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RESPONSE TO CITIZEN PETITION FILED BY MICHAEL BANNERSTER
DOCKET NO. 2006P-0089

Genentech, Inc. (Genentech) and Idec, Inc. (Biogen) submit these comments in response to the Citizen Petition submitted by Michael Bannester on February 24, 2006.¹ The Citizen Petition asks the Secretary of Health and Human Services and the Commissioner of Food and Drugs to stay the approval of pending supplemental biologics license applications (sBLAs) for RITUXAN (rituximab), contending the stay is necessary to deter off-label promotion. At the time of the filing, the only pending sBLA for RITUXAN was for the treatment of rheumatoid arthritis (RA). That sBLA was approved on February 28, 2006. Since that time, on March 30, 2006, Genentech and Biogen have submitted an sBLA for frontline treatment for indolent non-Hodgkin's lymphoma ("NHL").

As discussed in greater detail below, the arguments advanced in the Citizen Petition are severely flawed. To the extent that it seeks a stay of the approval of the RA sBLA, the Citizen Petition is moot because that approval has already occurred. To the extent that it seeks to defer approval of subsequently filed sBLAs, the Citizen Petition is ill-conceived. Staying approval of pending sBLAs is not within the scope of the actions that FDA is authorized to take in response to the alleged behavior. Seeking to punish Genentech and Biogen for providing truthful and non-misleading scientific information to health care practitioners by staying approval of sBLAs would conflict with the goals of FDA's policy in this area and would also raise very substantial First Amendment issues.

¹ Although dated February 24, the document was not received by DDB until February 27, 2006.

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The person filing the Citizen Petition is reportedly an employee of a law firm that is suing Genentech and Biogen.² FDA should, accordingly, recognize this document for what it is—a bald attempt to influence separate ongoing legal proceedings wholly unrelated to FDA approval—and should reject it out of hand. If, however, FDA decides to conduct a substantive review of the Citizen Petition, we respectfully request that it be denied.

I. BACKGROUND

A. Growing prevalence of B-cell mediated diseases

Lymphocytes are a type of white blood cell that protect the body from various external pathogens (e.g., bacteria and viruses) as well as internal abnormalities (e.g., cancer). When B-cells, which are one of two main types of lymphocytes, function normally, they produce antibodies to combat invading bacteria, viruses, cancer, etc. However, abnormal B-cell function results in a wide array of diseases such as lymphomas, leukemias, and autoimmune diseases.

Lymphomas are the result of an uncontrolled proliferation of lymphocytes in lymph nodes. The incidence of these cancers has increased steadily over the years.³ This year alone, there have been more than 59,000 new cases of Non-Hodgkin's Lymphoma (NHL) compared with roughly 8,000 new cases of Hodgkin's disease.⁴

The overwhelming majority of NHLs are B-cell lymphomas.⁵ B-cell lymphomas are either indolent or aggressive. Patients with indolent B-cell lymphomas tend to live longer than patients with aggressive B-cell lymphomas, but with a median life expectancy of 8 to 12

² McDermott ex. rel. United States v. Genentech, Inc., No. 2:05-cv-00147-GC (D. Me. filed Jul. 29, 2005).

³ Currently, approximately 67,000 people in the United States are diagnosed with lymphomas each year and roughly 20,000 people per year die from it. American Cancer Society, Cancer Facts and Figures 1997 (Apr. 2006), available at http://www.cancer.org/docroot/STT/stt_0_1997.asp?sitearea=STT&level=1.

⁴ Id.

⁵ B-cell lymphomas account for over 90 percent of all NHLs. Abramson Cancer Center of the University of Pennsylvania, Non-Hodgkin's Lymphoma: The Basics (Feb. 2006), available at <http://www.oncolink.com/types/article.cfm?c=10&s=36&ss=820&id=9539>.

years. Although aggressive NHL is curable, it is rapidly fatal if left untreated. Patients with untreated aggressive NHL have a life expectancy of 6 months to 2 years.

Chronic lymphocytic leukemia (CLL), like lymphoma, results from an uncontrolled proliferation of lymphocytes. Unlike lymphomas, the hyper-proliferation happens in the bloodstream, and not in the lymph nodes.⁶ Like the majority of NHLs, the overwhelming majority of CLLs are B-cell malignancies. CLLs behave much like indolent B-cell NHLs—they tend to progress slowly, but are currently incurable.

Autoimmune diseases, of which there are many, occur when the immune system (namely B-cells, T-cells, or both) attacks its own tissue. For example, in RA, the body's immune system attacks the tissue lining the joints, resulting in one of the most debilitating forms of arthritis. RA often causes unbearable joint pain that, when left untreated, progresses to joint deformation. The disease is fairly common in the U.S. population.⁷

B. Effects of RITUXAN (rituximab) on certain B-cell mediated diseases

All mature B-cells express a specific receptor on their surfaces known as CD20, which is not on the surface of other cells. This receptor is expressed on the surface of the B-cells that cause B-cell malignancies and other B-cell mediated diseases.

RITUXAN (rituximab) is a genetically engineered monoclonal antibody that selectively binds to CD-20 and recruits the body's natural defenses to attack and kill the marked B cells. RITUXAN therefore targets only mature B-cells (i.e., those that are involved in B-cell malignancies and other B-cell mediated diseases), sparing the others. Because precursor B-cells in bone marrow lack CD20, healthy B-cells are able to regenerate after treatment and can

⁶ In 2006 alone, more than 10,000 new cases of CLL have been diagnosed and almost 5,000 patients have died. American Cancer Society, Cancer Facts and Figures 2006 (April 2006), available at http://www.cancer.org/docroot/STT/stt_0.asp.

⁷ Scientists estimate that about 2.1 million people, or between 0.5 and 1 percent of the adult population in the U.S., have RA. National Institute of Arthritis and Musculoskeletal Diseases, Handout on Health: Rheumatoid Arthritis (May 2004), available at http://www.niams.nih.gov/hi/topics/arthritis/rahandout.htm#ra_3.

return to normal levels within several months. Since RITUXAN selectively attacks B-cells and not other cells, it has a significantly lower incidence of side effects than standard chemotherapy.⁸

FDA has found RITUXAN safe and effective in treating certain B-cell malignancies. In November 1997, FDA approved RITUXAN for the treatment of relapsed or refractory, low-grade (i.e., indolent) or follicular, CD20-positive, B-cell NHL. In April 2001, FDA approved an sBLA covering use of RITUXAN in the re-treatment of patients who have relapsed following initial treatment with RITUXAN.⁹ In February 2006, FDA approved RITUXAN for the first-line treatment of diffuse large CD20-positive B-cell NHL in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or other anthracycline-based chemotherapy regimens.

RITUXAN has been recognized by the National Comprehensive Cancer Network (NCCN) and the National Cancer Institute (NCI) as a component of the standard of care in a number of important disease states for which Rituxan has not been approved (so called "off-label" uses). RITUXAN has been identified by the NCCN as a component of: (1) 5 of the 7 suggested treatment regimens for first-line therapy of indolent B-cell NHL; (2) all of the suggested treatment regimens for first-line therapy of aggressive B-cell NHL; and (3) the suggested treatment regimen for both first- and second-line therapies for CLL.¹⁰ According to the NCI, RITUXAN is a standard treatment option for: (1) first-line therapy in indolent, noncontiguous stage II, III, and IV adult NHL;¹¹ (2) first-line therapy for aggressive,

⁸ NCI, Biological Therapies for Cancer: Questions and Answers (Aug. 2004), available at <<http://www.cancer.gov/cancertopics/factsheet/Therapy/biological>>.

⁹ In this sBLA, the FDA also approved the use of eight weekly doses of RITUXAN (compared to the original four) per course of treatment and treatment of patients with bulky disease (lesions > 10 cm).

¹⁰ NCCN, NCCN Clinical Practice Guidelines in Oncology (April 2006), available at <http://www.nccn.org/professionals/physician_gls/f_guidelines.asp?button=I+Agree#site>.

¹¹ NCI, Indolent, Noncontiguous Stage II/III/IV Adult Non-Hodgkin's Lymphoma (Sep. 7, 2005), available at <<http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/HealthProfessional/page7>>.

noncontiguous stage II, III and IV adult NHL in combination with CHOP;¹² and (3) first-line therapy to treat CLL stages I, II, III, and IV.¹³ FDA's Oncologic Drugs Advisory Committee has recognized RITUXAN as a standard-of-care therapy for relapsed, aggressive NHL.¹⁴ And the drug compendium United States Pharmacopoeia Drug Information (USP-DI) has long recognized RITUXAN as the standard treatment for many off-label uses.¹⁵

To determine the effectiveness of RITUXAN in treating RA, Genentech and Biogen conducted three randomized, double-blind, placebo-controlled studies, all of which yielded positive results.¹⁶ On February 28, 2006, FDA approved an sBLA for the use of RITUXAN in combination with methotrexate for the treatment of moderately- to severely- active RA in patients who have had an inadequate response to one or more tumor necrosis factor (TNF) antagonist therapies ("the RA indication").

¹² NCI, Aggressive, Noncontiguous Stage II/III/IV Adult Non-Hodgkin's Lymphoma (Sep. 7, 2005), available at < <http://www.cancer.gov/cancertopics/pdq/treatment/adult-non-hodgkins/HealthProfessional/page8>>.

¹³ NCI, Stage I, II, III, and IV Chronic Lymphocytic Leukemia (Feb. 22, 2006), available at <<http://www.cancer.gov/cancertopics/pdq/treatment/CLL/HealthProfessional/page5>>.

¹⁴ In December 2004, FDA's Oncologic Drugs Advisory Committee (ODAC) rejected Inex Pharmaceutical's application for accelerated approval of Marqibo, citing RITUXAN plus ICE and RITUXAN plus EPOCH as two of the "available therapies" for the treatment of relapsed aggressive NHL. See Oncology Drug Advisory Committee Meeting, Marqibo® (Vincristine Sulfate Liposomes Injection) Indication: Treatment of Patients with Aggressive Non-Hodgkin's Lymphoma Previously Treated with at Least Two Combination Chemotherapy Regimens (Dec. 1, 2004), available at <www.fda.gov/ohrms/dockets/ac/04/briefing/2004-4084B1_04_FDA-Marqibo.pdf>.

¹⁵ USP-DI has accepted RITUXAN as a treatment for (1) CLL; (2) Waldenstrom's Macroglobulinemia; (3) Immune thrombocytopenic purpura ("ITP"); (4) front-line aggressive, refractory aggressive, and front-line indolent NHL; and (5) maintenance therapy for NHL. See USP DI: DRUG INFORMATION FOR THE HEALTHCARE PROFESSIONAL 2624 (26th ed. 2006).

¹⁶ One pivotal study, a phase III trial called REFLEX, found that 51 percent of the 298 subjects randomized to the test arm (e.g., methotrexate plus RITUXAN) achieved at least a 20% improvement in the American College of Rheumatology (ACR) 20 score. By contrast, just 18 percent of 201 subjects in a methotrexate plus placebo arm (P<0.0001) showed such improvement. Moreover, RITUXAN demonstrated a significant improvement in ACR50 score (27% versus 5% [P<0.0001]) and ACR70 (12% of subjects reporting at least a 70 percent improvement in number of tender and/or swollen joints [P<0.0001]).

II. ARGUMENT

A. Petitioner's request for a stay of approval of RITUXAN's sBLA for the RA indication is moot, and any other request is irrational.

The relief requested in the Citizen Petition is moot. The overwhelming thrust of the petition is focused on asking that FDA "stay the approval of . . . Genentech and Biogen's request for a biologics license to market RITUXAN (Rituximab) for the treatment of patients with RA."¹⁷ Yet, as noted, on February 28, 2006, FDA approved Genentech and Biogen's request to supplement its biologics license (BLA# 103705) to include the RA indication.¹⁸

FDA has historically denied previous Citizen Petitions on the ground that the requested action was mooted by intervening events.¹⁹ Here, FDA can and should reject the Citizen Petition simply because approval of RITUXAN for the RA indication moots the petitioner's request to stay such an approval.

The Citizen Petition should likewise not impact the treatment of the new sBLA (for frontline treatment for indolent NHL)²⁰ because the Petition says nothing that begins to address uses of RITUXAN other than RA. To interpret the Petition as asking that the Secretary and the Commissioner "stay the approval of *any* pending supplements to biological license applications submitted by or on behalf of Genentech or Biogen for RITUXAN (Rituximab)" would

¹⁷ Petition at 1.

¹⁸ Letter from Bob A. Rappaport, Director, Division of Anesthesia, Analgesia and Rheumatology Products, FDA, to Robert L. Garnick, Senior Vice-President, Regulatory Affairs, Quality and Compliance, Genentech, Inc. (Feb. 28, 2006).

¹⁹ A Citizen Petition filed by Case Western Reserve University requesting an exception or an alternative to CGMP requirements for PET drugs was moot on the grounds that, in the intervening period, FDA revoked its regulation permitting the agency to approve such requests. See 62 Fed. Reg. at 66,522 (Dec. 19, 1997). FDA also denied a petition submitted by a device trade association on the ground that certain provisions of the Medical Device User Fee and Modernization Act of 2002 rendered the petition moot. Letter from Linda S. Kahan, Deputy Director, Center for Devices and Radiological Health, FDA, to Josephine M. Torrente, Association of Disposable Device Manufacturers (Dec. 29, 2004).

²⁰ Letter from Karen D. Jones, Chief, Product Management Staff, Division of Biologic Oncology Drug Products, Center for Drug Evaluation and Research, FDA, to Robert L. Garnick, Senior Vice-President, Regulatory Affairs, Quality and Compliance, Genentech, Inc. (Apr. 13, 2006).

lead to a number of untoward results. One is that such relief would bear virtually no relationship to the rest of the (unsubstantiated and false) allegations in the Citizen Petition. For the agency to respond to such allegations of illegal promotion in one context by staying all subsequent approvals for a product would be perverse, and would compromise the public health. Such a response would also undercut companies' incentives to do the work to secure further indications. In addition, the approval of the sBLA provides a means by which a company and FDA can lawfully communicate about a product's attributes to the benefit of health care practitioners and patients. No sound public policy would be served by FDA's responding to (false) accusations about illegal promotion about RITUXAN for RA by refusing to approve an sBLA for frontline treatment of indolent NHL.

B. Denial of pending sBLAs is the wrong remedy for petitioner's allegations.

1. The allegations in the Citizen Petition provide no cognizable ground for FDA to deny approval for any sBLA.

As FDA apparently recognized in approving the sBLA for the RA indication (at least implicitly), an sBLA should be evaluated on its own merits and approved if it meets the standards set forth in the statutes and the regulations. The RITUXAN sBLA for treatment of RA was approved after a thorough evaluation of safety and efficacy. The same should be true for the sBLA for frontline treatment for indolent NHL.

Congress has made clear that FDA does not have unlimited discretion to deny an NDA or a BLA (or supplement) on any grounds it chooses. Indeed, § 505(d) of the FDCA (21 U.S.C. 355(d)) specifically enumerates the sole grounds on which a denial of an application can be based. According to this section, the FDA "shall issue an order refusing to approve the application" only if:

- (1) the investigation included in the application "do not include adequate tests by all methods reasonably applicable to show whether or not such drug is safe for use under the conditions prescribed, recommended, or suggested in the proposed labeling";

- (2) "the results of such tests show that such drug is unsafe for use under such conditions or do not show that such drug is safe for use under such conditions";
- (3) "the methods used in, and the facilities and controls used for, the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity";
- (4) "upon the basis of the information submitted . . . as part of the application, or upon the basis of any other information . . . with respect to such drug, . . . [there is] insufficient information to determine whether such drug is safe for use under such conditions";
- (5) "there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling thereof";
- (6) "the application failed to contain the patent information prescribed by subsection (b)"; or
- (7) "based on a fair evaluation of all material facts, such labeling is false or misleading in any particular."

This section clearly delineates the only grounds recognized by the FDCA as valid for denying the approval of an application. In fact, § 505(c)(1)(A) clearly states that the Secretary shall "approve the application if he . . . finds that none of the grounds for denying approval specified in subsection (d) applies." Congress has thus made utterly clear that FDA must approve those applications for which the data are sufficient. Although the statutory provisions and regulations concerning BLAs differ slightly, there is no reason to believe that either the regime, or Congress's intent, differ in any way.²¹

²¹ Biologics are governed by the Public Health Service Act as well as by the FDCA. In 42 U.S.C. § 262(a)(2)(B), the statute delineates when the Secretary "shall approve" a biologics license application. The Secretary "shall approve" an application – (i) on the basis of a demonstration that – (I) the biological product . . . is safe, pure, and potent; and (II) the facility in which the biological product is manufactured, processed, packed, or held meets standards designed to assure that the biological product continues to be safe, pure, and potent; and (ii) if the applicant . . . consents to the inspection of the facility . . . in accordance with subsection (c) of this section." Considering the statistically significant results of the multiple investigations conducted on various off-label uses and in light of the fact that the facility and inspection provisions are undisputed, it is evident that RITUXAN has met all of these requirements with respect to the RA indication, and that the allegations are irrelevant to any other sBLAs.

The Citizen Petition points to no statutory or regulatory basis that might justify rejection of an sBLA.²² Instead, petitioner contends that the RITUXAN sBLA should be denied because the product is misbranded.²³ To the extent that the petitioner asks FDA to reject an sBLA for RITUXAN for an indication other than the one for RA, such as the recently filed sBLA for frontline treatment for indolent NHL, there is no way that any of petitioner's allegations can be said to concern "labeling" for such an indication. It is just not possible to conceive of such statements about RA as "accompanying" RITUXAN in this (much later in time) context of frontline treatment for indolent NHL.²⁴ It would be nonsensical to say that, because RITUXAN was (allegedly) at one time misbranded because of supposedly impermissible statements made about the utility of RITUXAN for RA, the labeling for frontline treatment for indolent NHL (or any other new indication) is somehow violative such that all new sBLAs must be rejected. Refusing to approve an sNDA or sBLA would be an unprecedented and unauthorized response to unsubstantiated allegations of inappropriate or illegal promotion, and would harm the public health.²⁵

²² 21 C.F.R. § 314.125 (b) lists 18 reasons where FDA "will refuse to approve the application." Seven of those essentially mirror the statute. *Id.* at § 314.125 (b)(1)-(6), (18). The remaining 11 reasons are unrelated to any of the allegations made by the petitioner and so do not offer any additional basis for granting the petitioner's request. *Id.* at § 314.125 (b)(7)-(17).

²³ Petition at 11-13.

²⁴ *See* 21 U.S.C. § 321(m) (labeling is defined in the statute as "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article").

²⁵ Moreover, to the extent that the Citizen Petition's now-mooted request is that FDA not approve the sBLA for RITUXAN for the RA indication, it is far from clear that any of the petitioner's allegations pertain to "labeling" of RITUXAN, as defined in the FDCA. "Labeling" includes "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article." At the same time, FDA recognizes that legitimate scientific exchange is permitted. 21 C.F.R. § 312.7. In any event, oral communications do not fit the definition of "labeling." Accordingly, even the allegations of misbranding would have provided no basis for refusing to approve an sBLA for the RA indication for RITUXAN (as FDA apparently recognized, at least implicitly).

2. FDA could not grant a denial without due notice to the applicant and an opportunity for a hearing.

Before denying an application, the Secretary must give the applicant notice of an opportunity for a hearing to determine whether that application is, in fact, approvable.²⁶ Thus, FDA could not honor the petitioner's request without first granting the company notice of the denial and an opportunity for a hearing.

C. Denying future sBLA approvals would raise substantial First Amendment concerns by failing to directly advance the government's interest in promoting sBLAs.

A governmental action that restricts or punishes certain speech must directly advance a substantial governmental interest. FDA has traditionally defended its limits on off-label promotion as necessary to induce companies to submit sBLAs. For FDA to punish off-label promotion by refusing to approve further sBLAs would thus thwart the very purpose of FDA's stated policy. The First Amendment would not allow such an irrational approach.

The speech at issue here is unquestionably entitled to constitutional protection. Some of the allegations concern purely scientific speech, which is entitled to the highest measure of constitutional protection.²⁷ A government attempt to punish such speech could not survive strict scrutiny.²⁸ Even to the extent that some of the allegations concern speech that might be considered commercial speech, the government would still have the burden to justify its decision to take any punitive actions based on that speech under the Supreme Court's

²⁶ See 21 U.S.C. § 355(c); 42 U.S.C. § 262(a)(2); 21 C.F.R. § 601.4(b).

²⁷ See, e.g., Board of Trustees of Leland Stanford Junior University v. Sullivan, 773 F. Supp. 472, 474 (D.D.C. 1991) (finding that the First Amendment protects scientific expression and debate just as it protects political and artistic expression). FDA's regulations acknowledge the importance of unrestricted speech within the scientific community, making clear that they are "not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media." 21 C.F.R. § 312.7(a).

²⁸ 773 F. Supp. 472, 474 (D.D.C. 1991).

Central Hudson test. For the reasons discussed below, staying sBLA approvals would fail to satisfy the requirement that its action directly advance its interests.

1. The FDA would have to justify any action it chooses to take under the Central Hudson test.

Truthful, not misleading, scientifically substantiated statements are entitled to robust protection under the Supreme Court's commercial speech jurisprudence. Central Hudson Gas & Elec. Corp. v. Public Service Commission of New York states that, to repress or punish truthful, non-misleading commercial speech about a lawful activity, the government must show that: (1) its interest is substantial; (2) the regulation directly advances the government interest asserted; and (3) the regulation is no more extensive than necessary to serve that interest.²⁹

There is no doubt the Central Hudson test applies and would have to be satisfied here. Central Hudson establishes that First Amendment protection applies to commercial speech unless it is (1) false and misleading, or (2) concerns an unlawful activity.³⁰ The Citizen Petition has not shown that any of the statements it discussed were false and misleading. Indeed, such a showing would be problematic, at best, given that FDA has, by approving the sBLA for the RA indication, confirmed that RITUXAN has utility in treating RA in certain contexts. Moreover, simply because a manufacturer may have been involved in the

²⁹ 447 U.S. 557 (1980). See also, Edenfield v. Fane, 507 U.S. 761, 770-771 (1993) (governmental body seeking to restrict commercial speech bears the burden of demonstrating that the harm is real and that the restriction on speech will in fact alleviate the harm to a material degree); Ibanez v. Fla. Dep't. of Bus. & Prof'l Regulation, 512 U.S. 136, 142 (1994) (the State bears the burden of showing that the restriction on speech directly and materially advances a substantial state interest in a manner no more extensive than necessary to serve that interest).

³⁰ 447 U.S. 557, 564 (1980) ("if the communication is neither misleading nor related to unlawful activity, the government's power is more circumscribed").

dissemination of information about off-label uses would not make that information inherently misleading, and thus outside the scope of First Amendment protection.³¹

Nor would it be credible to contend that any statement by a manufacturer concerning an off-label use automatically concerns an illegal activity.³² Indeed, FDA has repeatedly confirmed that off-label use is not only lawful and beyond its reach, but that it can also constitute the standard of care. As early as 1982, the FDA has stated:

The [Food, Drug and Cosmetic Act] Act does not . . . limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling. Such "unapproved" or, more precisely, "unlabeled" uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature.³³

This statement published in the FDA Drug Bulletin has been repeatedly confirmed over the years by the FDA.³⁴ In fact, FDA has openly stated that the "understanding of commercial promotion does not place limits on the free exchange of scientific information (e.g., publishing results of scientific studies, letters to the editor in defense of public challenges, investigator conferences)."³⁵

³¹ *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 68 (D.D.C. 1998) vacated on other grounds, *Washington Legal Found. v. Henney*, 202 F.3d 331, 337, n.7 (D.C. Cir. 2000) ("In disposing of the case in this manner, we certainly do not criticize the reasoning or conclusions of the district court. As we have made clear, we do not reach the merits of the district court's First Amendment holdings...").

³² In fact, in § 401 of FDAMA Congress created a pathway for manufacturers to communicate about as-yet unapproved new uses of a drug. 21 U.S.C. § 360aaa.

³³ 12 FDA Drug Bulletin 4 (April 1982).

³⁴ See, e.g., 59 Fed. Reg. at 59,280, 59,281 (Nov. 18, 1994); 48 Fed. Reg. at 26,720, 26,733 (Jun. 9, 1983); see also, Beck & Azari, FDA, Off-Label Use, and Informed Consent: Debunking Myths and Misconceptions, 53 FOOD & DRUG L.J., 71, 76-77 (1998) (stating that the FDA itself recognizes the value and propriety of off-label use).

³⁵ 52 Fed. Reg. at 19, 466 (May 22, 1987); see also, 21 U.S.C. § 396 (stating that "[n]othing in this Act shall be construed to limit or interfere with the authority of a health care practitioner to prescribe or administer any legally marketed device to a patient for any condition or disease").

The courts have likewise confirmed that FDA does not regulate the practice of medicine, which includes the prescription of products for unlabeled uses.³⁶ On that basis, it has been held that communications by manufacturers about off-label uses are not per se unlawful, and thus restrictions on such messages must pass muster under the Central Hudson test.³⁷

Thus, the agency may not rest on the mere notion that communications about off-label uses may have occurred. Rather, it would have to justify any refusal to approve further sBLAs due to the alleged communications by showing that such a response would satisfy the Central Hudson test. This it could not do.

2. Denying the approval of current or future sBLAs would fail to advance the government's substantial interest in protecting the integrity of the drug approval process.

Although FDA could satisfy the Central Hudson requirement that it articulate a substantial governmental interest, it could not demonstrate that refusing to approve future sBLAs would directly advance that interest. FDA has stated its interest in protecting the health and safety of the public by requiring manufacturers to get off-label treatments on-label.³⁸ FDA's primary justification for combating off-label promotion seems to be that, unchecked, such promotion could diminish a manufacturer's incentive to engage in post-approval research for

³⁶ See, e.g., *Buckman Co. v. Plaintiff's Legal Committee*, 531 U.S. 341, 350; *F.T.C. v. Simeon Management Corporation*, 532 F.2d 708 (9th Cir. 1976) (pointing out that the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient or may otherwise vary the conditions of use from those approved in the package insert without informing or obtaining the approval of the Food and Drug Administration); *Rhone-Poulanc Rorer Pharm., Inc. v. Marion Merrell Dow, Inc.*, 93 F.3d 511, 514 n.3 (8th Cir. 1996) (stating that doctors may prescribe an FDA-approved drug for non-approved uses); *United States v. Caputo* 288 F. Supp. 2d 912 (N.D. Ill., 2003); *United States v. Evers*, 453 F.Supp. 1141, 1149-1150 (claiming that a "physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patients or may vary the conditions of use from those approved in the package insert"), *aff'd*, 643 F.2d 1043 (5th Cir. 1981); *Weaver v. Reagen*, 886 F.2d 194, 198 (8th Cir. 1989) (finding that "FDA approved indications were not intended to limit or interfere with the practice of medicine nor to preclude physicians from using their best judgment in the interest of the patient).

³⁷ 13 F. Supp. 2d at 66; *see also*, *United States v. Caputo*, 288 F. Supp. 2d 912, 920 (N.D. Ill., 2003) ("Promotion of off-label uses does not concern an unlawful activity because off-label use of drugs and medical devices by physicians is not unlawful.").

³⁸ 13 F. Supp. 2d 51, 71 (D.D.C. 1998).

new, unlabeled uses.³⁹ FDA has also said that such promotion could raise safety concerns and undercut the efficacy standard.⁴⁰ Moreover, FDA is concerned that off-label promotion would result in presenting physicians with a biased and unbalanced view of the current state of the science.⁴¹

Yet denying valid sBLAs in response to alleged off-label promotion (especially about an entirely different indication) would directly conflict with all of these stated interests, thus failing the "directly advance" prong of the Central Hudson test. Denying a manufacturer approval of an sBLA, even if it were to comply with and satisfy all of FDA's requirements concerning additional indications, just because a third party litigant against that company were to accuse it of off-label promotion, would dramatically hinder, if not eliminate, manufacturers' incentives to dedicate the time, energy, and resources necessary for obtaining approval, as Genentech and Biogen have repeatedly done for RITUXAN.⁴²

³⁹ If a manufacturer is able to market its drugs for any use once its drug had been approved for one use, there would be no incentive to devote time and resources to study the safety and efficacy of other off-label uses. This would allow manufacturers to manipulate the system by getting an approval for a "the first narrowest/easiest indication and then heavily promote the product for other broader (and possibly more speculative) uses." More Information for Better Patient Care: Hearing on S. 1447 Before the S. Comm. on Labor and Relations, 104th Cong. (1996) (prepared statement by William B. Schultz, Deputy Commissioner for Policy, FDA).

⁴⁰ FDA has stated that "the approval of a drug... for one use does not provide assurance that the product is safe or effective for a different use or use in a different population." 62 Fed. Reg. 64,074 (Dec. 3, 1997). By eliminating a manufacturer's incentive to obtain definitive clinical study data, the statutory standard of proof for drug efficacy would be weakened and would result "in harm to patients from unstudied uses that actually lead to bad results, or that are merely ineffective." Janet Woodcock, Lecture to Drug Information Association, A Shift in the Regulatory Approach (June 23, 1997) available at <<http://www.fda.gov/cder/present/diamontreal/regappr/sld001.htm>>.

⁴¹ FDA has clearly expressed this concern; FDA has stated that "the promotion of unapproved uses... place[d] physicians and patients in positions where they cannot make an informed, unbiased decision. It... decrease[s] the incentive of sponsors to conduct the well-controlled clinical investigations.... Without well-controlled trials, physicians will not have the information needed to optimally use the product." 59 Fed. Reg. at 59,821-58,822 (Nov. 18, 1994).

⁴² In addition to the currently pending sBLA for frontline treatment of indolent NHL, for RITUXAN alone, Genentech and Biogen have submitted sBLAs pertaining to the following indications: (1) RA (submitted on August 2005 and approved on February 2006); and (2) frontline treatment of aggressive NHL in combination with CHOP (submitted on August 2005 and approved on February 2006).

Moreover, using denials of sBLA approval to punish manufacturers for allegedly engaging in off-label promotion would compromise the public's health and directly contravene FDA's own interests. By so doing, the FDA would be preventing the widespread, legitimate marketing of a drug for additional uses that may have the potential to save hundreds of thousands of lives. Indeed, it would be a gross perversion of FDA's stated commitment to safeguarding the integrity of the approval process by encouraging manufacturers to develop sufficient data to support amended labeling by trying to penalize Genentech and Biogen for the alleged conduct by rejecting future sBLAs.

D. The Petition represents a transparent attempt to affect public opinion and influence legal proceedings that are wholly unrelated to FDA approval.

In July 2005, Paul McDermott, a former employee of Genentech, filed a whistleblower lawsuit in U.S. District Court of Maine. That suit alleged, among other things, that the marketing of RITUXAN defrauded government health-care programs.⁴³ McDermott provided the government with a copy of the complaint as well as "substantially all [the] material evidence and information" he possessed.⁴⁴ Nonetheless, in December 2005, the Department of Justice (DOJ) concluded that it was not in the government's interest to pursue the claim. It therefore declined to intervene on behalf of the relator (i.e., McDermott), and asked that the lawsuit be unsealed.

After DOJ's decision, knowing that approval of RITUXAN for the RA indication was imminent,⁴⁵ an individual who is reportedly an employee of the law firm pressing the McDermott case instituted this proceeding in an apparent last-ditch effort to salvage their legal

⁴³ See, McDermott ex. rel. United States v. Genentech, Inc., No. 2:05-cv-00147-GC (D. Me. filed Jul. 29, 2005). Indeed, the Citizen Petition's many allegations relating to physician remuneration are not even properly directed to FDA.

⁴⁴ 31 U.S.C. § 3730(b)(2).

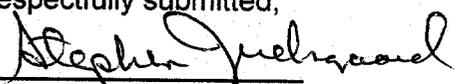
⁴⁵ It was publicly known that the company expected FDA action on its supplemental application for RA on February 28, 2006. See, e.g., Rop Zone, FDA Ruling Awaited on Use of Cancer Drug for Arthritis, THE SEATTLE TIMES, Feb. 9, 2006, at D3.

claims. Given the other fora in which these allegations are being addressed, FDA need not use its scarce resources duplicating the efforts of others.⁴⁶

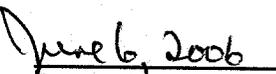
III. CONCLUSION

For the foregoing reasons, we respectfully request that the FDA deny the petitioner's requested relief.

Respectfully submitted,



Stephen G. Juelsgaard
Executive Vice President, General Counsel and Secretary
Genentech, Inc.



Date signed

Susan H. Alexander
Executive Vice President, General Counsel
Biogen Idec, Inc.

Date signed

cc: Andrew C. von Eschenbach, M.D.
Acting Commissioner, Food and Drugs

Scott Gottlieb, M.D.
Deputy Commissioner for Policy

Jesse L. Goodman, M.D., M.P.H.
Director, Center for Biologics Evaluation and Research

Maryann Malarky
Director, Office of Compliance and Biologics Quality

Steve Galson, M.D.
Director, Center for Drug Evaluation and Research

Thomas Abrams, R.Ph.
Director, Division of Marketing, Advertising and Communication

Sheldon Bradshaw, Esq.
Chief Counsel

⁴⁶ The U.S. Attorney's Office in Philadelphia, as part of its investigation into the alleged off-label promotion of RITUXAN, served Genentech with a subpoena on October 8, 2004, for documents pertaining to its promotion. From the outset, Genentech has fully cooperated with the investigation.

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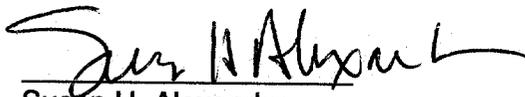
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Genentech, Inc.

Date signed



Susan H. Alexander
Executive Vice President, General Counsel
Biogen Idec, Inc.

6/6/06
Date signed

- cc: Andrew C. von Eschenbach, M.D.
Acting Commissioner, Food and Drugs
- Scott Gottlieb, M.D.
Deputy Commissioner for Policy
- Jesse L. Goodman, M.D., M.P.H.
Director, Center for Biologics Evaluation and Research
- Maryann Malarky
Director, Office of Compliance and Biologics Quality
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Gail Costello
Director, New England District Office

Barbara Cassens
Director, San Francisco District Office



SIDLEY AUSTIN LLP
1501 K STREET, N.W.
WASHINGTON, D.C. 20005
(202) 736 8000
(202) 736 8711 FAX

grao@sidley.com
(202) 736-8355

BEIJING GENEVA SAN FRANCISCO
BRUSSELS HONG KONG SHANGHAI
CHICAGO LONDON SINGAPORE
DALLAS LOS ANGELES TOKYO
FRANKFURT NEW YORK WASHINGTON, DC

FOUNDED 1866

June 8, 2006

By Hand Delivery

Jennie C. Butler, Director
Division of Dockets Management
Office of Management Programs
Office of Management
Food and Drug Administration
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Re: Docket # 2006P-0089

Dear Ms. Butler:

Please find enclosed Genentech, Inc. (Genentech) and Biogen Idec's (Biogen) response opposing the citizen petition filed by Michael Bannester on February 27, 2005 requesting the agency to stay approval of all supplements to biologics licenses issued with respect to RITUXAN (rituximab). Please date and stamp the enclosed four copies. Thank-you.

Sincerely,

Gayatri R. Rao

Attachment

cc: Andrew C. von Eschenbach, M.D.
Scott Gottlieb, M.D.
Jesse L. Goodman, M.D., M.P.H.
Maryann Malarky
Steve Galson, M.D.
Thomas Abrams, R.Ph.
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