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VIA HAND DELIVERY

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

Re: Comments on Behalf of Barr Laboratories, Inc.
Docket Nos. 2004P-0171, 2004P-0231, and 2003P-0176

Dear Sir or Madam:

On behalf of Barr Laboratories, Inc., we submit the attached comments addressing arguments made in the following citizen petitions:

(1) Genentech Citizen Petition Docket No. 2004P-0171;

(2) Pfizer Citizen Petition Docket No. 2004P-0231; and

(3) Biotechnology Industry Organization ("BIO") Citizen Petition Docket No. 2003P-0176.

Pursuant to 21 C.F.R. § 10.20(a), we include twelve (12) copies of the attached comments so that four (4) copies may be filed in connection with each docket noted above.

Should you have any questions regarding these comments, please do not hesitate to contact me. We appreciate the opportunity to comment on this important issue.

Very truly yours,

RAKOCZY MOLINO MAZZOCHI SIWIK LLP

Christine J. Siwik

CJS/cd
Enclosures

2003P-0176 C2

Comments on Behalf of Barr Laboratories, Inc.
(Docket Nos. 2004P-0171, 2004P-0231, and 2003P-0176)

INTRODUCTION

Without question, the Food and Drug Administration ("FDA") has the authority to issue a draft guidance document setting forth standards for determining the "similarity" or "sameness" of biologic products and to adopt a pathway for the approval of generic biologics.[1] In doing so, the Agency has the authority to, and should, draw on its considerable specialized experience and expertise with drug and biologic approvals.

The current state of the art with respect to biologic products allows FDA to develop a process for approving generic biologics. The now-existing technology allows the Agency to characterize biologic products without relying on the innovator data in the manner Genentech and others suggest. Indeed, the Agency itself noted years ago that "[i]mprovements in production methods, process and control test methods, and test methods for product characterization have led to the evolution of the regulation of biological products." (FDA Guidance Concerning Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products, at 2 (Apr. 1996) ("1996 Comparability Guidance")).

Further, even if FDA needed to rely as extensively as Genentech contends on an innovator's information, the Agency has the authority to do so. Such reliance does not violate any statute, nor does it constitute an unconstitutional taking by the government.

In the end, the Agency should see these petitions for what they are – a not-so-subtle attempt by brand companies to thwart generic competition so that they can reap monopoly profits indefinitely. (*See* Combating Generics: Pharmaceutical Brand Defense, Online Report Summary at 8-9 (2004) ("Executives at major biotech players such as Amgen and Genentech have started to believe that [the] lack of approval pathway means their drugs would enjoy near-monopolies even after patent expiry.") (Exhibit 1). According to one source, "[t]hrough 2006, over $10 billion worth of branded biologics are scheduled to go off patent." (*See* Generic Biologics: The Next Frontier at 4 (June 2001) (Exhibit 2). It likely is no coincidence that by 2005, Genentech will have had three biologic products come off patent. (*Id.* at 5). In 2000 alone, sales of those three Genentech products exceeded $400 million. (*Id.*). The American public should not be forced to pay monopoly prices for products that are no longer patent protected. Given the health care crisis currently facing the United States, FDA must complete this important draft guidance as soon as possible. In doing so, FDA should deny the entirety of each of these three petitions.

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[1] Genentech's petition focuses on the generic pathway provided in 21 U.S.C. § 355(b)(2). Barr's response addresses the Agency's authority to issue a draft guidance and to approve a generic biologics pathway.

DISCUSSION

FDA currently is developing a draft guidance document setting forth how a generic manufacturer might show that its product is "similar" to or the "same" as a pioneer biologic product. Genentech asks the Agency to refrain from publishing this critical draft guidance, arguing that: (1) knowledge of the manufacturing processes used to make a particular biologic is critical to assessing the safety and effectiveness of a generic alternative; and (2) federal law prohibits the Agency from either using or disclosing an innovator's data to approve a biologics application submitted by another company. (*See* Genentech Pet. at 7, 12-15, 17, 19-25).[2] Genentech is mistaken.

Genentech's argument rests upon two fundamental assumptions. First, Genentech assumes that FDA cannot issue a "sameness" guidance for biologics without relying extensively on and/or disclosing the innovator's data. Second, Genentech assumes that relying on an innovator's data and the Agency's specialized knowledge of biologic manufacturing processes to draft a guidance would be improper. Genentech's assumptions are erroneous, and its attempt to delay indefinitely generic competition must fail.

I. FDA Can Draft A Guidance Document And Establish An Approval Pathway For Generic Biologics Without Relying Upon Specific Innovator Data – The Current State Of The Art Allows Biologics To Be Characterized And Compared Analytically.

The Agency can draft a guidance and establish a generic biologics approval path without improper reliance on innovator data. The state of the art today allows biologics to be characterized and compared analytically. Genentech's "the product is the process" argument to the contrary cannot withstand scrutiny. Indeed, Novartis – one of the world's largest and most sophisticated pharmaceutical companies – agrees: "Old models and mantras are inhibiting progress – **the product is *no longer* the process.**" (Statement of Mathias Hukkelhoven, Ph.D., Senior V.P., Global Head, Drug Regulatory Affairs, Novartis, Sept. 14-15, 2004 FDA Public Workshop at 3 (emphasis in original) (Exhibit 3).

Genentech argues that FDA will rely on an innovator's trade secrets in drafting the guidance document. (Genentech Pet. at 4-6). According to Genentech, this necessarily is the case because analytical testing of a generic "biotechnology-derived pharmaceutical" to demonstrate similarity to an approved drug is insufficient to establish the safety and effectiveness of the generic. (*Id.* at 6). Instead, the argument goes, approving a generic biologic product necessarily requires the Agency to rely, directly or indirectly, on the innovator's data. (*Id.* at 6, 22). Genentech's argument presumes, of course, that the science cannot support a generic biologic pathway without relying on the innovator's manufacturing processes to perform

[2] The Pfizer and BIO petitions make essentially the same points. (*See* Pfizer Pet. at 5-8, 24-31; BIO Pet. at 3-5, 9-14, 38-51). Because Genentech's petition contains the most extensive discussion opposing FDA's issuance of its draft guidance, Barr's response focuses on that petition. Barr's arguments apply equally to all three petitions.

the comparative assessments necessary to ascertain the "similarity" or "sameness" of two biologic products. For support, Genentech relies on a 1974 FDA regulation. (*See* Genentech Pet. at 15 (citing 39 Fed. Reg. 44602, 44641 (Dec. 24, 1974))). Genentech's reliance is misplaced, and its argument fails on the merits.

Given the scientific techniques of the early-1970s, it might well have been inappropriate or impractical to demonstrate the safety and efficacy of a generic biologic by showing sufficient similarity to an approved biotechnology-derived drug. In 1974, genetic engineering was in its infancy. Scientists were years away from producing recombinant human proteins, even on a small-scale. The government project to map the entire human genome had not started. The first biotechnology-derived product, recombinant human insulin, was more than eight years away. The polymerase chain reaction (PCR) technique, which permits the rapid amplification of DNA and revolutionized molecular biology and genetic engineering, was a decade away. But science, of course, did not stand still the last three decades. The state of the art has progressed to the point where such a comparison is viable and reasonable, meaning that FDA need not rely on innovators' process information in the manner Genentech suggests. *See* G.E. Gamerman, *Regulation of Biologics Manufacturing: Questioning the Premise*, 49 FOOD & DRUG L.J. 213, 221 (1994) (recognizing that even by the 1980s, "[b]iotechnology companies [had] dissolved many of the traditional scientific boundaries between biologics and drugs and devices. New technologies enabled biologics manufacturers to purify and characterize their products to a degree which previously could be achieved only with pharmaceutical drugs.") (Exhibit 4).

Over the past thirty years, significant advancements have been made in the fields of genetic engineering, molecular biology, recombinant protein technology, and protein purification. For example, while the production of a clinically safe and efficacious recombinant human insulin and human growth hormone admittedly were extraordinary accomplishments in the 1980s, the molecular biological and biochemical techniques underlying the development of biotechnology-derived pharmaceuticals are now firmly established procedures in the art. Numerous biotechnology-derived pharmaceuticals have been developed and marketed for the treatment of a variety of clinical disorders, such as cardiovascular diseases, cancer, and rheumatoid arthritis. By the end of 2003, FDA had approved more than 50 therapeutic biologicals, including recombinant antibodies, enzymes, blood factors, and other proteins expressed and purified from bacteria, yeast, and animal cells. Many more biotechnology-derived products are in the pipeline.[3]

The fact is, the original scientific rationale for "process-based" regulation of biologics no longer applies. Today, several highly sophisticated analytical methods have been developed that permit characterization of complex proteins. Biologics now have properties similar to pharmaceutical drugs, including:

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[3] *See, e.g.*, Food and Drug Administration, Center for Drug Evaluation and Research, at http://www.fda.gov/cder/biologics/biologics_table.htm.

> (1) the identity and characteristics of the biologic can be determined and verified with exacting precision; (2) the biologic can be consistently produced with uniform purity, potency, and identity; and (3) the existence of low-level contaminants or microheterogeneity can be identified, characterized and controlled.

Gamerman, 49 FOOD & DRUG L.J. at 226-27. Indeed, even "CBER has stated, unlike traditional biologics, many modern biologics are characterized by sensitive physicochemical techniques and can be produced with 'drug-like' purity and consistency; the risk of biocontamination is minimal and no greater than for most drugs." *Id.* at 226. (*See also* 1996 Comparability Guidance, at 2 (acknowledging the "[i]mprovements in production methods, process and control test methods, and test methods for product characterization" of biologics)). Thus, Genentech's (as well as Pfizer's and BIO's) "the product is the process" position, while arguably true in the 1970s, is no longer scientifically valid and cannot form a basis for the Agency to refuse to issue its draft guidance.

Genentech also incorrectly argues that the Agency cannot properly rely on analytical comparisons of the end products of biotechnology-derived pharmaceuticals when reaching conclusions about how a product will behave clinically in humans. (Genentech Pet. at 9). This argument presumes the existence of but a single method for manufacturing and purifying a particular protein. In truth, the art is replete with recombinant protein expression and purification techniques that could be used to produce sufficiently similar protein-based products. The manufacturing processes Genentech and others seek to protect as trade secrets merely represent one way in which a particular safe and effective biotechnology-derived pharmaceutical can be produced. Indeed, even if these processes represent the "best" way to manufacture the product in terms of yield and cost, Genentech offers the Agency no reason to believe that alternative methods necessarily would fail to produce the same or a sufficiently similar product.

Finally, Genentech's argument on the science conveniently ignores the fact that biotech firms, like Genentech, routinely justify process changes via comparability protocols. The Agency's 1996 Comparability Guidance allows manufacturers to make manufacturing changes without performing additional clinical studies to demonstrate safety and efficacy by establishing "comparability between a product made before a manufacturing change and a product made after a manufacturing change." (1996 Comparability Guidance at 3). Drawing on its experience with biologics, the Agency issued just last year a Draft Guidance for Industry: Comparability Protocols - Protein Drug Products and Biological Products - Chemistry, Manufacturing, and Controls Information ("2003 Comparability Protocols Guidance"). That Guidance sets forth in detail the process for submitting comparability protocols for biologic products. The pharmaceutical industry anticipated and advocated the 2003 Comparability Protocols Guidance, voicing none of the objections raised in Genentech's petition. This is, of course, because companies like Genentech benefited significantly from that Guidance, which

allows them to avoid carrying out the very testing that Genentech now demands FDA force generic companies to conduct.

In sum, biotechnology-derived pharmaceutical products can be characterized and compared analytically. The expression and purification of recombinant proteins and the subsequent development of safe and effective biotechnology-derived pharmaceuticals from these purified proteins is well within current scientific knowledge. Genentech's arguments thus fail on the merits.

II. FDA Has The Authority To Issue A Draft Guidance Setting Forth Standards For Determining The "Similarity" Or "Sameness" Of Biologic Products, And To Establish A Generic Biologics Pathway, Even If Doing So Requires The Agency To Rely Upon Innovator Data.

A. The Agency Has The Authority To Issue A Draft Guidance And To Establish A Generic Biologics Pathway.

Even if FDA had to rely on innovator data when developing its guidance, Congress gave the Agency the authority to do so. FDA has, in fact, exercised its authority on numerous occasions to issue guidance documents analogous to the biologic guidance at issue here. The Agency did so in 1996 with its Comparability Guidance. It did so again in 2003 when it issued the Comparability Protocols Guidance. These guidances promote good science and serve a valuable function by informing the industry about the Agency's thoughts and best practices on a particular subject. The Agency's use of its institutional knowledge in this way is entirely appropriate and lawful.

First, several statutory provisions evidence the Agency's authority to rely on information in addition to the data submitted in the generic application when determining safety and efficacy. Congress granted FDA the authority to carry out the Agency's mission, including the authority to promulgate regulations governing the approval of drug and biologic products. *See* 21 U.S.C. § 393(d)(2); 21 C.F.R. Part 314; 21 C.F.R. Part 600; *see also* 69 Fed. Reg. 25404, 25405 (May 6, 2004). FDA's authority is limited only so far as the Agency is required to promulgate regulations consistent with the language of the statutes it administers, and their amendments. *See* H.R. REP. NO. 98-857, pt. I at 36 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2647, 2669. For instance, the Public Health Service Act ("PHSA") grants FDA authority to "establish, by regulation, requirements for the approval, suspension, and revocation of biologics licenses." 42 U.S.C. § 262(a)(2)(A). Section 262 further provides that FDA shall approve a biologics license application on the basis of "a demonstration" that, among other things, the biologic product is safe, pure, and potent. 42 U.S.C. § 262(a)(2)(B)(i). The Agency can approve a biologic product based upon data on "comparable" drugs, and does not require each applicant to complete clinical trials. *See* 42 U.S.C. § 262; *Berlex Labs., Inc. v FDA*, 942 F. Supp. 19, 25-26 (D.D.C. 1996). Indeed, FDA's own implementing regulations do not require the applicant to conduct the clinical studies offered to demonstrate a product's safety, purity, and

potency on that specific product. *See* 21 C.F.R. § 601.2; *see also Berlex*, 942 F. Supp. at 25. Thus, under the PHSA, there is no question that FDA has the authority to rely on innovator data when developing its guidance and establishing a generic biologics pathway.

Similarly, FDA has the authority under the Federal Food, Drug, and Cosmetic Act ("FFDCA") to rely on innovator data when developing a draft guidance and establishing a generic biologics pathway. When determining the safety or efficacy of a drug product, the FFDCA expressly allows FDA to make its determination on the basis of "the information submitted to [it] as part of the application, *or upon the basis of any other information before [it] with respect to such drug*". 21 U.S.C. § 355(d) (emphasis added); *see also* 21 U.S.C. § 355(j)(4)(H) (authorizing FDA to make safety determinations on the basis of information submitted with the application "or any other information available to the Secretary"); 21 U.S.C. § 355(b)(2) (permitting an application to be submitted for a drug "for which the investigations . . . were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use"); 21 U.S.C. § 355(j)(2)(A) (permitting an applicant for an Abbreviated New Drug Application ("ANDA") to rely on clinical testing of safety and efficacy submitted in a previously approved New Drug Application ("NDA")).

Second, the courts have consistently upheld FDA's authority to draw on its experience with specific applications when issuing guidance documents. In *Berlex*, a biotech innovator challenged the Agency's 1996 Comparability Guidance. Under that guidance, the Agency will approve a biologic product based, in part, on studies conducted on a "comparable" product. 942 F. Supp. at 22-26. A few weeks after issuing the 1996 Comparability Guidance, the Agency approved a biologic product without requiring clinical trials, allowing the applicant to rely on studies conducted on a comparable product. *Id.* at 22.[4] The innovator challenged, among other things, the Agency's authority to issue the guidance. The court rejected the innovator's challenge. The court found that the 1996 Comparability Guidance was an "interpretive" document "'issued by an agency to advise the public of the agency's construction of the statutes and rules which it administers,'" rather than a new "legislative" or "substantive" rule. *Id.* at 26 (quoting *Shalala v. Guernsey Mem'l Hosp.*, 514 U.S. 87, 99 (1995)). The court then held that the Agency has the "statutory authority to approve [a biologic product] without requiring clinical trials" and that the Agency could instead rely on data from clinical studies completed on comparable biological products. *Id.*

The *Berlex* decision is just one of the many instances where the courts have recognized the Agency's broad authority to establish safety and efficacy standards. In *Schering Corp. v. FDA*, 51 F.3d 390 (3d Cir. 1995), for example, the court noted that "judgments as to what is required to ascertain the safety and efficacy of drugs fall squarely within the ambit of the FDA's expertise and merit deference" from the courts. *Id.* at 399. The *Schering* court then rejected an innovator's challenge to FDA's regulations implementing the bioequivalence

[4] The court assumed for purposes of its analysis that the issuance of the guidance document and the approval of the drug at issue "were in fact related events." *Id.* at 26.

requirements of 21 U.S.C. § 355(j)(7)(B), allowing the generic product to enter the market. *Id.* at 399-400. Similarly, in *Serono Labs., Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998), the court recognized the Agency's broad authority to determine "sameness" when approving generic drugs. Specifically, the court stated that the "FDA's determination of what is required to establish 'sameness' for purposes of the Act rests on the 'agency's evaluations of scientific data within its area of expertise,' and hence is entitled to a 'high level of deference.'" *Id.* at 1320 (dissolving injunction that prevented FDA from approving a generic drug containing proteins) (citations omitted).

Given the relevant statutory provisions and case law, the Agency plainly has the authority to rely, if necessary, on innovator data when approving a generic biologic product. Genentech's arguments to the contrary thus cannot stand.

B. FDA's Internal Use Of Its Institutional Knowledge When Issuing The Proposed Guidance Or Approving Generic Biologics Would Not Violate Statutory Or Regulatory Protections For Innovator Intellectual Property Rights.

Genentech asserts that FDA is statutorily prohibited from not only publicly disclosing innovator data, but also from *internally* using such data when developing a guidance document on generic biologics and approving generic biologic products. (Genentech Pet. at 14-16, 20-24). Genentech's argument lacks merit. FDA not only has the statutory authority to establish a guidance document and generic biologics approval pathway, as noted above, but FDA may also lawfully use trade secret data and confidential information learned through the course of the Agency's duties to develop this guidance and biological approval pathway.[5]

At the heart of Genentech's argument lies its contention that "there is no practical difference between use and disclosure of Genentech's protected data" when FDA reviews an application for approval. (Genentech Pet. at n.29). Whether Genentech sees the distinction or not, the law in fact makes a significant distinction between publicly disclosing confidential information and internal agency use of confidential information. None of the statutory and regulatory authorities that Genentech cites supports its arguments. FDA is free to establish a generic biologic pathway and guidance, even if doing so requires internal Agency reliance on innovator trade secrets and other confidential commercial information.

Legally important differences exist between internal Agency use of confidential commercial and trade secret information, and public disclosure of that same information. A number of laws and regulations, for example, prohibit public disclosure of an applicant's trade secrets. Yet, significantly, none prohibits the Agency's *internal use* of confidential commercial information to develop a guidance document or a pathway for approval of generic biologics.

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[5] As discussed *infra*, Barr does not concede that manufacturing process data automatically qualify for trade secret protection.

The following statutory and regulatory provisions restriction FDA's use of confidential information:

- The Trade Secrets Act prohibits an agency from *disclosing*, "to any extent not authorized by law," trade secrets and related data. 18 U.S.C. § 1905.

- The Freedom of Information Act ("FOIA") prohibits agency *disclosure* of materials that are "trade secrets and commercial or financial information obtained from a person and privileged or confidential." 5 U.S.C. § 552(b)(4).

- The FFDCA prohibits any person *using "to his advantage" or revealing*, other than to Agency employees or a court in certain instances, information concerning "any method or process which as a trade secret is entitled to protection." 21 U.S.C. § 331(j) (emphasis added).

- FDA's regulations prohibit the "*public disclosure*" of trade secret or confidential commercial data submitted or divulged to FDA, 21 C.F.R. § 20.61(c) (emphasis added), and also prohibit the "public disclosure" of manufacturing methods and processes, 21 C.F.R. § 314.430(g)(1); 21 C.F.R. § 601.51(f)(1).

Each of these statutory or regulatory provisions, at the most, prohibits the public disclosure of trade secrets or an Agency employee's use of such information for the sole purpose of benefiting personally from such use. None of these provisions prohibits the internal Agency use that Genentech challenges. And, of course, the Agency considers the confidentiality provisions of each of these statutory provisions to be identical in scope. *See* 39 Fed. Reg. 44602, 44612 (Dec. 24, 1974).

The Supreme Court has expressly held that the Trade Secrets Act "cannot be construed as any sort of assurance against internal agency use of submitted data during consideration of the application of a subsequent applicant for registration." *Ruckelshaus v. Monsanto Co.*, 467 U.S. 986, 1009 (1984). In that case, which is discussed in more detail below, the Court held that the EPA did not violate the Trade Secrets Act when it considered the data of one applicant in connection with the application of another. *Id.* at 1009 n.13; *see also Chevron Chem. Co. v. Costle*, 641 F.2d 104, 115-16 (3d Cir. 1981) (stating that the Trade Secrets Act cannot reasonably be "the source of an expectation of general agency non-use").

The Agency reached the same conclusion about the statutory language found in FOIA. The Agency recognized long ago that, while trade secret information may not be disclosed, "[t]his does not mean, however, that agency research or regulatory requirements cannot be based upon trade secret information. For example, bioavailability data on a drug submitted by a manufacturer may constitute trade secret information that is not disclosable to the public. This trade secret status of the underlying information would not prevent the Food and Drug Administration from conducting and disclosing its own similar research, however, or from

imposing by regulation new requirements for the drug involved in order to protect the public health." 39 Fed. Reg. at 44626.

Similarly, there can be no question that, while public disclosure of confidential method or process information may be prohibited under the FFDCA, the Agency is permitted to rely on confidential commercial information and clinical studies in approving other subsequent applications. *See* 21 U.S.C. § 355(b)(2); § 355(j). Indeed, Genentech concedes this point. (*See* Genentech Pet. at 20). Despite this fatal concession, Genentech nevertheless maintains that, under 21 U.S.C. § 331(j) and 21 C.F.R. § 314.50(g)(3), "FDA may not use or disclose trade secret data submitted by any applicant without the express permission of that applicant." (*Id.* at 21). This is entirely inaccurate. As noted above and discussed in more detail *infra*, 21 U.S.C. § 331(j) only prohibits Agency employees from using to their own advantage, or revealing to the public, trade secret methods or processes. FDA's regulation merely states that *if* an applicant obtains a right of reference or use to investigations described in 21 U.S.C. § 355(b)(1), the application shall include a written statement by the owner of the data granting leave to the applicant to rely on such data. *See* 21 C.F.R. § 314.50(g)(3). The FFDCA does not, however, require that all subsequent new and generic drug applicants obtain a right of reference or use; nor does it require FDA to make generic biologic applicants obtain such a right of reference or use. *See* FDA Oct. 14, 2003 Ltr. Re: Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 at 9-10, 21-22, 34.

Continuing to ignore the clear language and import of these statutes and regulations, Genentech attempts to bolster its argument by observing that while FDA has the authority under the FFDCA to approve generic drugs via the ANDA route, the Agency has never exercised this authority to approve generic biologics. (Genentech Pet. at 20). Such an observation, however, fails to explain how and why the Agency would be prohibited from choosing to take advantage of this generic route if it so desired. This is, of course, because there is no such prohibition.[6]

The fact is, the Agency frequently makes internal use of information that it gains as a result of its review and approval of drug applications. As explained above, the Agency historically and repeatedly has drawn on its general experience in using – without publicly disclosing – its knowledge of a particular applicant's data in approving subsequent NDAs or ANDAs. The same holds true when the Agency develops guidance documents. FDA, for example, draws on its experience with paper NDAs and other application methods in developing

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[6] Genentech also implies that the doctrine of inevitable disclosure, relating to the law of trade secrets, applies here to prohibit Agency use of innovator information. (Genentech Pet. at 15). Not so. The inevitable disclosure doctrine applies only where an employee inevitably will disclose trade secrets discovered during the course of his employment to his (or his future employer's) benefit. *See PepsiCo, Inc. v. Redmond*, 54 F.3d 1262, 1268-71 (7th Cir. 1995). Genentech's challenge to FDA's internal Agency use of trade secret or confidential information is based on its concerns that the Agency will use such information to benefit another subsequent biologic applicant, and not that an Agency employee will himself or herself benefit, or that a future employer will benefit from the disclosure of such data. Thus, this doctrine is inapplicable.

the approval pathways that currently govern generic drugs. Similarly, FDA draws on its institutional knowledge about the manufacturing processes for certain biologic products in issuing Comparability Guidances. (*See* 1996 Comparability Guidance; 2003 Comparability Protocols Guidance). FDA could do the same in developing an approval pathway for generic biologics.

In sum, when developing guidance documents and approving subsequent drug applications, FDA acts in furtherance of its mission and within its authority to develop policies and processes to promote efficiency and competition. This, in turn, reduces the cost of drug and biologic products to consumers and the Government, while at the same time maintains scientific safety and effectiveness standards. To expect FDA to act otherwise would distort Congress's directives and grants of authority to the Agency. Accordingly, FDA's own internal use of trade secret or other confidential data in the analysis of, and conclusions about, a drug's safety and efficacy are outside the scope of the statutory and regulatory trade secret nondisclosure requirements.

C. FDA's Internal Use Of Innovator Data To Issue A Guidance Or Establish A Generic Biologics Pathway Would Not Constitute An Impermissible Fifth Amendment Taking.

Genentech argues that the unauthorized use of its protected data and information would constitute an unconstitutional taking. (Genentech Pet. at 24). According to Genentech, it is thus entitled to notice, hearing, and an opportunity for judicial review before FDA issues a guidance document or approves a generic copy of any Genentech biotechnology-derived product based on Genentech's protected data and information. (*Id.* at 25). Here, too, Genentech's arguments lack merit.

The Fifth Amendment to the U.S. Constitution forbids the taking of private *property* for public use without just compensation. Any takings analysis must then start with a precise understanding of the property at issue. As the U.S. Supreme Court has noted, "[p]roperty interests, of course, are not created by the Constitution. Rather, they are created and their dimensions are defined by existing rules or understandings that stem from an independent source such as state law – rules or understandings that secure certain benefits and that support claims of entitlement to those benefits." *Bd. of Regents v. Roth*, 408 U.S. 564, 577 (1972).

Genentech claims that its safety and effectiveness data constitutes trade secret information, which qualifies as a property right subject to Fifth Amendment protections. (Genentech Pet. at 10-12, 24). Barr does not concede this point. FDA's own regulations merely state that "[a] trade secret *may* consist of any commercially valuable . . . process . . . ." 21 C.F.R. § 20.61. And Genentech has made no showing that its safety and efficacy data, or its manufacturing information, qualifies as trade secrets under either federal or state law. Thus, while some information contained in a new biologic application *may* qualify as trade secret information, neither Congress nor FDA has mandated this result. Indeed, in FDA's notice of

proposed rulemaking for its FOIA regulations, FDA put biologic product pioneers on notice that their safety data was not subject to trade secret protection. *See* 39 Fed. Reg. at 44641. Specifically, the Agency "concluded that the safety and effectiveness data for a biologic regulated under section 351 PHSA is not properly classified as a trade secret." *Id.* Nevertheless, for purposes of Genentech's takings argument, Barr will assume that a pioneer's manufacturing process and safety and efficacy data qualifies for trade secret protection. Even with this assumption, however, Genentech's argument still fails because the Agency's internal use of such information does not constitute a taking under the Fifth Amendment.

A regulatory taking, such as that alleged by Genentech, occurs if and only if "some significant restriction is placed upon an owner's use of his property for which 'justice and fairness' require that compensation be given." *Philip Morris, Inc. v. Reilly*, 312 F.3d 24, 33 (1st Cir. 2002) (citation omitted). Regulatory takings can be analyzed either as *per se* takings or under the balancing test established by the Supreme Court in *Penn Central*, depending on the nature of the alleged taking.

A *per se* takings occurs in two principal contexts: (1) where a regulation results in a permanent physical occupation and thereby a denial of all rights to use, sell, or exclude the property in question (*see Loretto v. Teleprompter Manhattan CATV Corp.*, 458 U.S. 419, 435 (1982)); and (2) where a regulation denies *all* economically beneficial or productive use of the property (*see Lucas v. South Carolina Coastal Council*, 505 U.S. 1003, 1015 (1992)). Genentech does not, and cannot, allege that FDA's actions in issuing a guidance and/or developing a generic biologic pathway would operate to completely deprive it of the value of its confidential commercial data and information. Thus, Genentech's takings claim necessarily must be evaluated using the *Penn Central* factors outlined below. *See Tahoe-Sierra Preservation Council v. Tahoe Reg'l Planning Agency*, 535 U.S. 302, 330 (2002) (noting that the categorical rule requiring compensation for regulatory takings was limited to the extraordinary circumstance when no productive or economically beneficial use of the property is permitted; it "would not apply if the diminution in value were 95% instead of 100%").

Under *Penn Central*, a regulatory taking is analyzed by examining: (1) whether the government action interferes with reasonable investment-backed expectations; (2) the economic impact of the regulation; and (3) the character of the government action. *See Penn Cen. Transp. Co. v. City of New York*, 438 U.S. 104, 124 (1978). Genentech cannot establish that the Agency's use of innovator data, even if considered trade secrets, constitutes an unconstitutional regulatory taking.

1. Reasonable Investment-Backed Expectations.

A "reasonable investment-backed expectation" must be established before a regulatory taking can be found to have taken place. The Supreme Court has analyzed the concept in the context of trade secrets. *See Monsanto*, 467 U.S. 986. *Monsanto* involved a takings challenge to several provisions of the Federal Insecticide, Fungicide and Rodenticide

Act ("FIFRA"), which Congress enacted in 1947. Genentech cannot establish the reasonable investment-backed expectation required for a taking under the Supreme Court's decision in *Monsanto*.

a. In A Regulated Industry, Absent An Express And Specific Statutory Guarantee Of Confidentiality, No Reasonable Investment-Backed Expectation Exists.

In 1972, Congress amended FIFRA to create a comprehensive scheme for regulating the approval, use, sale, and labeling of pesticides. *See Monsanto*, 467 U.S. at 991-92. The 1972 amendments contained several changes regarding EPA's use and disclosure of application data. First, Congress allowed the applicant to designate portions of the data as "trade secrets or commercial or financial information," and prohibited EPA from publicly disclosing information containing such information. *Id.* at 992. Second, Congress permitted EPA to consider data submitted by one applicant to support a different application for a similar chemical. But in order to take advantage of this provision, the second applicant had to offer to compensate the first applicant who had submitted the original data. *Id.* Despite this "mandatory data-licensing scheme," Congress prohibited EPA from considering any trade secret, commercial, or financial information to support a second application without the consent of the original applicant. *Id.* at 992-93. Courts interpreted this information to include health, safety, and environmental data. *Id.* at 993.

In 1978, Congress again amended FIFRA to provide "for disclosure of all health, safety, and environmental data . . . notwithstanding the prohibition against disclosure of trade secrets" found elsewhere in the statute. *Id.* at 995-96. Monsanto challenged the 1978 amendment, arguing that the disclosure of trade secret information submitted by it to the Secretary of Agriculture constituted a regulatory taking in violation of the Fifth Amendment. *Id.* at 998-99.

Stating that a reasonable investment-backed expectation must be more than a "unilateral expectation of an abstract need," the Supreme Court held that after 1978, the statute could not give rise to any investment-backed expectations cognizable under the Takings Clause:

> Monsanto could not have had a reasonable, investment-backed expectation that EPA would keep the data confidential beyond the limits prescribed in the amended statute itself. Monsanto was 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 . . . . If . . . Monsanto chose to submit the requisite data in order to receive a registration, it can hardly argue that its reasonable investment-backed expectations are disturbed when EPA acts to use or disclose the data in a manner that was authorized by law at the time of the submission.

Id. at 1006-07. The result of this holding on data submitted for government approval is clear: "[A]s long as [the applicant] is aware of the conditions under which the data are submitted, and the conditions are rationally related to a legitimate Government interest, a voluntary submission of data by an applicant in exchange for the economic advantages of a registration can hardly be called a taking." *Id.* at 1007.

Most significantly, the Court then examined whether the pre-1972 FIFRA regime created sufficient conditions to give rise to investment-backed expectations concerning the confidentiality of submitted data. Prior to the 1972 amendments, the Court observed, the statute made no promises concerning the confidentiality of data. Although the Trade Secrets Act, 18 U.S.C. § 1905, creates criminal penalties for government employees who engage in unauthorized disclosure of trade secrets, the Court determined that the Act "*cannot be construed as any sort of assurance against internal agency use of submitted data during consideration of the application of a subsequent applicant* for registration." *Id.* at 1008-09 (emphasis added).

In the absence of any explicit and specific guarantee of confidentiality, the Court found that an applicant has "no reasonable investment-backed expectation that its information would remain inviolate in the hands of EPA." *Id.* at 1008. In fact, in regulated industries, the Court observed that applicants could expect that such information might be disclosed:

> In an industry that has long been the focus of great public concern and significant government regulation, the possibility was substantial that the Federal Government, which had thus far taken no position on disclosure of health, safety, and environmental data concerning pesticides, upon focusing on the issue, would find disclosure to be in the public interest.

Id. at 1008-09.

The Court contrasted the lack of express confidentiality guarantees of the pre-1972 statutory scheme with that of the scheme existing between 1972 and 1978. The 1972-78 scheme, among other things: (a) permitted the applicant to protect data by designating it a trade secret; (b) barred EPA from using trade secret data submitted during this period in considering another application; and (c) allowed non-trade secret data to be considered in connection with another applicant only if reasonable compensation was provided to the first applicant. *Id.* at 1010-11. The Court determined that, because these provisions gave Monsanto explicit assurances that the EPA was prohibited from using trade secret data submitted by an applicant in considering another application, "this explicit governmental guarantee formed the basis of a reasonable investment-backed expectation" that submitted data, designated as trade secrets by both the applicant and EPA, would be protected. *Id.* at 1011.

b. Genentech Cannot Establish The Reasonable Investment-Backed Expectation That Must Exist For A Taking To Occur.

Genentech cannot establish the reasonable investment-backed expectation needed before a taking will be found to have occurred. Neither the FFDCA nor the PHSA contain an explicit and specific guarantee of confidentiality. Absent such guarantees, an innovator such as Genentech has "no reasonable investment-backed expectation that its information would remain inviolate in the hands of [FDA]." *Id.* at 1008. Genentech's arguments to the contrary fail.

No reasonable investment-backed expectations for innovator companies exist under the PHSA or FFDCA statutory regime. As with the pre-1972 FIFRA scheme examined in *Monsanto*, the PHSA is silent with regard to the use of application data for the approval of subsequent biologic applications. *See* 42 U.S.C. § 262. Even FDA's regulations governing the confidentiality of data and information submitted in applications for biologics licenses fail to address this point. FDA's regulations prohibit the "public disclosure" of manufacturing methods or processes, 21 C.F.R. § 601.51(f)(1), but they do not prohibit internal agency use in considering subsequent biologic applications.

Even worse for Genentech, the FFDCA and FDA's implementing regulations are not silent on this point. The FFDCA, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (commonly known as the "Hatch-Waxman Amendments" or "Hatch-Waxman"), specifically permits FDA to approve an NDA or ANDA that relies on investigations conducted by or for another new drug applicant, even without a right of reference or use. *See* 21 U.S.C. §§ 355(b)(2) and (j); *see also* FDA Oct. 14, 2003 Ltr. Re: Docket Nos. 2001P-0323/CP1 & C5, 2002P-0447/CP1, and 2003P-0408/CP1 at 9-10, 21-22, 34. FDA's regulations do the same. *See* 21 C.F.R. § 314.54(a)(3). Even the legislative history behind Hatch-Waxman supports the use of an innovator's data in considering a generic application.

When enacting Hatch-Waxman, Congress considered the takings issue specifically in the context of a generic applicant's use of the pioneer's data before the pioneer's period of exclusivity ended. Congress concluded that such use was constitutional. *See* H.R. REP. NO. 98-857, part II, at 28-30 (1984), *reprinted in* 1984 U.S.C.C.A.N. 2686, 2712-14. The House Report explained:

> In this case the benefits to the government and the general citizenry will be substantial. As a result of Section 202 generic drugs will be able to be placed on the market between 18 months and 2 years earlier than without this provision. The availability of such generic substitutes will assist in the reduction of health care costs. In view of the high percentage of individual income devoted to medical costs, these reductions will be especially important to the poor, the under-insured, and the elderly. The government itself, as a purchaser of prescription drugs, will also save money as a result of this amendment.

> On the other hand, the competing claim of the pioneer drug companies holding the patents on these drugs seems much less tangible. . . . [I]t is not altogether clear that the "distinct investment backed expectations" of pioneer drug company patent holders are all that settled. . . .
>
> In this case the Committee has merely done what the Congress has traditionally done in the area of intellectual property law: balance the need to stimulate innovation against the goal of furthering the public interest. Just as we have recognized the doctrine of fair use in copyright, it is appropriate to create a similar mechanism in the patent law. That is all this bill does.

Id. at 2713-14 (footnote omitted). This rationale applies just as strongly to generic biologics.

Moreover, while the FFDCA does offer certain protections to trade secret information submitted with an NDA, these protections do not give rise to a reasonable investment-backed expectation, as defined by *Monsanto*. Section 331(j) of Title 21 prohibits:

> The using by any person to his own advantage, or revealing, other than to the Secretary or officers or employees of the Department, or to the courts when relevant in any judicial proceeding under this chapter, any information acquired under authority of section 334, 348, 350a, 350c, 355, 360, 360b, 360c, 360d, 360e, 360f, 360h, 360i, 360j, 360ccc-1, 360ccc-2, 374, 379, or 379e of this title concerning any method or process which as a trade secret is entitled to protection . . . .

This provision prohibits an individual from "using" information submitted to the Agency, if it qualifies as a trade secret, to his or her "advantage." It also prohibits the disclosure of this information except to other members of the Department of Health and Human Services or the courts. But 21 U.S.C. § 331(j) does not amount to a guarantee of confidentiality as described in *Monsanto*.

First, this provision is not a clear prohibition against the internal use of submitted data to approve subsequent applications. In *Monsanto*, for example, the 1972-78 FIFRA scheme explicitly prohibited the use of submitted data for such purposes. Section 331(j) contains no such express prohibition and is therefore akin to the Trade Secrets Act, which generally bars the unauthorized disclosure of trade secrets, but which the *Monsanto* Court found did *not* serve as a guarantee against future use of submitted data. Indeed, the *Monsanto* Court stated that "the Trade Secrets Act is not a guarantee of confidentiality to submitters of data, and, absent an express promise, [an applicant] ha[s] no reasonable, investment-backed expectation that its information would remain inviolate in the hands of [the agency]." 467 U.S. at 1008.

Second, on its face, § 331(j) does not prohibit the use of submitted data for official purposes, such as approving subsequent applications for the same biologic. Section 331(j) prohibits two types of conduct: (i) use of a trade secret by a government employee "to his own advantage"; and (ii) revelation of a trade secret outside the Department. Use of the information to approve a biologic does not amount to the type of private gain that concerned Congress in the first part of the statute. Indeed, § 331(j) permits the disclosure of the information within the Department. Thus, if, in approving a generic drug company's application for a biologic, FDA publicly stated that it had relied on earlier submitted data, but did not disclose the trade secret data, it would not be in violation of the second part of § 331(j). The second part of the statute only prohibits public disclosure, but not use by the Department of the information. In fact, in order to give every word of the statute meaning, § 331(j) must be read to permit the Department's official use of trade secret data. Because the statute specifically prohibits only use of the information by a government employee "to his own advantage," it necessarily permits use of trade secret information by the Department in its official functions so long as it does not publicly reveal that information.

Third, § 331(j) stands alone, and is not accompanied by other statutory provisions that, together, evidence Congress's intent to provide express guarantees to applicants that their data would remain confidential. Unlike the 1972-78 statutory scheme in *Monsanto*, nothing in the FFDCA indicates that Congress has drawn a careful line between the trade secret data that FDA may not rely on in evaluating subsequent applications and the non-trade secret data that it may rely on. For example, here, Congress has not created any compensation scheme by which the subsequent applicant is required to compensate the first applicant; has not included a mandatory procedure for negotiation or arbitration of the amount of compensation; nor has it guaranteed applicants that their data would not be used or disclosed for any other purpose – all key distinctions from the 1972-78 FIFRA scheme at issue in *Monsanto*.

In support of its takings claim, Genentech claims that FDA's past policy of protecting trade secret and confidential commercial data establishes a reasonable investment-backed expectation. (Genentech Pet. at 25 (citing 21 C.F.R. part 20; 21 C.F.R. § 314.430 (prohibiting the "public disclosure" of manufacturing methods and processes included in an NDA or ANDA))). But while FDA may have certain regulations in place that protect both brand and generic companies' data and manufacturing processes from being *disclosed to the public*, such protections do not prohibit internal use by the Agency to establish a guidance on generic biologics, nor do they prohibit the Agency from using such information in approving generic biologics. As discussed above, in issuing a guidance and/or developing a generic biologic pathway, FDA will not publicly disseminate Genentech's confidential commercial data and information. Genentech does not, and cannot, point to a single provision in either the PHSA or the FFDCA, nor to any FDA regulation, that guarantees that the information submitted by pioneer biologic companies will not be relied upon by FDA for such purposes.

Genentech relies on *Tri-Bio Labs., Inc. v. United States*, 836 F.2d 135 (3d Cir. 1988), where, according to Genentech, the court held that FDA was prohibited from considering

data submitted by a pioneer new animal drug applicant in the processing of the generic manufacturer's application. Genentech contends that because FDA has a similar regulation in place with respect to new (human) drug applications, this regulation provides the "explicit governmental guarantee" required for a taking, making the court's holding equally applicable to generic biologics.[7] (Genentech Pet. at 24-25). Genentech is mistaken. The process for gaining FDA approval for animal drugs and human drugs differs substantially. The FFDCA, for example, expressly permits a 505(b)(2) applicant to rely on the safety and effectiveness investigations of a pioneer applicant, even where no right of reference or use has been provided. *See* 21 U.S.C. § 355(b)(2). The animal drug approval procedure cited in *Tri-Bio Labs* contains no similar provisions.

In the end, applying the *Monsanto* Court's interpretation of a reasonable investment-backed expectation here, FDA's internal reliance on previously submitted safety and efficacy data in the consideration of generic biologics falls far short of a taking. As Genentech concedes, "a 'reasonable investment-backed expectation' must be more than a unilateral expectation or an abstract need." *Monsanto*, 467 U.S. at 1005. (*See also* Genentech Pet. at 25). But the significance of this statement is lost on Genentech. Genentech's expectations *are* unilateral. Neither the relevant statutes nor FDA's implementing regulations provide the necessary "explicit governmental guarantee" that a brand company's data will not be considered in future generic biologic determinations. Genentech's takings argument fails for this reason alone.

2. Economic Impact.

The law regarding economic impact is fairly straightforward: "The inquiry is whether the regulation 'impairs the value or use of the property' according to the owners' general use of their property." *Philip Morris*, 312 F.3d at 41 (quoting *Pruneyard Shopping Ctr. v. Robins,* 447 U.S. 74, 83 (1980)). In general, "loss of future profits – unaccompanied by any physical property restriction – provides a slender reed upon which to rest a takings claim. Prediction of profitability is essentially a matter of reasoned speculation that courts are not especially competent to perform. Further, perhaps because of its very uncertainty, the interest in anticipated gains has traditionally been viewed as less compelling than other property-related interests." *Andrus v. Allard,* 444 U.S. 51, 66 (1979) (prohibition of certain commercial transactions did not constitute a "taking" under the Fifth Amendment).

Distilled to its essence, Genentech's petition is an attempt to guard against the loss of future profits by preserving and extending its monopoly in the relevant market for biologics well beyond patent expiration by preventing generic manufacturers from entering the market even after the expiration of Genentech's patents. Such an economic impact is not

[7] The regulatory language upon which Genentech relies states that *if* an NDA applicant obtains a right of reference to use another applicant's safety and efficacy investigations, the application must include a written statement signed by the owner of the data conveying approval to rely on such data. 21 C.F.R. § 314.50(g)(3).

cognizable under the Fifth Amendment. Genentech's arguments must be rejected for this independent reason as well.

3. Character Of The Government Action.

The impact of the FDA's proposed guidance and/or the establishment of a pathway for generic biologics must be balanced against the interests that FDA seeks to protect, *i.e.*, increasing the availability of cost-effective biologics to millions of Americans, including those whose health care is currently paid for by the Government through Medicare, Medicaid, or other federally-funded programs. As noted above, Congress clearly outlined its position on this issue when it passed the Hatch-Waxman Act. The reasoning is no less compelling when applied to biologics.

In summary, Genentech cannot satisfy any of the criteria that the courts consider when deciding whether a regulatory taking has occurred. *See Penn Cen. Transp.*, 438 U.S. at 124. Thus, even if Genentech could establish that its data and information qualify as trade secrets, its argument nevertheless fails because FDA's internal use of such data and information for the purpose of drafting a guidance and/or establishing a pathway to approve generic biologics is not a regulatory taking.

CONCLUSION

The Genentech, Pfizer, and BIO petitions must be denied *in toto*. First, contrary to petitioners' arguments, the current state of the art allows the Agency to characterize biologic products without relying on the innovator data in the suggested manner. Second, even if FDA needed to rely on an innovator's information, the Agency has the authority to do so. Nothing in the FFDCA, PHSA, or any other statutory provision, or the U.S. Constitution, prevents such reliance. The American public needs and deserves access to lower-priced biologic products. The petitioners offer the Agency no legitimate reason whatsoever to force consumers to continue paying monopoly prices for such products, especially those no longer protected by patents. Thus, Barr strongly urges the Agency to issue its long-awaited guidance and to approve an approval pathway for generic biologics.

Respectfully submitted,

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