to attempting to use section 505(j) for biologic products.

[26] 21 C.F.R. § 314.92(a)(1).

[27] FDA, Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (April 1996).

[28] As noted above, pharmaceutical equivalence (a prerequisite for establishing therapeutic equivalence) would be very difficult, and in most cases impossible, to demonstrate for follow-on biologics. Even if pharmaceutical equivalence and bioequivalence could be shown, however, these criteria alone are not adequate to assure true therapeutic equivalence for biologics because it would not support the assumption of comparable safety (including immunogenic) and efficacy profiles. For biologics, in addition to pharmaceutical equivalence and bioequivalence, comparable safety and efficacy must be shown with well-designed, adequately powered clinical studies in order for two products to be deemed therapeutically equivalent.

B. Section 505(b)(2) Does Not Permit FDA To Rely On The Data Submitted In Another Application.

Section 505(b)(2) of the FDCA was enacted to codify FDA's "paper NDA" process. The term "paper NDA" describes an application that relies on published literature, rather than original research, to demonstrate the safety and efficacy of the proposed drug product. Section 505(b)(2) was enacted by Congress to allow for duplicate versions of existing drugs whose safety and efficacy had become well recognized in the medical and scientific literature. FDA, however, has interpreted 505(b)(2) to allow the agency to rely both on published literature and on data submitted in NDAs by innovators.

Most recently, FDA has suggested a further extension of its interpretation of section 505(b)(2) to accommodate the approval of follow-on biologics. As a matter of statutory construction, this interpretation cannot be supported, and a number of arguments have been made to that effect.[29]

Even assuming section 505(b)(2) could be legally interpreted to allow reliance on innovators' NDAs by manufacturers of follow-on biologics, however, use of this approval pathway is inappropriate for biological products. As discussed in the following section, the characteristics of each biological product -- whether innovator or follow-on -- are largely determined by the product's manufacturing process. Analytical evaluation techniques are currently inadequate to ensure that products manufactured in different facilities by different manufacturers are interchangeable without an intimate comparison between facilities and processes. Approval of a follow-on biologic under section 505(b)(2) would necessarily involve a series of broad assumptions about the "sameness" of two manufacturing processes, assumptions that could easily result in the approval of an ineffective or unsafe product.

FDA has not articulated any approach for safeguarding against these patient safety concerns. Nor has FDA explained how the agency can use section 505(b)(2) to approve follow-on biologics without drawing on innovators' trade secret and confidential commercial information.

In addition, one of the functions of section 505(b)(2) is to protect innovator patent rights by requiring patent certifications if there are patents listed on the reference drug. The

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[29] The argument that FDA's current interpretation of section 505(b)(2) exceeds the limits of the statute has recently been set forth in detail in a Citizen Petition submitted by the Biotechnology Industry Organization (BIO), *see* FDA Docket No. 2003P-0176, and in various filings by Pfizer Inc related to the section 505(b)(2) application for amlodipine, *see* FDA Docket No. 2002P-0447. PhRMA believes that the application of section 505(b)(2) to follow-on biologics is unsupported by either the text of the statute or the legislative history of section 505(b)(2). PhRMA has not submitted comments on the petition in Docket No. 2004P-0231, which concerns a matter involving two of our members.

patent certification process is based on the assumption that the relevant patents are patents claiming the drug or a method of using a drug. Accordingly, process patents are not listable (although product-by-process patents are listable because they claim a product).[30] For biologic products, however, each product is defined by the manufacturing process used in its creation, and process patent protection can be a fundamental and critical form of protection relevant to biologic products, particularly biotechnology products. If a follow-on application for a biotechnology product were submitted under the procedures of section 505(b)(2), the patent certification procedure could be ineffective because highly relevant patents may not be listable. The procedures under section 505(b)(2) were not designed for biologic products, and should not be applied to such products.

Any process for approval of follow-on biologics must assure the safety and effectiveness of the product. Given that section 505(b)(2) was clearly enacted without biologics in mind, and the standards for approving all biologics should be universal, it does not seem appropriate to create a standard under section 505(b)(2) that could differ from other statutory provisions and from what Congress may ultimately consider to be a standard for such products.

IV. Approval Of Follow-On Biologics Without Adequate Product-Specific Data Could Jeopardize Patient Safety.

Currently, analytical methods do not exist to ensure that a follow-on biologic will meet the same standards of safety and efficacy as an innovator reference product. The types of widely known methodologies for characterizing small-molecule drugs that provided a basis for Hatch-Waxman do not exist for biological products. Rather, the identity of each biological product -- whether innovator or follow-on -- is inseparable from the process used to manufacture it. Under these circumstances, any approval of follow-on biologics without a submission of comprehensive product-specific data could pose a substantial public health risk.

A. Biological Products Are Composed Of Complex Substances That Are Defined By Their Manufacturing Process.

The manufacturing process for a biologic product typically includes a series of interconnected and highly controlled steps, including the creation of a unique master cell bank, fermentation of the cell bank to create the desired protein, purification of the proteins and removal of impurities, formulation of the finished drug product, and packaging of the product for shipment.

As FDA has recognized on many occasions, the safety and efficacy of biological products are inherently tied to the manufacturing processes used to create them. In guidance, for example, FDA has stated that

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[30] *See* 68 Fed. Reg. 36676, 36679-80 (June 18, 2003).

> [b]ecause of the limited ability to characterize the identity and structure and measure the activity of the clinically-active component(s), *a biological product was often defined by its manufacturing process*... FDA recognized that changes in the manufacturing process, equipment or facilities could result in changes in the biological product itself and sometimes required additional clinical studies to demonstrate the product's safety, identity, purity and potency.[31]

Even minor differences in the manufacturing process for a follow-on biologic can have a significant impact on the clinical attributes of the product.[32] Unlike small synthetic molecules, all biologically-derived products have the potential to elicit immunogenic responses. Immunogenicity can cause the patient to produce antibodies that inactivate the therapeutic protein, reducing the efficacy of the product or potentially triggering other adverse effects.

Immunogenicity has many causes, and is not predictable. Scientific literature has documented that immunogenicity can be influenced by a variety of factors, including amino acid sequence variation, glycosylation, host cell proteins, manufacturing-related contaminants and impurities, formulation, oxidation, and conditions of storage, among other factors.[33] One cannot assume that a follow-on biologic product would have the same immunogenicity profile as the innovator product.

Because of the highly sensitive nature of biological products, all manufacturers employ a host of extensively validated manufacturing controls. Each stage of the production process is carefully monitored using well-established standards and release specifications. Generally only modest changes to the production process can be implemented, and even then each change is subject to extensive validation. Although these validation methods are increasingly sophisticated, they still have limitations. FDA has recognized this, stating: "Physiochemical assays[:] may not fully characterize [a] product, may not discriminate all variants and impurities, [and] may change [the] product while testing...Bioassays[:] may be

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[31] FDA, Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (April 1996) (emphasis added). The Agency went on in the Guidance to provide a limited exception for certain changes by a single manufacturer, but not unrelated manufacturers. *See* also note 35, infra.

[32] FDA, Guidance for Industry, Exposure-Response Relationships -- Study Design, Data Analysis, and Regulatory Applications (April 2003) ("In the case of biological drugs, changes in the manufacturing process often lead to subtle unintentional changes in the product, resulting in altered pharmacokinetics.").

[33] *See* BIO Citizen Petition at 45, *citing* Schellekens, H., *Bioequivalence and the immunogenicity of biopharmaceuticals*, Nature Reviews Vol. 1 (June 2002).

imprecise, may not measure all activities, [and] may not measure clinically important activity."[34] Reliance on such methods and assays would not be adequate to ensure that follow-on products will be therapeutically equivalent to innovator products.[35]

Accordingly, the manufacture of biological products presents substantial challenges even for innovator manufacturers with long histories of producing a given product. But these challenges are increased exponentially for follow-on manufacturers that will not have access to critical data about the manufacturing process of the innovator product, or personnel experienced in the relevant production methods. Without this knowledge or experience, there is no way under current science for a follow-on manufacturer to assure FDA how similar its product is to the innovator product.

B. To Ensure Patient Safety, FDA Must Require Appropriate Clinical Trials For Every Biological Product.

Given that the manufacturing process for biologics is so sensitive and can be so critical to the safety of the product, clinical testing is necessary to determine the safety and efficacy of follow-on biologics. Product-specific clinical testing remains the best, and under current science, the only way to ensure that biologic products are safe and effective. Until the science of biotechnology advances to the point that biological products are capable of precise characterization, and immunogenicity can be predicted, FDA must require every product to be supported by product-specific studies, including appropriate preclinical work, clinical safety and effectiveness trials, robust postmarket surveillance, and full chemistry, manufacturing, and controls information.

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[34] Jay P. Siegel, former Director, Office of Therapeutics Research and Review, CBER, *Comparability of Biotechnology Derived Protein Products: Lessons from the U.S. Experience*, DIA Meeting (Basel 2002).

[35] Generic manufacturers have cited the comparability determinations used to validate innovators' manufacturing process changes as a basis for allowing follow-on biologics. The shortcomings of this argument are obvious. When changes to an approved manufacturing process are made, the innovator has complete knowledge of the entire manufacturing process (and may be using the same starting materials), as well as significant historical experience with manufacturing the product and validating manufacturing changes. Under these circumstances a modest process change can be meaningfully evaluated. In contrast, the manufacturing process for a follow-on biologic (which, of course, uses different starting materials than the innovator) must be evaluated independently, and in its entirety, without access to the manufacturing process of the innovator, including specifications, internal standards, intermediates and validation packages. Therefore, it would not be appropriate to apply comparability principles designed as a means to assess changes made by the innovator of a biological product as the basis to approve a follow-on product developed and produced by another manufacturer.

V. FDA Must Ensure That The Intellectual Property Rights Of Innovator Manufacturers Are Protected.

Any mechanism for approval of follow-on biologics raises significant intellectual property issues. First, FDA cannot legally allow any generic manufacturer to reference, rely upon, or otherwise use the trade secrets and confidential commercial information submitted by an innovator in an NDA, BLA or other application. Second, any process established by the agency for considering follow-on biologics -- whether it be a guidance document issued by the agency, or some other process that allows for greater public participation -- must be carefully monitored by agency officials to ensure that trade secrets and other intellectual property of innovators are protected.

A. FDA May Not Rely Upon Or Use Trade Secret Data or Confidential Commercial Information Submitted By An Innovator To FDA.

Last year, FDA approved a section 505(b)(2) application submitted by Dr. Reddy's Laboratories seeking approval of a generic form of amlodipine maleate. The application was approved over the objection of Pfizer, the manufacturer of the only marketed single-agent amlodipine product. However, FDA later stayed the approval of Dr. Reddy's 505(b)(2) application because "questions [were] raised about the source of the data the [FDA] relied on in approving the NDA."[36] No other details were provided about this situation, but it is possible that FDA reviewers improperly relied on data and trade secrets contained in Pfizer's NDA. As this incident illustrates, innovators have good reason to be concerned about protection of their intellectual property. Given the complex issues raised by follow-on biologics (inherently more complex than issues raised by small-molecule generics), improper agency reliance on innovator data could recur, or even become regular agency practice.

As discussed above, biologic products are defined by the manufacturing processes used to create them. Under current science, FDA cannot evaluate a follow-on product without comparing the proposed manufacturing and controls of the follow-on to those of the innovator. In response to questions from the Senate Judiciary Committee, FDA suggested that review staff is permitted to review manufacturing specifications in one application before providing comments on another manufacturer's specifications.[37] However, this scenario is expressly prohibited by law. The information that innovators submit to FDA in applications for marketing approval is subject to important intellectual property protections as trade secret and confidential commercial information.[38]

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[36] *See* Administrative Stay of Action (Feb. 4, 2004).

[37] Senate Comm. Tr. at 65-66.

[38] These intellectual property protections also apply to information obtained by FDA through other means, such as through facility inspections.

Under section 301(j) of the FDCA, FDA is prohibited from "using ... or revealing ... any method or process which as a trade secret is entitled to protection."[39] Similarly, the Federal Trade Secrets Act[40] prohibits any federal employee from disclosing trade secrets, and provides for criminal penalties against any federal employee who misappropriates protected trade secrets. Although the Freedom of Information Act (FOIA) is intended to promote disclosure of information held by government agencies, the FOIA disclosure provisions specifically exempt from disclosure trade secrets[41]. Moreover, even where Congress has permitted FDA to use certain data for consideration of another application, such as safety and effectiveness data under section 505(j), trade secret data is excluded from such use.[42]

FDA's regulations define "trade secret" as any "commercially valuable plan, formula, process, or device" that is used to make, prepare, compound, or process trade commodities, and that is "the end product of either innovation or substantial effort."[43] Indisputably, all undisclosed information included in the chemistry, manufacturing, and controls (CMC) section of an NDA or BLA -- which contains detailed information about product formulation and manufacturing process -- is protected as trade secrets. This has been FDA's longstanding position, and is reflected in regulations that expressly prohibit FDA's release of any manufacturing or control information contained in an innovator's application.[44]

Information submitted in other sections of an innovator's marketing application, including unpublished clinical and nonclinical data on safety and effectiveness, is also protected from disclosure. These data represent an important commercial asset that is "customarily held in strict confidence" by the innovator and "not disclosed to any member of the public."[45] At a minimum, therefore, and regardless of whether the product under approval is a biological product or a traditional small-molecule drug, clinical and nonclinical data on safety and

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[39] 21 U.S.C. § 331(j).

[40] 18 U.S.C. § 1905.

[41] 5 U.S.C. § 552(b)(4).

[42] *See* 21 U.S.C. §§ 331(j), 355(j)(2), 360j(c).

[43] 21 C.F.R. § 20.61(a). *See also* 39 Fed. Reg. 44602, 44614 (Dec. 24, 1974) (FDA's definition of trade secret "is intended to serve as a general definition, and not to catalog all information that may have trade secret status").

[44] *See* 39 Fed. Reg. 44602, 44640 (innovator's "manufacturing methods and processes, quality control procedures, and quantitative formulas" exempt from disclosure); *see also* 21 C.F.R. § 314.430(g) (prohibiting release of manufacturing and control information except to the extent the information has been previously released to the public or can be shown to fall outside the definition of trade secret).

[45] 21 C.F.R. § 20.61(b) (defining confidential commercial information).

effectiveness constitute confidential commercial information.[46] FDA has previously determined that safety and effectiveness information submitted in a BLA could not be used for approval of a second applicant for a biologic product.[47] If it were able to be used, it would be confidential commercial information that could not be disclosed. [48] FDA could only change its position on use by a second applicant after notice and comment rulemaking.

In an NDA or BLA for a biologic product, however, the safety and effectiveness profile of the product cannot be completely documented in the sections of the application entitled "nonclinical pharmacology and toxicology" and "clinical data."[49] Rather, processes detailed in the innovator's CMC section -- such as data on the development of the manufacturing process, and the scaling-up of that process for commercial production -- are critical to the product's safety and efficacy. Thus, a reviewer would not be able to evaluate completely the safety and effectiveness of a biologic product without accessing data submitted in connection with the design of the manufacturing process. For example, a manufacturer considering a change in the master cell bank will often conduct preclinical testing to assess the impact of that change on the product's safety and efficacy.

For biological products, therefore, an innovator's clinical and nonclinical data on safety and efficacy are closely integrated with trade secret CMC data. Even if otherwise permitted, reliance only on the releasable portions of an innovator's safety and effectiveness data would be insufficient to ensure the safety and efficacy of the follow-on product.

B. FDA Must Establish A Process To Monitor Any FDA Review And Approval Activities, Including The Drafting Of Regulatory Guidance, For Considering Follow-On Biologics, To Ensure That Trade Secrets And Confidential Commercial Information Are Protected.

FDA is currently developing a guidance document intended to establish a scientific framework for considering follow-on biologics. As discussed in the Citizen Petition,

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[46] *See* 37 Fed. Reg. 9128, 9130-9131 (May 5, 1972); 39 Fed. Reg. 44602, 44612-44614; 45 Fed. Reg. 82052, 82058 (Dec. 12, 1980); *see also Public Citizen Health Research Group v. FDA*, 185 F.3d 898, 905 (D.C. Cir. 1999) (clinical safety and effectiveness data in innovator's investigational new drug application (IND) properly withheld under FOIA as confidential commercial information).

[47] 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974).

[48] *See* 21 C.F.R. § 314.430(f). As FDA has recognized, the safety and effectiveness data contained in innovators' NDAs and BLAs must be protected from disclosure wherever possible because if competitors could take advantage of a sponsor's data for their own use, "it is entirely possible that the incentive for private pharmaceutical research will be adversely affected." 39 Fed. Reg. 44602, 44634.

[49] *See* 21 C.F.R. §§ 314.50(d), 601.2.

any guidance issued by FDA on these topics could be based -- directly or indirectly -- on the scientific information submitted to FDA by innovator manufacturers. For years, innovators have submitted trade secret and confidential commercial data to FDA concerning the formulation and manufacture of their products. These data, developed at great expense, were provided to FDA for the limited purpose of obtaining an approval of a specific product. FDA has no authority to use this intellectual property for purposes of advising generic manufacturers on how they can obtain approval of follow-on biologics.

At a minimum, FDA is obligated to establish and maintain a strict process for controlling the precise type and source of data that FDA relies upon when drafting such a guidance document to ensure that FDA does not rely on data improperly. Certainly, FDA may not reference specific examples drawn from protected trade secret data. Nor may the agency provide, in effect, a "roadmap" for generic competitors to produce new versions of innovator products. More broadly, FDA must put in place a system of internal controls to prevent the use of trade secret information by FDA staff in drafting and publishing any guidance document. This includes a review by persons with expertise and training in trade secret law. Absent such controls, FDA will risk violating the law and significantly harming the commercial interests of the very companies that helped build FDA's knowledge base.

C. Unauthorized Use Of Protected Trade Secrets Or Confidential Commercial Information By FDA Is An Unconstitutional Taking.[50]

The United States Constitution prohibits the government from taking protected property without providing just compensation and prior due process.[51] FDA's regulations protecting innovators' manufacturing information as trade secrets creates a "reasonable investment-backed expectation" that such information is protected under the Fifth Amendment.[52] Accordingly, unauthorized release or use of a manufacturer's trade secrets constitutes a taking under the Fifth Amendment. In addition, under longstanding case law, FDA would be required to provide a manufacturer with notice, a hearing, and an opportunity for judicial review before releasing any trade secret data.[53]

VI. FDA Should Establish A Process For Expanding Public Input On All Of The Complex Issues Raised By Follow-On Biologics.

Recently, FDA appeared to recognize that the fundamental issues presented by follow-on biologics require meaningful input from stakeholders. On June 7, 2004, FDA Acting

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[50] PhRMA plans to submit additional information on the takings issue.

[51] U.S. Const. Amend. V, XIV.

[52] *PruneYard Shopping Center v. Robins*, 447 U.S. 74, 83 (1980); *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1011 (1984).

[53] *American Sumatra Tobacco Corp. v. SEC*, 93 F.2d 236, 239 (D.C. Cir. 1937).

Deputy Commissioner for Operations Janet Woodcock indicated that the guidance document that had been expected to issue this summer would be delayed. Citing the fact that "there's been so much interest" in the guidance, Dr. Woodcock stated that the agency had found it necessary to "broaden the scope" of its consideration.[54]

Subsequently, FDA held a public stakeholder workshop on "Scientific Considerations Related to Developing Follow-On Protein Products."[55] The workshop was a step toward gathering appropriate input from stakeholders, but is only a first step, given the limited time given to presenters, the specific nature of the questions posed by the Agency, and that there was not interaction between presenters. FDA has also stated that it will hold a co-sponsored workshop in 2005 with the Drug Information Association.[56] Perhaps that will provide additional information, such as on safety considerations, for making more informed policy decisions, and allow movement toward developing consensus on scientific issues. Extensive fact-finding through such public proceedings involving interested stakeholders is necessary to develop the full appreciation of the relevant scientific issues that should be obtained by FDA to enable the agency to develop appropriate policies based on sound science and patient safety.

According to the notice for the recent public stakeholder workshop, however, the workshop was "not intended to address legal or regulatory issues."[57] Similarly, FDA stated at the Senate Judiciary Committee hearing that it is still considering a separate process for legal and regulatory issues that would be after the scientific issues. Moreover, FDA said that the proposed Guidance is not expected to address legal questions.[58] PhRMA believes that legal and regulatory issues should be considered by FDA prior to the agency issuing any scientific guidance document. The statutes reflect the views of Congress on how best to ensure patient welfare while balancing the need to ensure future innovation of new therapies and provide the structure for any discussions. In addition, legal and regulatory issues form the basis for determining what scientific issues would be relevant and appropriate for any scientific guidance.

FDA should therefore provide opportunities to engage in a meaningful dialogue with key stakeholders concerning intellectual property protection issues that are raised by the pursuit of follow-on biologics, as well as other regulatory or legal issues.[59] While citizen

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[54] The Pink Sheet, *FDA Follow-On Biologics Guidance Delayed Because of Broadened Scope* (June 14, 2004).

[55] 69 Fed. Reg. 50386 (Aug. 16, 2004).

[56] *See, e.g.*, Senate Comm. Tr. at 8, 10 (testimony of Dr. Crawford).

[57] 69 Fed. Reg. 50386, 50387 (Aug. 16, 2004).

[58] *See* Response to Questions, Senate Comm. Tr. at 66.

[59] For example, in response to a question from the Senate Judiciary Committee referring specifically to the trade secret issue and asking FDA to identify other "major factors that will be discussion points on how to regulate follow-on proteins," FDA identified the following as legal and policy issues to be considered: "protecting trade secrets and confidential commercial (continued...)

petitions like these permit some discussion of scientific, patient safety, and intellectual property or other legal or regulatory issues, they may not necessarily permit full discussion of all of the relevant issues because they focus on the subject matter of the petition and typically result in incomplete and serialized responses. For issues this complex and controversial, public discourse with different views represented and participating at once is much more comprehensive, transparent and efficient. Thus, the agency should engage in extensive public hearings that allow full substantive input from interested stakeholders, with the initial goal of developing a concept paper that addresses the relevant scientific issues as well as the intellectual property considerations that apply to the disclosure and use of information submitted to the agency. Such a paper could serve as the basis for an informed and focused discussion and debate among all stakeholders and ultimately for the development of legislation and consideration by Congress.

PhRMA appreciates FDA's consideration of these comments and looks forward to engaging in a productive dialogue with the agency about these issues.

Sincerely,

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information; making sure that nothing [FDA does] amounts to an unconstitutional taking of property without due process of law; assuring that patent rights are protected; maintaining incentives for industry to innovate, while appropriately balancing the need for lower cost follow-on products; and minimizing, to the extent compatible with assuring product safety and effectiveness, the regulatory burden." Senate Comm. Tr. at 64.