



April 5, 2005

BY HAND DELIVERY

Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5630 Fishers Lane, Room 1061  
Rockville, MD 20852

**Re: Comments in Support of the Citizen Petition Filed by Genentech, Inc.  
(2004P-0171/CP1) Regarding Follow-on Biologics**

Ladies and Gentlemen:

Novo Nordisk Inc. submits these comments in support of the Citizen Petition submitted to the above-referenced docket by Genentech, Inc. on April 8, 2004 (the "Genentech Petition").<sup>1</sup> Novo Nordisk is a pioneer in the promise of biotechnology and a worldwide leader in healthcare innovation. The company produces half of the world's insulin, and manufactures additional biotechnology products such as recombinant human growth hormone and recombinant coagulation factor VIIa.

The Genentech Petition requests that the Food and Drug Administration ("FDA") refrain from approving any follow-on biotechnology-derived product relying in whole or in part on the innovator's trade secret or confidential commercial data to establish safety or effectiveness of the follow-on product.<sup>2</sup> As the Petition points out, and as subsequent comments have reiterated, manufacturing data, as well as other data in a New Drug Application ("NDA") or a Biologics License Application ("BLA") constitute trade secret data that are protected from disclosure by the Federal Food, Drug, and Cosmetic Act, the Trade Secrets Act, and the Freedom of Information Act.

Novo Nordisk strongly agrees with these comments and believes the protections afforded by these statutes prevent FDA from approving a follow-on biologic because FDA would necessarily be required to rely, directly or indirectly, on innovator trade secret data. Novo Nordisk is submitting these comments, however, to point out that use of such trade secret data by FDA would also constitute a taking without just compensation under the United States Constitution. As a result, current law does not provide any suitable pathway for the approval of

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<sup>1</sup> See Genentech, Inc., *Citizen Petition*, FDA Docket No. 2004P-0171 (April 8, 2004) (hereinafter the "Genentech Petition").

<sup>2</sup> See *id.* at 1.

a follow-on biologic, whether the innovator product was originally approved through an NDA or a BLA.

## **I. Background**

### **A. Statutory Authority for Approval of Follow-on Biologics**

Most biotechnology-derived products are approved under section 351 of the Public Health Services Act (“PHSA”). As FDA has conceded already, that section provides absolutely no authority for the approval of follow-on products without an independent showing of safety and effectiveness.<sup>3</sup> There is no analog in the PHSA to the Hatch-Waxman ANDA provisions in section 505(j) of the Federal Food, Drug, and Cosmetic Act (“FDCA”) or the “paper-NDA” provisions of section 505(b)(2).

For bureaucratic, non-scientific reasons, some biologics have been approved under section 505 of the FDCA. Nevertheless, neither the ANDA provisions of section 505(j) nor the “paper-NDA” provisions of section 505(b)(2) are suitable for approval of follow-on versions of biotechnology-derived products. In addition to other limitations, both of these approval pathways would require FDA to rely, directly or indirectly, on confidential, legally protected trade secret data, particularly manufacturing data, in the innovator’s NDA.

### **B. Approval of a Follow-On Biologic Under Either Section 505(j) or Section 505(b)(2) Would Require FDA to Rely on Legally Protected Manufacturing Data From the Innovator’s NDA**

The “Hatch-Waxman” provisions of section 505(j) permit FDA to approve generic versions of NDA small-molecule chemical drugs so long as the generic applicant demonstrates that its product is the “same as” the innovator’s product and is bioequivalent.<sup>4</sup> This requirement squarely places the burden on the generic applicant to demonstrate that its product’s active ingredient(s), among other things, is identical to the innovator’s.

Because of the complex nature of biotechnology-derived products, however, it is highly unlikely – if not impossible – that generic manufacturers could meet this burden for follow-on biologics. For traditional small-molecule chemical drugs, a generic applicant can meet the “same as” requirement relatively easily, by demonstrating that its product contains the same chemical active ingredients as the innovator’s. Such active ingredients are, generally, fully-

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<sup>3</sup> See, e.g., Congressional Testimony of Dr. Les Crawford, Acting Commissioner, FDA (June 23, 2004) (stating that “the decision to proceed with a program for follow-on biologics regulated under section 351 rests with Congress.”).

<sup>4</sup> 21 U.S.C. § 535(j).

characterized, and well-understood. A small-molecule chemical may be synthesized by any one of several different processes, but the product of any of these methods would be expected to be chemically identical and can be so characterized using well-accepted analytical methods.

For biotechnology-derived products, however, current analytical science does not permit characterization of active ingredients at a level that is scientifically acceptable to demonstrate sameness. This is because unlike small-molecule chemical drugs, the structure of biotechnology-derived products are highly dependant upon the manufacturing processes used to create them. Whereas small-molecule chemical drugs are the product of synthesis using known chemical compounds, biotechnology-derived products are the result of synthesis by living cells, which are highly sensitive to the precise growth conditions under which they are cultivated.

Furthermore, some types of changes, even seemingly minor changes, to an established manufacturing and/or formulation process used to create biotechnology-derived products have the potential to change the end product in a way that can alter its safety and efficacy profile such as, for example, increasing its immunogenicity in humans. Similarly, small deviations in growth conditions under which a reaction is induced may create significant variations. As these seemingly minor changes to an established manufacturing process can have profound effects, as well as result in an entirely new product, it follows that a full complement of independent data should be required.

As a result, it would be nearly impossible for a generic applicant to establish that its proposed follow-on biologic is "the same" as the innovator's without knowing (and following) the innovator's multi-step manufacturing process to the last detail. Generic manufacturers, however, do not have this information because it is the legally protected trade secret information belonging only to the proprietor. The only way that FDA could ensure that a generic applicant is employing the precise manufacturing process required would be to reference the manufacturing data submitted by the innovator in the chemistry, manufacturing, and controls ("CMC") section of the innovator's NDA.

FDA would encounter a similar problem if it tried to approve a follow-on biologic through the provisions at section 505(b)(2) of the FDCA. Section 505(b)(2) authorizes FDA to approve generic versions of NDA small-molecule chemical drugs where the generic applicant does not have a right of reference to all of the clinical studies necessary to establish safety and effectiveness. FDA has interpreted this statutory provision as permitting it to reference clinical trials contained in the innovator's NDA to help establish that the generic small-molecule chemical drug is safe and effective.<sup>5</sup>

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<sup>5</sup> Other comments to this docket have forcefully argued that Congress sought only to codify FDA's "paper NDA" policy in enacting section 505(b)(2). *See, e.g.,* PhRMA Comment, at 9-10.

Even assuming that FDA has correctly interpreted the statute, the clinical studies contained in the innovator's NDA are relevant only to the extent that the generic small-molecule chemical drug is the same as the innovator product. As discussed above, however, biotechnology-derived products are highly complex, unique products, that are defined by their manufacturing processes. If a generic manufacturer has employed different techniques in manufacturing the follow-on biotechnology-derived product (e.g., different host cells, medium, growth conditions, purification procedures, etc.), the "active ingredients" in the two products could be substantially different. In that case, the clinical studies in the innovator's NDA could not provide reliable information about the follow-on product.

As a result, for FDA to apply the data in the innovator's clinical trials to a proposed follow-on, it would first have to establish that the two products share the same "active ingredients". The only way that FDA could do this is to reference the innovator's protected manufacturing data contained in its NDA, which was entrusted to FDA under longstanding legal guarantees of confidentiality. Only after FDA has confirmed that the two products employed identical manufacturing processes could it conclude that the innovator's clinical trials would be relevant to the follow-on biotechnology-derived product.

### **C. Innovator Manufacturing Information Constitutes Trade Secret Data**

Information in an NDA or BLA, however, represents trade secret data, and as such is the property of the innovator. As a result, it is protected from disclosure by at least three Federal statutes: section 301(j) of the FDCA, the Trade Secrets Act, and the Freedom of Information Act (the "FOI Act"). Section 301(j) of the FDCA prohibits FDA or its employees from revealing "any method or process which as a trade secret is entitled to protection."<sup>6</sup> FDA's regulations define a "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."<sup>7</sup> Additional FDA regulations make clear that this

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<sup>6</sup> 21 U.S.C. § 331(j).

<sup>7</sup> 21 C.F.R. § 20.61(a). Previously, FDA's definition of "trade secrets," for FOI Act purposes, mirrored the broad definition of the term found in section 757 of the Restatement of Torts (1939). See 21 C.F.R. § 20.61(a) (1982). In *Public Citizen Health Research Group v. FDA*, 704 F.2d 1280 (D.C. Cir. 1983) (the "Intraocular Lens Case"), however, the D.C. Court of Appeals rejected this definition as too broad for FOI Act purposes. Instead, the Court concluded that the definition of trade secret for FOI Act purposes should be more restrictive, reserving trade secret status "for information involving 'the productive process itself, as opposed to collateral matters of business confidentiality such as pricing and sales volume data, sources of supply and customer lists.'" *Public Citizen* at 1286-87 (quoting Connely, *Secrets and Smokescreens: A Legal and Economic Analysis of Government Disclosures of Business Data*, 1981 WIS L. REV. 207, 230). The distinction, however, is irrelevant for purposes of this case. Not only did the *Public Citizen* (continued...)

definition of trade secret data includes the detailed manufacturing information contained in an NDA or BLA.<sup>8</sup>

Similarly, the Trade Secrets Act provides for criminal sanctions against any “employee of the United States Government who discloses, in any manner not authorized by law, any trade-secret information that is revealed to him during the course of his official duties.”<sup>9</sup> FDA itself has described the statute as a “general Federal prohibition against disclosure of trade secret information” under which “[d]isclosure of information . . . constitutes a criminal offense.”<sup>10</sup> Finally, Exemption 4 of the FOI Act excludes from mandatory disclosure “trade secrets and commercial or financial information obtained from a person and privileged or confidential.”<sup>11</sup>

## **II. Disclosure of or Reference to Trade Secret Data in an Innovator’s NDA or BLA Would Constitute A Taking Without Just Compensation Under the 5th Amendment to the United States Constitution**

### **A. Takings Law Under the United States Constitution**

The Fifth Amendment to the U.S. Constitution provides that “[N]or shall private property be taken for public use, without just compensation.”<sup>12</sup> The courts have established two major categories of takings - namely, *per se* takings and regulatory takings. A *per se* taking occurs when the government “physically takes possession of an interest in property for some public purpose . . . regardless of whether the interest that is taken constitutes an entire parcel or merely a part thereof.”<sup>13</sup> Thus, the courts have found *per se* takings when the government has: taken a

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Court clearly limit its use of the restrictive definition of trade secrets to FOI Act cases, but the restrictive definition outlined by the Court, focusing on the productive process, clearly includes information on a biotechnology-derived product’s manufacturing process submitted to the FDA in an NDA. This conclusion is supported by the fact that when FDA changed its regulations to adopt the more restrictive definition, the agency noted that “[t]he amendment to section 20.61 will not affect Agency practice . . . .” See 39 Fed. Reg. 531, 532 (January 5, 1994).

<sup>8</sup> See, e.g., 21 C.F.R. § 314.430(g)(1) (prohibiting the disclosure of “[m]anufacturing methods or processes, including quality control procedures” contained in an application for marketing authorization unless such information has been previously disclosed, relate to a product that has been abandoned, or is shown to fall outside of the definition of a trade secret).

<sup>9</sup> 18 U.S.C. § 1905.

<sup>10</sup> 39 Fed. Reg. 44602, 44612 (Dec. 24, 1974).

<sup>11</sup> 5 U.S.C. § 552(b)(4).

<sup>12</sup> U.S. Const. amend V.

<sup>13</sup> *United States v. Pewee Coal Co.*, 341 U.S. 114 (1951).

leasehold and occupied the property for its own purposes;<sup>14</sup> appropriated part of a private rooftop in order to provide cable TV access for apartment tenants;<sup>15</sup> or required that its planes be permitted to use private airspace to approach a government airport.<sup>16</sup>

A “regulatory” taking occurs when government action restricts a property owner’s right to use its property but does not actually dispossess the owner of its property or force it to share its property with others.<sup>17</sup> In determining whether a regulatory taking has occurred, the courts balance three factors developed by the *Penn Central* Court: (1) does the government action interfere with “the reasonable investment-backed expectation” of the property owner, (2) the economic impact of the government action on the property owner, and (3) the character of the government action.<sup>18</sup> Thus, for example, courts have considered under regulatory takings analysis cases where the government: prohibits a landlord from evicting tenants who refuse to pay a higher rent;<sup>19</sup> bans certain private uses of a portion of an owner’s property;<sup>20</sup> or prohibits the private use of certain airspace.<sup>21</sup>

#### **B. The Takings Clause Applies to Trade Secrets and Other Intellectual Property**

In *Monsanto v. Ruckelshaus*<sup>22</sup> the Supreme Court made clear that the Takings Clause protects trade secrets and other intellectual property rights. In *Monsanto*, the Court considered provisions of the Federal Insecticide, Fungicide, and Rodenticide Act (“FIFRA”)<sup>23</sup> regarding registration of pesticides. Prior to 1972, FIFRA had been simply a labeling statute, but was amended by Congress in 1972 to become a comprehensive regulatory statute. Congress amended FIFRA again in 1978 to change several provisions of the act.

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<sup>14</sup> See *United States v. General Motors Corp.*, 323 U.S. 373 (1945).

<sup>15</sup> See *Loretto v. Teleprompter Manhattan CATV Corp.*, 458 U.S. 419 (1982).

<sup>16</sup> See *United States v. Causby*, 328 U.S. 256 (1946).

<sup>17</sup> See, e.g. *Penn Central Trans. Co. v. City of New York*, 438 U.S. 104, 124 (1978).

<sup>18</sup> *Penn Central*, at 124.

<sup>19</sup> See *Block v. Hirsh*, 256 U.S. 135 (1921).

<sup>20</sup> See *Village of Euclid v. Amber Realty Co.*, 272 U.S. 365 (1926).

<sup>21</sup> See *Penn Central Trans. Co. v. City of New York*, 438 U.S. 104, 124 (1978).

<sup>22</sup> 467 U.S. 986 (1984).

<sup>23</sup> 7 U.S.C. § 136, *et seq.*

As amended in 1978, FIFRA required that pesticide manufacturers register pesticides with the Environmental Protection Agency (“EPA”) and supply health, safety, and environmental data to demonstrate that each pesticide will not cause “unreasonable adverse effects on the environment.”<sup>24</sup> FIFRA also gave EPA certain authority to use and disclose health, safety, and environmental data submitted to EPA by pesticide manufacturers in the consideration and approval of subsequent applicants for similar pesticides.<sup>25</sup>

Monsanto, a major manufacturer of pesticides, had submitted several applications for registration to EPA throughout the 1960s, 70s, and 80s, which included health, safety, and environmental data about its products. Pursuant to FIFRA, as amended in 1978, EPA proposed to consider Monsanto’s health, safety, and environmental data in evaluating follow-on applications for registration by other manufacturers. Monsanto sued for injunctive relief in Federal Court claiming that such use would effect a taking of property without just compensation, in violation of the Fifth Amendment to the United States Constitution.<sup>26</sup>

The Court first considered whether the Takings Clause applies to intangible property such as trade secrets. To the Court, the “general perception of trade secrets as property is consonant with a notion of ‘property’ that extends beyond land and tangible goods and includes the products of an individual’s ‘labour and invention.’”<sup>27</sup> It therefore unequivocally held that trade secrets are protected by the Takings Clause of the Fifth Amendment.<sup>28</sup>

Having made this initial determination, the Court proceeded to examine whether a taking would occur were EPA to disclose or consider Monsanto’s data in evaluating another application. After acknowledging that this situation does not involve actual government acquisition or physical destruction of property, the Court began to consider the case under the *Penn Central* factors for regulatory takings. The Court focused, however, on the “reasonable investment-backed expectation” prong, because the Court felt that this prong alone “dispose[d] of the taking question regarding [Monsanto’s] data.”<sup>29</sup>

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<sup>24</sup> *Monsanto*, at 991-92.

<sup>25</sup> *Monsanto*, at 992.

<sup>26</sup> *Monsanto*, at 998-99.

<sup>27</sup> *Monsanto*, at 1002-04.

<sup>28</sup> *Monsanto*, at 1003-04.

<sup>29</sup> *Monsanto*, at 1005. Because of its focus on the “reasonable, investment-backed expectation” prong, the *Monsanto* Court’s analysis strongly resembles *per se* takings doctrine. Subsequent lower court opinions therefore have suggested that *per se* takings analysis may be highly appropriate for trade secrets cases. See, e.g., *Lariscey v. United States*, 949 F.2d 1137 (Fed. Cir. (continued...))

The Court first considered data that Monsanto had submitted between the first FIFRA revision in 1972 and the second revision in 1978. It noted that during this period, FIFRA specifically stated that trade secrets or commercial or financial information submitted with an application could not be considered at all by EPA to support another registration application unless the original submitter consented.<sup>30</sup> The Court concluded that this “gave Monsanto explicit assurance that EPA was prohibited from disclosing publicly, or considering in connection with the application of another, any data submitted by an applicant.”<sup>31</sup> This explicit statutory language gave Monsanto a reasonable investment-backed expectation in the protection of its data.

The Court’s discussion regarding data Monsanto submitted prior to 1972 or after 1978 is equally illuminative of the relevant takings analysis. For the period before 1972, for example, the Court noted that FIFRA was silent on the release of trade secret data such as Monsanto’s. Thus, Monsanto could not have had a reasonable investment-backed expectation in the protection of such data submitted prior to 1972.<sup>32</sup> In arriving at this conclusion, the Court specifically noted that up to that time, the government “had thus far taken no position on disclosure of . . . data.”<sup>33</sup>

Regarding data submitted by Monsanto after the 1978 FIFRA amendments, the Court noted that post-1978 FIFRA contained provisions explicitly stating that such information could be released to competitors after a 10-year exclusivity period. Monsanto was therefore “on notice of the manner in which EPA was authorized to use and disclose any data turned over to it by an applicant for registration.”<sup>34</sup> The Court concluded that Monsanto could have no reasonable investment-backed expectation in protection of data submitted to EPA after 1978 when it was on notice that such information could be disclosed.

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1991), *reh’g granted*, 862 F.2d 1047 (Fed. Cir. 1992), *aff’d*, 981 F.2d 1244 (Fed. Cir. 1992) (applying *per se* takings analysis to case involving forced disclosure of prisoner’s trade secret); *Phillip Morris, Inc. v. Reilly*, 312 F.2d 24, 51 (1st Cir. 2002) (en banc) (Selya, J., concurring) (“*per se* takings analysis warrants very serious consideration in regards to the expropriation of trade secrets.”).

<sup>30</sup> *Monsanto*, at 992-93.

<sup>31</sup> *Monsanto*, at 1011.

<sup>32</sup> *Monsanto*, at 1008-09.

<sup>33</sup> *Id.*

<sup>34</sup> *Monsanto*, at 1006

**C. Innovators Have a Reasonable Investment-Backed Expectation in the Protection of Their Trade Secret Manufacturing Information**

Whether they submitted their products under NDAs or BLAs, all innovators of biotechnology-derived products have a reasonable investment-backed expectation that FDA will not disclose their trade secret manufacturing data, or rely, directly or indirectly, on such data for approval of a competing product. This investment-backed expectation is based on at least three factors:

- 1) FDA's own regulations explicitly protect innovators' trade secret data, particularly manufacturing data;
- 2) FDA has maintained a consistent policy against disclosure of or reliance on innovator trade secret data; and
- 3) FDA has maintained a consistent policy against approval of follow-on biologics;

**1. FDA's Own Regulations Explicitly Protect Innovator Trade Secret Data**

FDA's own regulations provide explicit assurance that trade secret manufacturing data submitted in an NDA or BLA will not be disclosed. For example, FDA's regulations at 21 C.F.R. § 314.430 govern FDA's policy on public disclosure of data and information in an NDA. Section 314.430(g)(1) specifically states that "[m]anufacturing methods or processes, including quality control processes" will not be disclosed "unless they have been previously disclosed to the public . . . or they relate to a product or ingredient that has been abandoned and they do not represent a trade secret or confidential commercial or financial information . . ." <sup>35</sup> The same provision exists covering manufacturing data submitted in a BLA in FDA's regulations at 21 C.F.R. § 601.51(f). <sup>36</sup>

Similarly, FDA's regulations at 21 C.F.R. Part 20 govern FDA's release of such information under the FOI Act. Section 20.61(c) specifically states that "[d]ata and information submitted or divulged to the Food and Drug Administration which fall within the definitions of a trade secret or confidential commercial or financial information are not available for public

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<sup>35</sup> 21 C.F.R. § 314.430(g)(1).

<sup>36</sup> "The following data and information in a biological product file are not available for public disclosure unless they have been previously disclosed to the public . . . or they relate to a product or ingredient that has been abandoned and they no longer represent a trade secret or confidential commercial or financial information . . . . (1) Manufacturing methods or processes, including quality control procedures." 21 C.F.R. § 601.51(f).

disclosure.”<sup>37</sup> As discussed above, FDA’s regulations define a “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.”<sup>38</sup> This definition clearly includes manufacturing data in an innovator’s NDA or BLA.

These regulations have been in place as early as 1974,<sup>39</sup> and have been relied upon by innovators submitting confidential trade secret data in support of their NDAs. They thus create “explicit assurance” of the type that was dispositive in *Monsanto*, that FDA is “prohibited from disclosing publicly, or considering in connection with the application of another, any [trade secret] data submitted by an applicant.” As was also the case in *Monsanto* during the 1972-1978 period, this explicit assurance was in place at the time that most current innovators submitted their NDAs and BLAs. The “explicit assurance” relied upon in *Monsanto* need not come from a statute, but can come instead from agency policy and regulation. In *Tri-Bio Laboratories, Inc. v. United States*, for example, the Court observed that an FDA regulation providing that “any reference to information furnished by a person other than the applicant may not be considered” in follow-on animal drug applications unless authorization in writing by the innovator created a reasonable investment-backed expectation necessary to support a takings claim.<sup>40</sup> Explicit assurance in the statute was not necessary.

## **2. FDA Has Maintained a Consistent Policy Against Disclosure of or Reliance on Innovator Trade Secret Data**

For over sixty years, FDA has protected the confidentiality of trade secret data in NDAs.<sup>41</sup> After implementing this policy in 1938, concurrent with the introduction of the FDCA,

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<sup>37</sup> 21 C.F.R. § 20.61(c).

<sup>38</sup> 21 C.F.R. § 20.61(a). *See also* 39 Fed. Reg. 44602, 44614 (stating that FDA’s definition “is intended to serve as a general definition, and not to catalog all information that may have trade secret status”).

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

<sup>40</sup> 836 F.2d 135 (3d Cir. 1988).

<sup>41</sup> *See, e.g.*, Comments of George P. Larrick, Commissioner, FDA, “Interagency Coordination in Drug Research and Regulation,” *Hearings Before the Subcommittee on Reorganization and International Organizations, Senate Committee on Government Operations*, 88th Cong. 1899-1900 (1963) (noting that since 1938, FDA has respected the confidentiality of trade secret data submitted by innovators); 39 Fed. Reg. 44602 (Dec. 24, 1974) (noting FDA policy prior to enactment of the Freedom of Information Act against disclosure of records submitted to FDA, and continuing policy against disclosure of trade secret data subsequent to enactment).

the agency formalized this policy in the early 1970s with its regulations, discussed above, implementing the FOI Act.<sup>42</sup> This longstanding, oft articulated FDA policy has given innovators a reasonable, investment-backed expectation in the protection of their NDA or BLA trade secret data.

FDA has re-affirmed this policy favoring protection of trade secret data frequently and in several different media. For example, FDA officials have reiterated this policy on several occasions in testimony before congressional committees. In 1963, Arthur Ruskin, M.D., Acting Director of FDA's Bureau of Medicine in the Division of New Drugs stated that although he looked forward to the day when drug firms could publish reports of clinical investigations, he specifically noted that this should not include "manufacturing secrets."<sup>43</sup> Again in 1976, FDA officials restated FDA's policy of protecting trade secret data as developed in FDA's FOI Act regulations.<sup>44</sup> FDA has also reiterated this policy in court briefs filed by the Department of Justice on behalf of the United States,<sup>45</sup> and in reports that have considered the matter.<sup>46</sup>

FDA has reaffirmed this policy as recently as 2003. In 2002, FDA granted tentative approval to a section 505(b)(2) application for a follow-on version of amlodipine maleate. In October 2003, however, FDA reversed its position and stayed approval of the application on the ground that "questions [were] raised about the source of the data the [FDA] relied on in approving the NDA."<sup>47</sup> Although the agency provided no further explanation for its actions, it is

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<sup>42</sup> See 37 Fed. Reg. 9128, 9130-31 (May 5, 1972); 39 Fed. Reg. 44602, 44612-14, 44634-38.

<sup>43</sup> Comments of Arthur Ruskin, M.D., "Interagency Coordination in Drug Research and Regulation," *Hearings Before the Subcommittee on Reorganization and International Organizations, Senate Committee on Government Operations*, 88th Cong. 1893 (1963).

<sup>44</sup> "Drug Safety Amendments of 1976," *Hearings Before the Subcommittee on Health and the Environment, House Committee on Interstate and Foreign Commerce*, 94th Cong. 60 (1976). See also, "Competitive Problems in the Drug Industry," *Hearings Before the Subcommittee on Activities of Regulatory Agencies, House Select Committee on Small Business*, 90th Cong. 743-46, 748-49, 755, 761 (1967); "Small Business Problems in the Drug Industry," *Hearings Before the Subcommittee on Activities of Regulatory Agencies, House Select Committee on Small Business*, 90th Cong. 370, 383 (1967 & 1968); "Drug Listing Act, 1971," *Hearing Before the Senate Committee on Labor and Public Welfare*, 92nd Cong. 31-32, 46, 50, 54, 59 (1971).

<sup>45</sup> See, e.g., Briefs for FDA in: *Morgan v. FDA*, 495 F.2d 1075 (D.C. Cir. 1974); *Weinberger v. Hynson, Westcott & Dunning*,

<sup>46</sup> See, e.g., Review Panel on New Drug Regulation, *Interim Report: An Evaluation of FDA's Trade Secrets and Freedom of Information Policies 2*, 17-27 (November 1976).

<sup>47</sup> See Letter from Janet Woodcock, FDA, to Ms. Sanzo and Messrs. Chasnow, Lawton, and Rakoczy (October 14, 2003). In response to questions posed by the Senate Judiciary following a June 2004 hearing, FDA suggested that review staff is permitted to review manufacturing (continued...)

likely that FDA concluded that its reviewers improperly relied on trade secret data in the innovator's NDA to approve the follow-on application. And as recently as this year, the United States Court of Appeals for the 8th Circuit confirmed the trade secret status of manufacturing data associated with Premarin, Wyeth's biotechnology-derived conjugated estrogen product.<sup>48</sup>

Thus, FDA has established a clear, long-standing, well articulated policy against the use of innovator manufacturing data in the consideration of competing drug and biologic applications for approval. This contrasts sharply with the pre-1972 time period in *Monsanto*, where the Court found that the government "had thus far taken no position on disclosure of . . . data." The lack of such a longstanding policy by EPA figured prominently in the *Monsanto* Court's holding that no taking had taken place for data submitted to EPA prior to 1972. It follows, therefore, that FDA's longstanding policy would persuade a court that a taking had occurred should FDA reverse its longstanding position and rely on or reference trade secret data in an innovator's NDA or BLA. Courts are "generally deferential to longstanding policies or statutory interpretations of an agency, and they closely examine recent departures from such agency precedent."<sup>49</sup>

The case presented here is also easily distinguishable from the *Monsanto* Court's refusal to find a taking for data Monsanto submitted to EPA after 1978. FIFRA, as amended in 1978, set forth precisely how, and under what circumstances, EPA could use Monsanto's data in its consideration of subsequent applications. The *Monsanto* Court determined that because EPA proposed to use Monsanto's data, as was clearly permitted under the statute, Monsanto "was on notice of the manner in which EPA was authorized to use and disclose" Monsanto's data.<sup>50</sup> Monsanto could therefore not be heard to complain if EPA acted on its authority under FIFRA with respect to data Monsanto had submitted after 1978.<sup>51</sup>

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specifications in one application before providing comments on another manufacturer's specifications. See "The Law of Biologic Medicine, 2004," *Hearing Before the Senate Comm. on The Judiciary*, 108th Cong., 2d Sess. at 65-66 (June 23, 2004). Not only would such an approach be unlawful, it would also represent a sudden and unjustified departure from long held and well established FDA policy. Comments such as these, and others regarding follow-on biologics, form part of the basis for the Genentech Citizen Petition and subsequent comments filed to that docket.

<sup>48</sup> See *Wyeth v. Natural Biologics, Inc.* No. 03-3651, slip op. at 5 (8th Cir. Jan. 25, 2005).

<sup>49</sup> *AFL-CIO v. Brock*, 835 F.2d 912, 917 (D.C. Cir. 1987) (citing *NLRB v. Bell Aerospace Co.*, 416 U.S. 267, 274-75 (1974)).

<sup>50</sup> *Monsanto*, at 1006 (emphasis added).

<sup>51</sup> *Id.*

The FDCA, however, does not put innovator companies on notice that their manufacturing data may be used in consideration of follow-on applications. Even if it is conceded that sections 505(j) and/or 505(b)(2) provide FDA with authority to rely on certain innovator data in its consideration of follow-on applications for products regulated as drugs, this authority is expressly limited. Under 505(j), FDA is authorized to rely on innovator safety and effectiveness findings if, and only if, the generic applicant first demonstrates that its product is “the same as” the innovator’s. Nowhere, however, does section 505(j) authorize FDA to use manufacturing data in an innovator’s NDA to make such a characterization. Similarly, FDA has argued that section 505(b)(2) gives it authority to rely on its findings of safety and efficacy based on clinical trials in the innovator’s NDA to demonstrate a generic’s safety and effectiveness profile.<sup>52</sup> Nowhere, however, does section 505(b)(2) authorize reliance on or disclosure of innovator manufacturing data. Thus, although innovator’s may be on notice of a certain limited “manner” in which FDA may use or rely on certain innovator data to evaluate follow-on products, that “manner” clearly does not include the use of trade secret manufacturing data in an innovator’s NDA.

### **3. FDA Has Maintained a Consistent Policy Against Approval of Follow-On Biologics**

In addition to its longstanding position against disclosure of trade secret data in an NDA or BLA, FDA has also maintained a longstanding policy against approval of follow-on biologics. As discussed above, FDA has always recognized that it lacks the statutory authority to approve follow-on versions of biotechnology-derived products originally approved under section 351 of the PHSA.<sup>53</sup> Even for those biotechnology-derived products approved under section 505 of the FDCA, however, FDA has also long-recognized that current science does not render approval of *any* follow-on version of a biotechnology-derived product unless that product has undergone clinical testing to separately demonstrate the safety and effectiveness of the follow-on product.

For example, in FDA’s 1974 regulations implementing the FOI Act, the Agency noted that “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.”<sup>54</sup> As detailed above, and in other comments submitted to this docket, the fact that “all biological products are to some extent different” applies as much to biotechnology-derived products approved under section 505 of the FDCA as it does to such products originally approved under the PHSA. As a result, FDA’s policy against “me-too” biologics applies whether the innovator product was approved through an NDA or BLA.

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<sup>52</sup> See FDA letter of October 14, 2003, *supra* note 47.

<sup>53</sup> See *supra* note 3.

<sup>54</sup> 39 Fed. Reg. 44602, 44641 (December 24, 2974).

**D. The Other *Penn Central* Factors Weigh in Favor of a Finding of a Taking**

As discussed above, in finding that a taking had occurred for data submitted from 1972 to 1978, the *Monsanto* Court focused exclusively on the “reasonable investment-backed expectation” prong of the *Penn Central* test. Other courts have strongly suggested that disclosure of trade secrets may constitute a *per se* taking rather than a regulatory taking. As a result, having established that innovators of biotechnology-derived products have a reasonable investment-backed expectation in the protection of their trade secret data (particularly manufacturing data) submitted in their NDA or BLA, it may not be necessary to establish the remaining *Penn Central* factors.

Nevertheless, the remaining *Penn Central* factors strongly favor a finding of a taking should FDA disclose or rely, directly or indirectly, upon such trade secret information in approving a follow-on biologic. For example, were FDA to rely upon innovator manufacturing data to approve a follow-on biologic, the economic impact on the innovator would be severe. The research and development costs for new biotechnology-derived products are tremendous. These expenditures are feasible only if innovators can recoup these costs through exploitation of the advantages of market position and scientific know-how that naturally inure to innovators over follow-on manufacturers. As the *Trio-Bio* Court recognized, were FDA to use that know-how (manifested in the trade secret data contained in the innovator’s NDA or BLA) to approve a follow-on product, it would “amount to a virtual government subsidy of the generic . . . manufacturers.”<sup>55</sup> Not only would the financial consequences to innovators be severe, such a policy would jeopardize the prospects for future innovation for the entire biotechnology industry.

Similarly, the character of the government action would favor the finding of a taking. As the *Penn Central* Court suggested, “[a] ‘taking’ may be more readily found when the interference with property can be characterized as a physical invasion by government than when interference arises from some public program adjusting the benefits and burdens of economic life to promote the public good.”<sup>56</sup> Were FDA to use innovator manufacturing data to approve competitor products, it would virtually destroy the fundamental right to exclude, which is inherent in intellectual property. As the *Monsanto* Court recognized, “if an individual discloses his trade secrets to others who are under no obligation to protect the confidentiality of the information, or otherwise discloses the secret, his property right is extinguished.”<sup>57</sup> This type of

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<sup>55</sup> *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135, 141 (3d Cir. 1988).

<sup>56</sup> *Penn Central*, at 124.

<sup>57</sup> *Monsanto*, at 1002.

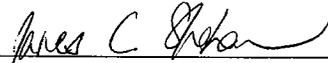
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“extinguishment” of trade secret rights was dispositive in the First Circuit’s takings analysis in *Phillip Morris v. Reilly*.<sup>58</sup>

### III. Conclusion

FDA’s explicit regulations prohibiting FDA disclosure of trade secrets, as well as the Agency’s clear and longstanding policies against disclosure of trade secret data in a manufacturer’s NDA or BLA and against the approval of “me-too” biologics, have given innovators of biotechnology-derived products a reasonable investment-backed expectation that their trade secret data and confidential commercial information will not be used to approve a follow-on biologic. Whether their products were approved through an NDA or a BLA, innovators have relied on this reasonable investment-backed expectation in submitting sensitive trade secret data to FDA for the sole purpose of assisting the Agency in making its safety and effectiveness determinations. As a result, were FDA to use this data in any way to approve a follow-on biologic, it would constitute a taking without just compensation under the United States Constitution.

Respectfully submitted,

  
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<sup>58</sup> 312 F.3d 24, at 41-42 (1st Cir. 2002).