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General Counsel

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July 1, 2004

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
Department of Health and Human Services  
5630 Fishers Lane, Room 1061  
Rockville, Maryland 20852

**Re: Citizen Petition Filed by Genentech Concerning Adoption of Standards for  
"Similarity" or "Sameness" of Biotechnology-Derived Products, Docket No. 2004-0171**

Dear Sir or Madam:

On behalf of Johnson & Johnson (J&J), I am writing to supplement the docket established in connection with the above-referenced citizen petition filed by Genentech on April 8, 2004 (hereafter "Genentech petition"). In that petition, Genentech formally requested FDA not to approve any application for a follow-on therapeutic protein product or issue any new guidance, whether in draft or final form, that would facilitate approval of such products. Genentech claims that FDA cannot take these actions since they would necessarily entail the unlawful use of trade secret and confidential commercial information previously submitted to the agency by the company. Genentech filed this citizen petition pursuant to both the Federal Food, Drug, and Cosmetic Act ("FDCA"), 21 U.S.C. §§ 301 et seq., and the Public Health Service Act ("PHSA"), 42 U.S.C. § 262.

The Johnson & Johnson family of companies is the world's most comprehensive and broadly based manufacturer of health care products. It is also one of world's largest, and oldest, biotechnology businesses with some of the world's leading biomedicines. The three drivers of the biotech platform at Johnson & Johnson are internal research and development; licensing of novel, therapeutically relevant products, technologies and tools; and small biotech company acquisitions.

Before turning to our specific comments on Genentech's petition, Johnson & Johnson would like to emphasize that expanding access to safe and affordable medicines and therapeutic biologics is a critical public health objective for the nation. To that end, we welcome the opportunity to participate in the discussion about the development of legislation and scientifically-based standards that would govern approval of follow-on biologic products by FDA.<sup>1</sup> ***Such standards must make patient safety of paramount importance.*** As FDA has consistently recognized, the scientific complexities surrounding biological medicines make them

<sup>1</sup> For the purposes of these comments, the term follow-on biologic product is meant to refer to a biologic product that purports to be similar enough to the innovator's product that the follow-on manufacturer may rely, in some way, on data and information developed by the innovator for approval.

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fundamentally different from chemically-based drugs. Thus, to ensure the safety and efficacy of a follow-on biologic product, any new regulatory scheme would need to establish a set of standards and policies markedly different from those currently used for generic drug products. At the same time, as FDA has also long acknowledged, that regulatory framework cannot involve reliance on information in an innovator's biologics license application ("BLA"). Indeed, ***FDA must not undermine legal protection for an innovator's trade secret information. Such information forms the foundation for, and is critical to, the discovery and development of new treatments and cures for diseases.***

It is with this background that we submit three general comments on Genentech's petition. First, we provide additional insights on the example discussed in the petition concerning the incidence of pure red cell aplasia in patients being treated with the epoetin product (Eprex®) marketed in non-U.S. countries, including Europe, by affiliates of Johnson & Johnson. That experience properly centers the issue of follow-on biologics on patient safety and risk. Second, in light of those safety issues, we focus on how a manufacturer of a follow-on product could establish an acceptable range of lot-to-lot variability for its product. If the manufacturer of a follow-on biologic does not undertake its own set of clinical trials, we believe it would almost certainly need to rely on an innovator's trade secret information to assure the safety and efficacy of its product. Finally, we underscore the point that an innovator's trade secret information may not be used to approve follow-on biologic products. Moreover, to the extent that the law is modified to establish such a mechanism, serious constitutional issues would arise if it were applied to biologic products currently on the market.

A. **Immunogenicity From Subtle Manufacturing Changes Involving Eprex Highlights the Potential for Substantial Safety Issues Arising From Approval of Follow-On Biotechnology-Derived Protein Products**

In its petition, Genentech points out that even minor changes in the manufacturing process for a product can lead to changes in the product that are difficult to detect but nonetheless have significant effects in patients.<sup>2</sup> In support of that proposition, Genentech cites the fact that certain patients using Eprex developed pure red cell aplasia ("PRCA") after certain manufacturing changes were adopted for this product. PRCA is a severe and rare form of anemia characterized by an almost complete and sudden absence of red cell precursors from an otherwise normal bone marrow. We support Genentech's position that even small changes in the manufacturing process for a complex protein product can have adverse and unanticipated

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<sup>2</sup> The FDA has consistently acknowledged this point. See e.g., FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-Derived Products, (April 1996) ("... a minor alteration in one or more product characteristics, with no previously documented effect, can have either no effect or a substantial effect on the pharmacology of the product."); and A. Mires-Sluis, FDA-CDER, State of the Art Analytical Methods for the Characterization of Biological Products and Assessment of Comparability, Bethesda, MD (June 10-13, 2003) ("Analytical methods have often failed to identify differences between products produced before and after process changes that have significantly different immunogenic profiles.")

immunogenic effects in patients, and we believe that it is helpful to expand the information and provide the current thinking involving PRCA and Eprex.

Specifically, Genentech indicated that the increased incidence of PRCA in certain patients using Eprex resulted from a change in the manufacturing process to replace human serum albumin in the product with another stabilizer. That change, which was prompted by regulations established by European Health authorities to address concerns about the potential transmission of Creutzfeldt-Jacob disease, coincided with the heightened frequency of PRCA in patients using Eprex.

As a result, investigators hypothesized that this manufacturing change resulted in an increased incidence of PRCA in individuals using Eprex. An extensive investigation undertaken by Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) over a period of four years involved both technical and clinical experts who reviewed historical data to define the affected patient population and identify any product related change that might have increased the immunogenicity of the product. A major portion of this investigation involved the review of historical manufacturing records, the development of additional and more sensitive analytical methods, and the retesting of historically retained samples of drug substance and drug product.

These extensive investigations indicate that the main cause of the increased incidence of PRCA is most likely to be due to a physical interaction that occurred between the new stabilizer, polysorbate 80, and the uncoated rubber syringe stoppers used at that time in certain strengths of pre-filled syringes used to deliver Eprex. The polysorbate 80 leaches organic chemical compounds from the rubber stopper and, in animal models, such leachates increase the immunogenicity of epoetin. In 2003, we ceased distribution of Eprex pre-filled syringes with uncoated rubber stoppers and, as a precautionary measure, recalled all Eprex pre-filled syringes with such stoppers then in the marketplace. After changing the stoppers used in these syringes from plain rubber to FluoroTec®-coated stoppers, and instituting other measures, including changing the recommended route of administration from S.C. to I.V. in chronic renal failure patients, incidents of PRCA in patients using Eprex have returned to the baseline rate seen with all marketed epoetin products.<sup>3</sup>

No matter what the ultimate cause or causes of PRCA may be, the foregoing demonstrates the potential for immunogenicity from even slight changes in any facet of the manufacturing process for a biotechnology-derived protein product. At the same time, it confirms that such immunogenic reactions may occur even if there are no detectable changes in the nature of the product. Routine analytical studies of Eprex undertaken by J&JPRD using approved methods did not detect anything that would have predicted the increased incidence of PRCA. The leachates were discovered only after extensive investigations and the development of a number of additional testing methods. That, of course, suggests that it will be

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<sup>3</sup> Other measures adopted include an intensive storage and handling program, changing the route of administration of the product, and implementing a large multi-national surveillance program to track the incidence of PRCA.

extraordinarily difficult to predict, or even to know what to look for to determine, whether a follow-on product could cause immunogenicity in certain patients. Accordingly, as one leading scientist recently declared, “the many factors that influence immunogenicity – some of which have not yet been defined – show that it is inconceivable at present to manufacture a biopharmaceutical that can be shown to be therapeutically equivalent to another product, other than by extensive clinical comparisons.”<sup>4</sup>

**B. Any Effort by FDA to Establish An Acceptable Range of Batch-to-Batch Variability For Follow-On Products Will Necessarily Involve the Use of Trade Secret Information Belonging to an Innovator**

Given the adverse effects that may stem from even slight changes in the manufacturing process for products such as Eprex, it will be important for FDA to require any manufacturer of a follow-on product to be especially careful when establishing an acceptable range of batch-to-batch variability for its product. Yet, a follow-on manufacturer cannot know what degree of variability is consistent with safety and efficacy, and thus establish specifications (or a process) that ensure safety and efficacy, without relying on trade secret and confidential commercial information belonging to an innovator company. That is because biologics have intrinsic batch-to-batch variability that can influence safety and efficacy. But only FDA and the original manufacturer know the range of variability that was observed in the original product used to generate such safety and efficacy data and the relationship of those parameters to lot specifications. Thus, unless FDA relies on or shares such confidential information with a follow-on manufacturer, or clinical studies are pursued, it will be impossible for the agency to confirm that the follow-on product is safe and effective.

The FDA has consistently recognized the importance of batch-to-batch variation of biologics in various contexts. For example, it is well established that many mammalian proteins are glycosylated and therefore substantial variability may exist from batch to batch. The FDA has indicated that complete chemical identification of all carbohydrate variants in a protein product is not possible or feasible. Instead, the agency has focused on how much batch-to-batch variation is acceptable to assure consistent identity, purity, and potency of the product.<sup>5</sup> At the

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<sup>4</sup> See Schellekens, H., Bioequivalence and the Immunogenicity of Biopharmaceuticals, *Nature Reviews*, Vol. 1, pgs. 457-462 (2002). With respect to epoetin products such as Procrit, investigators have declared that “the potential risk for induction of neutralizing antibodies needs to be considered for all second generation molecules and generic preparations of recombinant Epo.” See Eckardt, K. and Casadevall, N., Pure Red-Cell Aplasia Due to Anti-erythropoietin Antibodies, *Nephrol Dial Transplant*, Vol. 18, pgs. 865-869 (2003). See also Locatelli, E. et al., Erythropoiesis-Stimulating Agents and Antibody-Mediated Pure Red-cell Aplasia: Where We Are Now and Where Do We Go From Here?, *Nephrol Dial Transplant*, Vol. 19, pgs. 288-293 (2004) (“ . . . it is important to note that as patents on currently licensed ESAs [erythropoiesis-stimulating agents] expire, safety implications of generic compounds may also become a major issue.”)

<sup>5</sup> See Letter from Dr. Janet Woodcock, Director, CDER, FDA to Mr. Peter Frank, Serono Laboratories, June 17, 1997 (concerning denial of a citizen petition involving approval of generic menotropins products under Section 505(j) of the FDCA).

same time, FDA has found that even modest changes in the concentration of an excipient in different batches of a biologic product can impact safety and efficacy. For example, when FDA evaluated different levels of sodium dodecyl sulfate levels in different batches of Proleukin®, it detected potentially significant and different effects on the pharmacokinetics and *in vivo* effects of the product.<sup>6</sup>

With issuance of a recent guidance document concerning comparability protocols and chemistry, manufacturing and controls (“CMC”) information for protein products, FDA has also acknowledged the importance of ensuring consistent lot-to-lot variation where manufacturers adopt manufacturing changes for their products. After describing the specific tests and studies to be performed as part of a comparability protocol to govern this situation, FDA declared that the “results from postchange material should fall within the normal batch-to-batch variation observed for prechange material.”<sup>7</sup> In addition, in connection with its approval of a generic version of a glycosylated protein product (follicle-stimulating hormone) under Section 505(j) of the FDCA, FDA sought to ensure that the generic manufacturer achieved the same potency and degree of batch-to-batch uniformity for its product as had been established for the pioneer drug.<sup>8</sup>

While FDA has emphasized the importance of controlling batch-to-batch variation in complex biological products within limits that have been associated with safety and efficacy of the product, it is unclear precisely how the manufacturer of a follow-on product could do so without relying on an innovator’s trade secret information as the new manufacturer would not have data necessary to determine what those limits should be. To be sure, in the first case described above where a company changes its own manufacturing process, the manufacturer and FDA could obviously rely on the manufacturer’s trade secret information to ensure that the changes do not impact safety and efficacy. And, in the second instance described above involving approval of a generic product, FDA was able to rely on a monograph established by the United States Pharmacopoeia (“USP”) that prescribed methods for measuring batch variation and potency. These measures, however, do not apply in cases involving follow-on versions of biological products.

For example, USP monographs primarily focus on measuring variability and potency of the Active Pharmaceutical Ingredient or the final dosage form. For biotechnology products, it has long been asserted by FDA that this is not sufficient since control of the entire manufacturing process is critical in assuring the safety and potency of the biological product. This information is generally considered confidential and trade secret by companies. Therefore, the only way that the manufacturer of a follow-on recombinant protein product could establish that differences in its product do not fall outside the variation or range of an innovator’s product (without undertaking clinical studies) would be to reference confidential or trade secret information. And, as described next, that is impermissible under current law and the United States Constitution.

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<sup>6</sup> See FDA Summary Basis of Approval for Proleukin® (aldesleukin), Part V.D., May 5, 1992.

<sup>7</sup> See FDA Guidance Concerning Comparability Protocols, Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information, (September 2002).

<sup>8</sup> See *Serono Laboratories v. Shalala*, 158 F. 3d 1313 (D.C. Cir. 1998)

**C. The Use of Trade Secret Data to Facilitate Approval of a Biologic Product Would Require FDA to Pay Just Compensation Under the Takings Clause of the U.S. Constitution**

As Genentech explained in detail in its citizen petition, trade secrets and other types of confidential information lie at the heart of the biotechnology industry. In fact, based on both the common law definition of trade secrets and FDA's own regulatory definition of that term,<sup>9</sup> there can be no question that a substantial body of knowledge about a biological product constitutes trade secret information. That is particularly true because the unique characteristics of a biologic product are determined by the distinct processes used by a manufacturer to produce and test its product. Such information takes many years to develop and frequently holds the key to a fundamental understanding of the biologic product and of the innovation leading to the development of even better products. Thus, trade secrets relating to a biotechnology-derived product represent an enormous value, and Johnson & Johnson (like other manufacturers of biologic products) has established strict safeguards to protect against disclosure and use of this information.

In its citizen petition, Genentech asserted that any use of its trade secret or confidential information for approval of a follow-on product would result in a taking of property without just compensation, in violation of the Fifth Amendment. There is no question that the use of trade secret and confidential commercial information for approval of a follow-on biologic product under the PHSA is prohibited. The FDA and the Congress have consistently acknowledged this point. As a result, unless FDA fully reversed course, this constitutional issue should not arise under current law.<sup>10</sup> Nevertheless, the takings argument would have direct and persuasive application if Congress were to enact new legislation authorizing FDA to reference an innovator's trade secret and confidential commercial information to approve a follow-on version of a biologic product currently on the market. In that instance, FDA would be required to pay just compensation.

In *Ruckelshaus v. Monsanto*, 467 U.S. 986 (1984) ("*Monsanto*"), the Supreme Court considered the closely related question whether certain provisions of the Federal Insecticide, Fungicide, and Rodenticide Act ("*FIFRA*"), 7 U.S.C. § 136 *et seq.*, allow the Environmental Protection Agency ("*EPA*") to use pesticide registration data submitted by one applicant to

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<sup>9</sup> Under FDA's regulations, a "trade secret" may "consist of any commercially valuable plan, formula, process, or device that is used for the making, preparing, compounding, or processing of trade commodities and that can be said to be the end product of either innovation or substantial effort. There must be a direct relationship between the trade secret and the productive process." 21 C.F.R. § 20.61(a)

<sup>10</sup> To the extent that the PHSA could be viewed as unclear on this point, any court considering the propriety of approval by FDA of a follow-on product would be required to construe the PHSA so as to avoid a constitutional infirmity. *See Jones v. United States*, 529 U.S. 848, 858 (2000) ("guiding principle" is that "where a statute is susceptible of two constructions, by one of which grave and doubtful constitutional questions arise and by the other of which such questions are avoided, [the court's] duty is to adopt the latter").

evaluate the application of another applicant. In considering this question, the court first held that proprietary information submitted to an agency in support of an application to market a product constitutes a property interest that is protected by the Takings Clause of the Fifth Amendment. *Monsanto*, 467 U.S. at 1003. The Supreme Court then analyzed whether the use of such data by EPA to evaluate other parties' applications brought about a taking of that property interest. Although no "set formula" exists for such determinations, the court focused principally on the extent to which EPA's actions would interfere with the "reasonable investment-backed expectations" of the applicant at the time it submitted its data to the agency. *Monsanto*, 467 U.S. at 1007.

Specifically, with respect to trade secret information submitted to EPA between amendments to FIFRA in 1972 and 1978, the court found that the federal government had explicitly guaranteed to applicants an extensive measure of confidentiality and exclusive use. And, this governmental guarantee formed the basis for a reasonable investment-backed expectation. As a result, even though EPA was authorized by Congress in 1978 to use an applicant's registration information in connection with its review of other applications, the agency could not do so in a manner not authorized by the version of FIFRA in effect between 1972 and 1978. Rather, the court declared, such action would violate the Takings Clause since it is the "right to exclude others [that] is generally one of the most essential sticks in the bundle of rights that are commonly characterized as property." Once others are allowed to use those data, the holder of the trade secret has lost his property interest in the data. *Monsanto*, 467 U.S. at 1012.

The same rationale and result would apply to products that have been approved under the PHSA. That is because FDA has long taken the position that safety and effectiveness data in a BLA would not be available for use by others. For example, in 1974, FDA expressly declared that "[t]here is no such thing as a 'me-too' biologic" and "data afford no competitive advantage because, unlike the situation with new drugs, no competitor can utilize it to gain approval for his product."<sup>11</sup> Moreover, shortly following adoption of the Hatch-Waxman Amendments, FDA advised Congress that biological products are not subject to approval under Title I of the amendments.<sup>12</sup> Furthermore, when FDA issued its regulations implementing these provisions eight years later, it reiterated its position that the new ANDA procedures for duplicate versions of drugs are "inapplicable to . . . biological drug products licensed under 42 U.S.C. § 262."<sup>13</sup> And, most recently, FDA again indicated that the agency does not have the legal authority to

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<sup>11</sup> See 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974).

<sup>12</sup> See Letter from Harry M. Meyer, Jr., Director, Center for Drugs and Biologics, FDA (Nov. 16, 1984). In full, FDA wrote that: "[t]here is no specific provision in Title I that includes . . . biologicals . . . . The Act refers to generic versions of those drugs originally approved under Section 505(b)... of the Federal Food, Drug and Cosmetic Act. Biologicals are approved under the Public Health Service Act . . . . Accordingly, we do not consider these products to be covered by Title I."

<sup>13</sup> See 57 Fed. Reg. 17950, 17951 (Apr. 28, 1992).

reference information in an innovator's BLA.<sup>14</sup> Accordingly, if FDA were to use trade secret information to approve a follow-on version of a biologic product currently on the market, the federal government would be required to pay just compensation.

**D. Conclusion**

In sum, it is clear that the adoption of any regulatory scheme to govern review and approval of follow-on biologic products raises both complex scientific questions and potentially intractable legal issues. Indeed, new legislation would need to be enacted before FDA may approve follow-on biologic products. While FDA may nonetheless intend to proceed toward the development of such a framework, the agency must do so carefully and with full consideration of the views of all interested parties. In this respect, we understand that FDA plans to issue a draft guidance document that establishes a "general framework" for scientific methodologies that could be used to demonstrate the "similarity" or "sameness" of various types of biologically derived products, including therapeutic proteins.

Given the complexity of this issue, and the fact that even draft guidance documents have a tendency to fix thinking on particular matters, we thank FDA for recently indicating that it would hold a public workshop in advance of releasing a draft guidance on comparability of follow-on biological products.<sup>15</sup> J&J believes that public participation throughout this process is essential, and it looks forward to participating in this workshop and other meetings that may be necessary to fully involve interested parties in these complex issues. ***Ultimately, J&J believes that this type of involvement from the public will help achieve the twin goals of establishing a mechanism that ensures the safety and efficacy of follow-on biologic products without intruding on trade secret and confidential information that drives the development of new medicines.***

Thank you for your consideration of these comments.

Sincerely,



Kathy J. Schroeder  
Associate General Counsel  
Johnson & Johnson

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<sup>14</sup> See FDA Follow-On Biologics Guidance: A Preview (remarks by Dr. Steven Galson), *The Pink Sheet*, Vol. 66, No. 19, p. 4 (May 10, 2004).

<sup>15</sup> FDA's regulations governing "Good Guidance Practices" provide the agency with ample authority to solicit public input before issuing draft guidance documents. See e.g., 21 C.F.R. § 10.115(g)(1)(i).