February 24, 2006

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

CITIZEN PETITION

REQUEST FOR STAY OF FURTHER APPROVALS OF RITUXAN

The undersigned submits this Petition under 21 C.F.R. § 10.30, § 351 of the Public Health Service Act and the Federal Food, Drug and Cosmetic Act ("FDCA") to request that the Secretary of Health and Human Services (the "Secretary") and the Commissioner of Food and Drugs (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), and more specifically, Genentech's and Biogen's request for a biologics license to market *Rituxan* (Rituximab) for the treatment of patients with rheumatoid arthritis. The Petitioner hereby requests such a stay as a deterrent to Genentech, Inc. ("Genentech") and IDEC Pharmaceuticals Corporation (now operating as Biogen Idec, Inc.) ("Biogen") to stop their wide-spread and illegal marketing of *Rituxan* (Rituximab) for uses not approved in their biologics licenses. The bases for this Citizen Petition and request for Stay of Approval are set forth below.

A. ACTION REQUESTED

The Petitioner requests that the Commissioner stay the further approval of all supplements to biologics licenses issued to Genentech (BLA# 103705) and Biogen (BLA# 103737) for *Rituxan* (Rituximab). Copies of the letters approving these licenses are attached hereto as **Exhibits A and B**. Copies of the letters approving supplements to these licenses are attached hereto as **Exhibits C, D, E and F**.

The Petitioner specifically requests that the Commissioner stay the approval any pending supplemental biological license application submitted by or on behalf of Genentech or Biogen for *Rituxan* (Rituximab), including their application to market *Rituxan* (Rituximab) for the treatment of patients with rheumatoid arthritis.

Because the illegal conduct of Genentech and Biogen is ongoing, and because the FDA's decision with respect to Genentech's and Biogen's application to market *Rituxan* (Rituximab) for the treatment of rheumatoid arthritis is anticipated on February 28, 2006, the Petitioner requests that the Commissioner immediately stay the approval of the supplemental application or that this Petition be decided on an **expedited basis**. The Petitioner requests a decision on this Petition on or before any final agency action is taken with respect to the *Rituxan* (Rituximab) supplemental application for the treatment of rheumatoid arthritis or, in the alternative, that the FDA stay its decision on Genentech's and Biogen's application to market *Rituxan* (Rituximab) for rheumatoid arthritis until an investigation is undertaken, a decision has been made on this Petition and the Petitioner is given the opportunity to exhaust all administrative remedies.

B. STATEMENT OF GROUNDS

I. Introduction

The Federal Food, Drug, and Cosmetic Act is designed to protect the public from unsafe and unproven drugs while minimizing its interference with the practice of medicine by allowing physicians to prescribe new and developing drugs to their patients based on their independent medical judgment. Thus, while physicians are free to discuss with their patients the risks and benefits of the use of a particular drug that has not been approved by the FDA, and may freely prescribe the drug for that "off-label" use, drug manufacturers are prohibited from marketing or promoting a drug for a use that has not received FDA approval. 21 U.S.C.A. § 331(a), (b) and (d); 21 C.F.R. § 202.1(e)(4) and (6).

The purpose of these regulations is simple. FDA approval is granted only after it has been proven, through independent investigations and studies, that a drug is both safe and effective in use. 21 U.S.C.A. § 355(b). When a new drug has not been proven safe and effective, drug companies, who have a substantial financial incentive to promote positive aspects of their drugs while minimizing negative aspects, are prohibited from marketing the drug. On the other hand, physicians are equipped with the requisite experience, educational background and familiarity with a patient's medical history to provide unbiased and candid information with respect to both the benefits and the risks associated with a drug whose safety and efficacy have not been fully investigated and vetted. These regulations, as one court put it, were designed to "protect consumers from the products of a profit-seeking drug industry bent on increasing its sales and profits." *Richardson v. Miller*, 44 S.W.3d , * 10 (Tenn. Ct. App. 2000), *citing* James R. Bird, Package Inserts for Prescription Drugs as Evidence in Medical Malpractice Cases, 44 U. Chi. L. Rev. 398, 406 (1977).

Prohibiting drug manufacturers from promoting unapproved uses also provides an incentive for the sponsoring drug manufacturer "to conduct the adequate and well-controlled clinical investigations that are necessary to demonstrate whether products are safe and effective for each of their intended uses, and prevents patients from being exposed to unnecessary harms." *Final Guidance on Industry-Supported Scientific and Educational Activities*, 64 FR 64074, 64081, 1997 WL 740420 (F.R. 1997) (citing examples of drug manufacturers' efforts, through

lectures, presentations and other means, to promote drugs for unapproved uses that were later discovered to be harmful, and even fatal, to patients).

The importance of these regulations cannot be understated. Until a drug has been proven safe and effective to the FDA, only the independent and unbiased advice of medical professionals can be disseminated in the public domain. If a drug company violates this policy, federal laws and regulations and sound public policy require the FDA to fully investigate the matter and take appropriate enforcement action seeking large civil fines, criminal penalties and a consent decree to send a strong message to companies who continuously and willfully violate the FDCA and FDA regulations by promoting products for unapproved uses.

Genentech and Biogen have made a mockery of these regulations and frequently market and promote their drugs for uses that have not been proven safe and effective under the FDCA. Genentech and Biogen, among other things, have paid kickbacks to physicians for promoting off-label uses of *Rituxan*, promoted off-label uses of *Rituxan* to physicians during so-called "Roundtable Dinners" and "Regional Advisory Board Meetings," and paid physicians to be named as purported authors of articles and case studies promoting off-label uses of *Rituxan* that were drafted in part by Genentech and/or Biogen. The intended purpose and result of this illegal scheme was to skew the informed and impartial judgment of medical professionals in order to increase *Rituxan* sales and, ultimately, company profits.

And this is not an isolated incident. Genentech was previously the subject of a criminal investigation and charges involving the illegal marketing of another drug, Protropin. Protropin was approved for "the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion." From 1985 to 1994, however, Genentech promoted Protropin for the treatment of other medical conditions that were not approved by the FDA. Genentech plead guilty to the criminal charges and paid $50 Million in criminal fines and civil restitution. A copy of the plea agreement in that case is attached hereto as **Exhibit G**.

This prior criminal indictment and corresponding multimillion dollar fine has not deterred Genentech from continuing to illegally market drugs or biologics for non approved uses. In its Memorandum in Aid Of Sentencing in the Protropin case, as part of its plea for leniency, Genentech trumpeted its role in the development and introduction of *Rituxan*. Shortly after the resolution of the Protropin indictment by the payment of $50 Million dollars in fines and restitution, Genentech commenced its campaign to illegally market *Rituxan* for non-approved uses. *Rituxan* sales in the U.S. for 2005 were in excess of $1.8 Billion dollars. Approximately 75% of these sales were for non-approved uses. To date, Genentech has treated criminal fines and indictments as a cost of securing additional market places for its products and it has not been deterred from continuing to aggressively illegally market this biologic for non-approved uses.

The only way to get the full attention of Genentech and Biogen is for the FDA to pursue criminal investigations, lawsuits and impose large civil fines and seek a consent decree to deter drug manufacturers from illegally marketing their drugs and frustrating the policies of the FDCA. The sanctions imposed by the agency must be large enough and sufficiently severe so that they cannot be swept aside by a simple cost-benefit analysis. Repeat, willful offenders such as Genentech can not be permitted to blatantly disregard the law.

II. Factual Background

In 1997, Genentech and Biogen obtained approval from the FDA to market *Rituxan* for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, non-Hodgkin's lymphoma, a cancer of the immune system. A copy of *Rituxan's* initial FDA approved label is attached hereto as **Exhibit H**. Supplements to these licenses were subsequently approved in 2002, 2003 and 2004. *See* **Exhibits C, D, E and F**. In February of 2006, Genentech and Biogen obtained approval from the FDA to market *Rituxan* for the first-line treatment of diffuse large B-cell, CD-20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens. A copy of *Rituxan's* most recent FDA approved label is attached hereto as **Exhibit I**. Other than for these treatments, and supplements thereto, the FDA has not approved the use of *Rituxan* for any other purpose.

Under applicable federal laws and regulations, Genentech and Biogen, as manufacturers of a prescription drug regulated by the FDA, may not promote or market to physicians prescription drugs such as *Rituxan* for purposes or in dosages other than those approved by the FDA. 21 U.S.C. § 331(a), (b) and (d); 21 C.F.R. § 202.1(e)(4) and (6). The uses of a prescription drug for purposes other than those approved by the FDA are referred to as "off-label" uses.

After obtaining FDA approval of *Rituxan* for treatment of patients with non-Hodgkin's lymphoma in 1997, Genentech and Biogen jointly developed a scheme to illegally market and promote *Rituxan* for off-label uses. Among other off-label uses, Genentech and Biogen have illegally marketed *Rituxan* for the treatment of rheumatoid arthritis, or RA. The use of *Rituxan* for treating RA is not included in the FDA-approved package insert, nor is it recognized as an FDA-approved indication in widely accepted pharmacy/medical publications such as the American Hospital Formulary Service Drug Information, the United States Pharmacopeia-Drug Information, or the American Medical Association Drug Evaluations, or by any peer-reviewed medical literature.

The illegal scheme of Genentech and Biogen was implemented by employing, among other things, the following:

1. The Illegal Direct Solicitation of Physicians for Off-Label Uses of *Rituxan*

Genentech and Biogen directly solicited physicians and their medical professional staff members to illegally market off-label uses of *Rituxan* for treating RA. For example, in 1994 and 1995, Genentech BioOncology sales representatives solicited physicians and medical professionals associated with Rheumatology Associates, a rheumatology practice located at 49 Seekonk Street, in Providence, Rhode Island, to participate in roundtable dinner meetings and advisory panels marketing and promoting the use of *Rituxan* in treating rheumatory arthritis patients. The solicitations included in office visits to discuss these marketing and promotional efforts.

As part of these marketing and promotional efforts, Genentech BioOncology sales representatives promised staff members that they would forward written instructions and materials demonstrating the ease with which they could administer *Rituxan* to their RA patients through intravenous injections. Genentech and Biogen do not offer any drugs for sale that are FDA approved for treating rheumatic diseases including arthritis or related disorders of joints, muscles and bones. Rheumatologists do not treat patients with non-Hodgkin's lymphoma. The only purpose for Genentech BioOncology or Biogen sales representatives to conduct in-office visits to rheumatologist offices is to solicit the illegal promotion of off-label uses of *Rituxan* for treating RA.

2. The Formation of a Nationwide Network of Employees Assigned to the Promotion of Off-Label Sales and Marketing

Genentech and Biogen created a nationwide network of employees falsely referred to as "Professional Educations Liaison's" ("PEL's") and "Clinical Education Liaisons" ("CEL's") whose assigned duties involve the marketing and promotion of off-label sales rather than any legitimate educational activity.

3. The Illegal Kickbacks of Monies and Consideration to Physicians Who, Under the Guise of "Consultants," Promote Off-Label Uses of *Rituxan*

Genentech and Biogen provide illegal kickbacks of monies and other consideration to physicians through the use of "sham" consulting agreements to illegally market *Rituxan* for off-label uses. PEL's employed by Genentech and Biogen are responsible for identifying and selecting rheumatologists as Key Opinion Leaders ("KOL's"). Once a KOL is identified, it is the PEL's responsibility to persuade the KOL to enter into a "Synergy Consulting Agreement" with Genentech or Biogen.

Once a rheumatologist is signed to a "Synergy Consulting Agreement," he or she receives payments for sham services. The purpose of Genentech and Biogen in having KOL's sign sham "Synergy Consulting Agreements" is to convert rheumatologists into active promoters of the off-label use of *Rituxan* for treating RA. With the execution of a "Synergy Consulting Agreement," Genentech and Biogen attempt to transform a KOL from a practicing rheumatologist (with whom Genentech and Biogen could not legally discuss or disseminate information regarding off-label uses of *Rituxan*) into a consultant (with whom Genentech and Biogen could ostensibly promote off-label uses of *Rituxan* for RA).

Once a rheumatologist was purportedly transformed into a "consultant," Genentech and Biogen could leverage the physician's credibility in his or her professional community to identify additional target rheumatologists and to expand their promotion of off-label uses of *Rituxan*. Materials promoting *Rituxan* for off-label treatment of RA are more fully accepted and integrated into physicians' personal belief systems when they are presented as educational in nature in contrast to material that is clearly identified as promotional.

Using these sham consulting agreements, Genentech and Biogen were able influence and control the content of presentations made by consulting rheumatologists to their peers at

purported educational presentations without disclosing the payments and consideration provided to such "consulting" speakers.

4. The Illegal Kickbacks of Monies and Consideration to Physicians Who, Under the Guise of Acting as Moderators of Roundtable Dinners, Promote Off-Label Uses of *Rituxan*

Once a physician is signed to a sham "Synergy Consulting Agreement," the next step in Genentech's and Biogen's illegal scheme is to further leverage such a physician through a series of dinner meetings known as "RA Roundtable Dinners." The "consulting" rheumatologist is paid a fee, typically $2,000-$2,500, to "moderate" an RA Roundtable Dinner. The purpose of such dinners is to use the rheumatologist "moderator" as an advocate in promoting the sales of *Rituxan* for off-label treatment of RA.

Pharmaceutical company sales and marketing research demonstrate that the use of physicians to pitch and promote drugs in a peer-to-peer context is much more effective than the use of pharmaceutical company salesman. A Genentech PEL or Biogen CEL will obtain from the "consulting" rheumatologist his physician letterhead and with his assistance prepare a targeted list of at least fifteen area rheumatologists. Using the "consulting" rheumatologist's professional letterhead, invitations are forwarded to area rheumatologists under his signature.

Genentech and Biogen contract with a third party pharmaceutical sales promotion firm, Health Answers Education, to assist in organizing and holding the dinners. Health Answers Education is utilized as a "sham" front for the dinners. Genentech and Biogen exploit Health Answers Education as a façade in order to present the RA Roundtable off-label promotional dinners under the guise of an educational event produced by an independent continuing medical education organization. Health Answers Education maintains a website, www.RARoundtables.healthanswers.com, for meeting information and materials.

All decision making regarding the substance of RA Roundtable dinners is controlled and dictated by Genentech and Biogen and their sales and marketing staffs. In addition to jointly planning the RA Roundtable Dinners, each Roundtable Dinner would typically have at least one attendee from Genentech and one from Biogen. Biogen employees that attended Roundtable Dinners included William Reiss, Trista King and Henry Leher. A standard topic for the RA Roundtable dinner series is "*Pathogenesis of Rheumatoid Arthritis: An in-depth look at B-cells*". The venues for RA Roundtable dinners are usually up-scale area restaurants or dining facilities.

The following is a list of RA Roundtable Dinners held in 2004, including the date, location, the attending personnel from Genentech and Biogen and the attending personnel from the third-party pharmaceutical sales training firm Health Answers Education:

1) August 4, 2004 RA Roundtable Dinner at Morton's, 551 Fifth Avenue, New York, New York, attended by Dan Yip of Genentech and P. Evans of Health-Answers;

2) August 5, 2004 RA Roundtable Dinner at Ruth Chris, 431 North Dearborn, Chicago, Illinois, attended by Dan Yip of Genentech, Margaret Masterson of Genentech and J. Thompson of Health Answers;

3) August 18, 2004 RA Roundtable Dinner at Morton's, 699 Boylston Street, Boston, Massachusetts, attended by Paul McDermott of Genentech, Bill Reiss of Biogen and J. Thompson of Health Answers;

4) September 8, 2004 RA Roundtable Dinner at Morton's, 1411 Walnut Street, Philadelphia, Pennsylvania, attended by Lisa Kruse of Genentech, Bill Reiss of Biogen, Larry Grogan (affiliation), and M.J. Holden of Health Answers;

5) September 8, 2004 RA Roundtable at Ruth Chris, 2525 N. Federal Highway, Ft. Lauderdale, Florida, attended by J. Thompson of Health Answers;

6) September 9, 2004 RA Roundtable at Fleming Steakhouse, 103 Summit Blvd., Birmingham, Alabama, attended by Dan Yip of Genentech, J. Thompson of Health Answers;

7) September 15, 2004 RA Roundtable at Morton's, 501 Elm Street, Dallas, Texas, attended by Margie Murdock of Genentech, Henry Leher of Biogen, and M.J. Holden of Health Answers;

8) September 22, 2004 RA Roundtable at Morton's, 1050 Connecticut Ave. NW, Washington, D.C., attended by Dan Yip of Genentech and J. Thompson of Health Answers;

9) September 28, 2004 RA Roundtable at Ruth Chris, 800 Fifth Avenue, Seattle, Washington, attended by Tina Chang of Genentech, Susan Peper of Genentech, Bill Reiss of Biogen, and R. Trovinger of Health Answers;

10) September 29, 2004 RA Roundtable at Morton's, 30 State House Square, Hartford, Connecticut, attended by Karen Dittrich of Genentech, Trista King of Biogen, and J. Thompson of Health Answers;

11) October 7, 2004 RA Roundtable at Maize, 50 Park Place, Newark, New Jersey, attended by Dave Metzer of Genentech, Henry Leher of Biogen, and M.J. Holden of Health Answers;

12) October 12, 2004 RA Roundtable at Morton's, 7822 Bonhomme Avenue, Clayton, Missouri, attended by Margie Murdock of Genentech and J. Thompson of Health Answers;

13) October 13, 2004 RA Roundtable at Morton's, One Towne Square, Southfield, Michigan, attended by Henry Leher of Biogen, Margaret Masterson of Genentech and J. Thompson of Health Answers; and

14) October 27, 2004 RA Roundtable Dinner at Morton's, 300 South Charles St., Baltimore, Maryland, attended by Dave Metzer of Genentech, Bill Reiss of Biogen, Larry Grogan of Genentech, and Renee Trovinger of Health Answers.

The following RA Roundtable dinners were also scheduled to be held in 2004 and, upon information and belief, were held on the following dates and with the following Genentech, Biogen and Health Answers attendees:

1) October 28, 2004 RA Roundtable Dinner at Morton's, 435 South La Cienaga, Beverly Hills, California, attended by Darlene Fujimoto from Genentech, Bill Reiss from Biogen, and P. Evans from Health Answers;

2) October 28, 2004 RA Roundtable Dinner at Morton's, 400 Post Street, San Francisco, California, attended by Kerri Ford of Genentech, Trista King of Biogen, and J. Thompson of Health Answers;

3) November 4, 2004 RA Roundtable Dinner at Third Street Pier, 1110 N. Old World 3rd Street, Milwaukee, Wisconsin, attended by Margaret Masterson of Genentech, Trista King of Biogen, Elizabeth Haney of Genentech and J. Thompson of Health Answers;

4) November 4, 2004 RA Roundtable Dinner at Morton's, 1710 Wynkoop Street, Denver, Colorado, attended by P. Evans of Health Answers;

5) November 10, 2004 RA Roundtable Dinner at Morton's, 1200 Brickell Avenue, Suite 100, Miami, Florida, attended by Margie Murdock of Genentech and J. Thompson of Health Answers;

6) November 11, 2004 RA Roundtable Dinner at Ruth Chris, 1700 Westshore Blvd, Tampa, Florida, attended by S. D. Doolan of Genentech, Henry Leher of Biogen and P. Evans of Health Answers;

7) November 16, 2004 RA Roundtable Dinner in Cincinnati, Ohio, attended by Margaret Masterson of Genentech and M.J. Holden of Health Answers;

8) November 17, 2004 RA Roundtable Dinner at Morton's, 1600 West Second Street, Cleveland, Ohio, attended by Margaret Masterson of Genentech and M.J. Holden of Health Answers.

Although RA Roundtable dinners are structured to present the appearance that the information being provided has been developed, at least in part, by the "consulting" moderator as a practicing rheumatologist, in fact, the moderator is presenting information and materials prepared and packaged by Genentech and Biogen marketing personnel and consultants. Moderators are not allowed to make any additions, deletions or edits to the materials given to them by Genentech and Biogen for presentation. The materials given to the moderator for presentation are prepared by Genentech and Biogen marketing personnel or consultants

including Dr. Alvin Wells, Kerri Ford, and William Reiss. Reiss was originally employed by Biogen and now is employed by Genentech. Ford is a Genentech employee. Wells is a rheumatologist that consults with Genentech and Biogen and was previously employed by Abbott Laboratories.

The presentation materials prepared by Genentech and Biogen do not fairly balance the available information on B-cell therapy and the efficacy of available medications. In some instances, prospective moderators have refused to "moderate" such RA Roundtable dinners after reviewing the packaged materials prepared by Genentech and Biogen because they failed to present independent, fair and balanced information and data.

As an example, Genentech and Biogen secured the agreement of a KOL rheumatologist in Providence, Rhode Island, to moderate an RA Roundtable dinner on or around October of 2004. Upon being advised by Genentech and Biogen, however, that he could not make any changes to, and was required to present, the Genentech and Biogen slide decks as prepared, the KOL rheumatologist decided not to proceed with the planned dinner. The KOL rheumatologist recognized the role that Genentech and Biogen intended for him was a sham, namely, the promotion of *Rituxan* off-label uses of in treating RA under the guise of a medical educational program regarding the treatment of RA.

Genentech and Biogen use these RA Roundtable dinners to promote *Rituxan's* attributes in treating RA and to disseminate data to generate off-label use in treating RA. Genentech and Biogen have been very successful in their off-label promotion as evidenced by the tremendous growth in the last four years of *Rituxan* sales in the United States along with its correspondingly high percentage of off-label use.

5. The Illegal Kickbacks of Monies and Consideration to Physicians Who, Under the Guise of Participating in Regional Advisory Boards, Promote Off-Label Uses of *Rituxan*

The next level in Genentech's and Biogen's scheme to promote off-label uses of *Rituxan*, involves the use of "Rituxan in Rheumatoid Arthritis Regional Advisory Board" meetings. Unlike the RA Roundtable promotional dinners held locally in the community of each "consulting" rheumatologist moderator, the Regional Advisory Board meetings are two day events held regionally at exclusive hotels in major cities throughout the United States. For example, the Regional Advisory Board meeting on March 25-26, 2004 was held at The Carlyle Hotel in New York City.

Genentech and Biogen again leverage "consulting" rheumatologists under contract to promote off-label use of *Rituxan* in treating RA under the guise of acting as a "chair" for a Regional Advisory Board Meeting. A stock agenda created by Genentech and Biogen is used for Regional Advisory Board meetings. The agenda and materials distributed at these meetings are created by Genentech and Biogen and the sham "chair" is not allowed to make any additions, deletions or edits to the packaged materials provided. Genentech and Biogen marketing personnel also attend and present at these meetings. Genentech and Biogen use these meetings to promote *Rituxan's* attributes in treating RA and to disseminate off-label treatment data. The

sham "chair" is used as a vehicle to present this information which includes an unbalanced presentation of information regarding the inadequate responses of other RA therapies.

6. The Illegal Kickback of Monies and Consideration to Physicians Who, Under the Guise of Publishing Independent Articles and Case Studies, Promote Off-Label Uses of *Rituxan*

As an additional prong to their illegal strategy, Genentech and Biogen identify and persuade rheumatologists to participate in the publication of articles promoting *Rituxan's* use in off-label treatments of RA. The subject and scope of such articles would be selected by Genentech marketing staffers. Genentech staffers would assist in drafting the articles and the "consulting" rheumatologists would be listed as authors. Articles purportedly authored by rheumatologist peers would be used to induce other physicians both to prescribe *Rituxan* for off-label treatment of RA and to recommend its use to others.

7. The Training of Genentech and Biogen Employees in Methods of Avoiding the Detection of Their Off-Label Sales and Marketing Activities Regarding *Rituxan*

In order to implement their illegal scheme to market *Rituxan* for off-label uses, Genentech and Biogen trained their employees in methods of concealing and avoiding detection of their off-label sales and marketing activities. For example, upon reporting to Genentech management his knowledge of the existence of direct in-office promotional and marketing of *Rituxan* for off-label treatment of RA by Genentech BioOncology sales representatives, Paul McDermott, a former Genentech PEL, was warned by Genentech management to avoid creating any record by fax, e-mail or voicemail of these discussions.

Upon hiring, the job title assigned by Genentech to Mr. McDermott was "Professional Educational Liaison Rituxan RA" (RA is an abbreviation for rheumatoid arthritis) as reflected on Mr. McDermott's business card provided by Genentech. More than six months after his hiring, the "Rituxan RA" language was deleted from Mr. McDermott's business cards identifying him as a Genentech Professional Education Liaison. Mr. McDermott understands that the "Rituxan RA" deletion was ordered by Genentech's Legal Department when it discovered that his real, but illegal, job responsibility was being openly listed on his business card. No substantive changes were made in Mr. McDermott's job responsibilities or the techniques described previously other than deleting this language from his business card so as to avoid the detection of PEL off-label sales and marketing activities regarding the use of *Rituxan* in treating RA.

In November of 2004, a meeting was held at Genentech World Headquarters in South San Francisco, California hosted by Douglas Love, a member of Genentech's Legal Department. At that meeting, *Rituxan* RA PEL's were cautioned to make sure that their business communications in promoting *Rituxan* for off-label treatment of RA did not adversely effect Genentech's position in any investigation or litigation. The PEL's were counseled to avoid communicating in writing unless necessary and to confer with the Legal Department before putting any sensitive material relating to their promotional work in writing. The PEL's were cautioned that, if anything was required to be put into a permanent writing or e-mail, it must be

written in a way where it could be published in the New York Times without any negative impact. The PEL's were cautioned that conduct that they personally deemed to be unethical or immoral was not necessarily improper or unlawful and therefore they should avoid describing it as such. During the meeting, Legal Department attorney Love characterized United States Government investigations of the pharmaceutical industry as nothing more than improper efforts to extort monies from pharmaceutical companies. The meeting ended with a reminder from Love for PEL's to comply with Genentech's record retention policy. No such policy was ever provided.

The promotion or marketing by Genentech and Biogen of "off-label" uses of prescription drugs such as *Rituxan* for the treatment of rheumatoid arthritis is illegal and contrary to the explicit policies and regulations of the United States government. 21 U.S.C. § 331(a), (b) and (d); 21 C.F.R. § 202.1(e)(4) and (6). In addition to rheumatoid arthritis, Genentech and Biogen also market *Rituxan* for other non-FDA approved uses, including uses for front-line therapy, alone or in combination, for treating low-grade non-Hodgkin's lymphoma; front-line therapy, alone or in combination, for treating chronic lymphocytic leukemia; front-line therapy, alone or in combination, for treating intermediate/high-grade non-Hodgkin's lymphoma; alone or in combination for treating patients with relapsed chronic lymphocytic leukemia; alone or in combination for treating intermediate/high-grade non-Hodgkin's lymphoma; alone or in combination for treating patients with autoimmune disease, idiopathic thrombocytopenic purpura (also known as immune thrombocytopenic purpura); autoimmune hemolytic anemia; Waldenstrom's macroglobulinemia; Mantle cell lymphoma; bone marrow transplants; pure red cell aphasia; Hodgkin's disease; systemic lupus erythematosus; and generally for maintenance therapy and front-line therapy in any of the above listed lymphomas or leukemias.

III. Legal Grounds

1. Misbranding *Rituxan*

Through their illegal promotion of *Rituxan* for the treatment of RA, Genentech and Biogen have caused the product to be misbranded under the FDCA.

Under 21 U.S.C.A. § 352(f)(1), a drug is deemed to be "misbranded" if its labeling does not include "adequate directions for use." In addition to information on how the drug is to be used, this section also requires a drug's labeling to include information on all intended uses of the drug. *Alberty Food Products Co. v. U.S.*, 185 F.2d 321 (9th Cir. 1950) (finding a drug "misbranded" because its labeling failed to state the intended uses of the drug (arthritis and rheumatism) suggested by the drug company in newspaper advertisements). The "intended use" of a drug refers to the "objective intent of the persons legally responsible for the labeling of drugs." 21 C.F.R. § 201.128. This intent "is determined by such persons' expressions or may be shown by the circumstances surrounding the distribution of the article." *Id.*

Not only can the intended use or uses of a drug be determined from the actual label or labeling, but also from "advertisements, promotional material, oral statements by the product's manufacturer or representatives, and any other relevant source." *Decision in Washington Legal Foundation v. Henney*, 65 FR 14286, 14286, 2000 WL 278003 (F.R. 2000) ("The intended use

or uses of a drug or device may also be determined from advertisements, promotional material, oral statements by the product's manufacturer or its representatives, and any other relevant source."), *citing Action on Smoking and Health v. Harris*, 655 F.2d 236, 239 (D.C. Cir. 1980) ("[I]t is well established that the 'intended use' of a product, within the meaning of the [FDCA], is determined from its label, accompanying labeling, promotional claims, advertising, and any other relevant source") (internal citations omitted); *see also* 21 C.F.R. 201.128. If these statements or materials promote a use of the drug inconsistent with its approved labeling, the drug is misbranded under 21 U.S.C.A. § 352(f)(1) for failure to bear labeling with adequate directions for all intended uses. *Henney*, 65 FR at 14286 ("An approved new drug that is marketed for a 'new use' is also 'misbranded' under the FDCA, because the labeling of such a drug would not include 'adequate directions for use.' 21 U.S.C. 352(f)."), *citing U.S. v. Articles of Drug*, 625 F.2d 665, 673 (5th Cir. 1980).[1]

As set forth above, Genentech and Biogen presented information regarding uses of *Rituxan* that are not contained in its approved labeling. While Genentech and Biogen attempted to skirt federal laws and regulations by employing practicing physicians to actually present this information, these individuals were paid by Genentech and Biogen to act on their behalf and were not allowed to make additions, deletions or edits to the packaged materials created by Genentech and Biogen marketing personnel. The dissemination of this information is inconsistent with *Rituxan's* approved labeling and, thus, results in the drug being "misbranded" under the federal laws and regulations set forth above.

Furthermore, 21 C.F.R. § 202.1 provides that an advertisement constitutes misbranding in violation of Section 502(n) [21 U.S.C.A. § 352(n)] of the FDCA, if it:

> Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is ... useful in a broader range of conditions or patients....
>
> [or]

[1] "Labeling" is defined 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." 21 U.S.C.A. § 321(m). The phrase "accompanying such article" has been interpreted to include all materials and literature used in the sale of drugs, regardless of whether it is distributed separately from the label or product. *Kordel v. U.S.*, 335 U.S. 345, 349, 69 S. Ct. 106, 109 (1948) (holding that false or misleading material distributed separately from the article still constitutes "misbranding" of a drug); *U.S. v. Urbuteit*, 335 U.S. 355, 357, 69 S. Ct. 112, 113 (1948) (same); *V.E. Irons, Inc. v. U.S.*, 244 F.2d 34, 39-40 (1st Cir. 1957) (holding that "labeling" must be defined to include all literature used in the sale of food and drugs regardless of whether or not it is shipped into interstate commerce along with the article); *see also* 21 C.F.R. § 202.1(l)(2) (defining "labeling" as "[b]rochures, booklets, mailing pieces, detailing pieces, file cards, bulletins, calendars, price lists, catalogs, house organs, letters, motion picture films, film strips, lantern slides, sound recordings, exhibits, literature, and reprints and similar pieces of printed, audio, or visual matter descriptive of a drug and references published (for example, the 'Physicians Desk Reference') for use by medical practitioners, pharmacists, or nurses, containing drug information supplied by the manufacturer, packer, or distributor of the drug and which are disseminated by or on behalf of its manufacturer, packer, or distributor.").

> Uses literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling.

21 C.F.R. § 202.1(e)(6)(i) and (xi).

The FDA has interpreted the term "advertisement" to include "information (other than labeling) that originates from the same source as the product and that is intended to supplement or explain the product." *Final Guidance on Industry-Supported Scientific and Educational Activities*, 64 FR 64074, 64076, 1997 WL 740420 (F.R. 1997). The information provided by Genentech and Biogen about *Rituxan* during Roundtable Dinners, Regional Advisory Board Meetings and other events was clearly "intended to supplement or explain the product." By representing and suggesting uses for *Rituxan* that are not permitted in its FDA approved labeling through these means, Genentech and Biogen have "misbranded" *Rituxan* under 21 C.F.R. § 202.1(e)(6) as well.

2. Submission of a False Certification in Applications for FDA Approval

Genentech and Biogen have, on information and belief, provided false and misleading certifications to the FDA in seeking prior biologics licenses, and supplements thereto, for *Rituxan*. According to the most recent form application (Form FDA 356h) to market a new drug or biologic, all drug companies are required to certify as follows:

> **If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following**:
>
> 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606 and/or 820.
> 2. Biological establishment standards in 21 CFR Part 600.
> 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
> 4. **In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.**
> 5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99 and 601.12.
> 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
> 7. Local, state and Federal environmental impact laws.
>
> The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

A copy of the most recent Form FDA 356h is attached as **Exhibit J** (emphasis added).

Prior versions of this form application, going back to at least 1997, contain identical or equivalent certifications. On information and belief, Genentech and Biogen submitted certifications in their applications for biologics licenses for *Rituxan*, and supplements thereto, in

which they represented that they would abide by all applicable laws, including those prohibiting off-label marketing.

As set forth above, Genentech and Biogen violated the "applicable laws and regulations that apply to approved applications" of *Rituxan* by misbranding the drug in violation of 21 U.S.C.A. § 352. Genentech and Biogen also violated 21 C.F.R. § 202.1, the specific drug advertising regulation cited in the Form FDA 356h certification. Among other things, 21 C.F.R. § 202.1 provides that:

> An advertisement for a prescription drug covered by a new-drug application ... or any approved supplement thereto, shall not recommend or suggest any use that is not in the labeling accepted in such approved new drug application or supplement.

21 C.F.R. § 202.1(e)(4).

As set forth above, 21 C.F.R. § 202.1 also provides that an advertisement is in violation of the FDCA, if it:

> Contains a representation or suggestion, not approved or permitted for use in the labeling, that a drug is ... useful in a broader range of conditions or patients....
>
> [or]
>
> Uses literature, quotations, or references for the purpose of recommending or suggesting conditions of drug use that are not approved or permitted in the drug package labeling.

21 C.F.R. § 202.1(e)(6)(i) and (xi).

The submission of false or misleading information to the FDA with respect to the labeling and promotion of a drug is a violation of 18 U.S.C.A. § 1001. In applying for prior biologics licenses for *Rituxan*, and supplements thereto, Genentech and Biogen, on information and belief, submitted false or misleading certifications to the FDA regarding their labeling and promotion of *Rituxan* and thus knowingly and willfully:

> (1) falsified, concealed, and covered up by trick, scheme, and device a material fact;
>
> (2) made materially false, fictitious, and fraudulent statements and representations; and
>
> (3) made and used false writings and documents knowing the same to contain materially false, fictitious, and fraudulent statements and entries.

See 18 U.S.C.A. § 1001.

IV. Conclusion

As set forth above, Genentech's and Biogen's wide-spread marketing of *Rituxan* for unapproved uses in violation of federal laws and regulations provides sufficient legal bases for the Commissioner to stay the approval of any pending supplements to biological license applications submitted by or on behalf of Genentech or Biogen for *Rituxan*, and more specifically, Genentech's and Biogen's request for a biologics license to market *Rituxan* for the treatment of patients with rheumatoid arthritis.

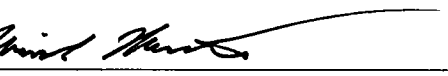
The Petitioner requests that the Commissioner immediately stay the approval of any pending supplements submitted for *Rituxan* for the treatment of patients with rheumatoid arthritis and to fully investigate this matter and take appropriate enforcement action, including the imposition of large civil fines, criminal penalties and a consent decree to send a strong message to companies who continuously and willfully violate the FDCA and FDA regulations by promoting products for unapproved uses.

C. Environmental Impact

The Petitioner requests a categorical exclusion for an environmental impact analysis under 21 CFR §§ 25.30, 25.31.

D. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this Petition includes all information and views on which the Petition relies, and that it includes representative data and information known to the Petitioner which are unfavorable to the Petition.

(Signature) 

(Name of petitioner) Michael Bannester

(Mailing address) 1720 W. Wabansia Avenue, Chicago, IL 60622

(Telephone number) 312-593-8330

cc: Desk Copies to the following:

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

Scott Gottlieb, M.D., Deputy Commissioner for Policy

Jesse L. Goodman, M.D., MPH
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

Ms. Gail Costello, Director, New England District Office

Ms. Barbara Cassens, Director, San Francisco District Office

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

Our Reference No.: 97-0244

November 26, 1997

M. David MacFarlane, Ph.D.
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. MacFarlane:

Your biologics license application for Rituximab is approved effective this date. Genentech, Inc., South San Franciso, California, is hereby authorized to manufacture and ship for sale, barter, or exchange in interstate and foreign commerce Rituximab under Department of Health and Human Services Biologics License No. 1048.

Rituxumab is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, B-cell non-Hodgkin's lymphoma.

Under this authorization, you are approved to manufacture Rituximab utilizing Formulated Bulk Rituximab (For Further Manufacturing Use) manufactured by IDEC Pharmaceuticals Corp. (Biologics License No. 1235) under a shared manufacturing arrangement. Any addition or deletion of establishments involved in the shared manufacturing arrangement will require the submission of appropriate supporting data in order to ensure continued compliance with the approved standards for the manufacture of Rituximab.

In accordance with approved labeling, your product will bear the tradename RITUXAN and will be marketed in 10 mL and 50 mL fill sizes.

You are not currently required to submit samples of future lots of this product to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER, under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for this product shall be 24 months from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the product. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

Exhibit A

We acknowledge your written commitments of October 17, 1997 to:

1. Submit the results of your study evaluating the time and temperature specifications for the transport of Rituximab Formulated Bulk and filled vials between buildings to CBER upon completion.

2. Submit the results of the environmental monitoring survey to CBER by January 31, 1998.

3. Include Lot E9054A in your ongoing Rituximab stability program.

4. Establish a maximum fill duration for 500 mg Rituximab in 50 mL vials, supported by media fill data.

Any changes in the supplier of the Formulated Bulk Rituximab (For Further Manufacturing Use), or in the manufacture, packaging or labeling of the product or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12.

It is requested that adverse experience reports be submitted in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) and that distribution reports be submitted as described (21 CFR 600.81). All adverse experience reports should be prominently identified according to 21 CFR 600.80 and be submitted to the Center for Biologics Evaluation and Research, HFM-210, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA Form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA Form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other similar products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Sincerely yours,

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Exhibit A, 1

Product Approval Information - Licensing Action

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

November 26, 1997

Our Reference No.: 97-0260

Alice Wei
Director, Regulatory Affairs
IDEC Pharmaceuticals Corporation
11011 Torreyana Road
San Diego, CA 92121

Dear Ms. Wei:

This letter hereby issues Department of Health and Human Services Biologics License No. 1235 to IDEC Pharmaceuticals Corporation, San Diego, California, in accordance with the provisions of Title III Part F of the Public Health Service Act of July 1, 1944 (58 Stat. 702) controlling the manufacture and sale of biological products. This license authorizes you to manufacture and ship for sale, barter, or exchange, in interstate and foreign commerce, those products for which your company has demonstrated compliance with establishment and product standards.

Under this license you are authorized to manufacture and ship for sale the product Rituximab Formulated Bulk (For Further Manufacturing Use). Under this authorization, you are approved to manufacture Rituximab Formulated Bulk at your facility in San Diego, California for use in the manufacture of Rituximab by Genentech, Inc., under a shared manufacturing arrangement. Final containers of Rituximab will be filled, labeled, packaged and distributed under the tradename RITUXAN by Genentech, Inc. at their facility in South San Francisco, California.

You are not currently required to submit samples of future lots of Rituximab Formulated Bulk to the Center for Biologics Evaluation and Research (CBER) for release by the Director, CBER,

Exhibit B

under 21 CFR 610.2. FDA will continue to monitor compliance with 21 CFR 610.1 requiring assay and release of only those lots that meet release specifications.

The dating period for Rituximab Formulated Bulk shall be 60 days from the date of manufacture when stored at 2-8°C. The date of manufacture shall be defined as the date of final sterile filtration of the formulated bulk. Results of ongoing stability studies should be submitted throughout the dating period as they become available including the results of stability studies from the first three production lots.

Any changes in the manufacturing, testing, packaging or labeling of Rituximab Formulated Bulk, or in the manufacturing facilities will require the submission of information to your biologics license application for our review and written approval consistent with 21 CFR 601.12. Any such changes which may affect the safety, purity and potency of the product should also be reported simultaneously to Genentech, Inc., the manufacturer of the drug product.

We acknowledge your written manufacturing commitments of November 18, 1997, to:

1. Revise production batch records and conduct assessments to minimize variances.

2. Improve production oversight by increasing the number of personnel in Manufacturing and Quality areas.

We also acknowledge your written clinical commitments of November 25, 1997, to:

3. Submit the final study report, including case report form tabulations for Protocol 102-08R, the study of Rituximab retreatment, within 12 months of enrolling the last patient. Data which are not mature (e.g., response duration or outcome resolution for CD19+ depletion or immunoglobulin levels, pharmacokinetic data at six or nine months) will be supplied when mature.

4. Submit the final study report, including case report form tabulations for Protocol 102-O8B, the study of Rituximab treatment in patients with bulky disease (>lO cm in largest diameter) within 12 months of enrolling the last patient. Data which are not mature (e.g., response duration or outcome resolution for CD19+ depletion or immunoglobulin levels, pharmacokinetic data at six or nine months) will be supplied when mature.

5. Submit the final study report, including case report form tabulations for Protocol 102-09, entitled "Pilot Study to Compare and Evaluate the Safety and Impact of IDEC-C2B8 on Immunization Potential" within 12 months of enrolling the last patient. Additionally, the following amendments to the protocol will be submitted within 60 days:

    a. timepoints prior to six months after the second immunization will be added for all study arms for patients who have not reached six months;

    b.t he analytic section will be revised to clarify both the primary efficacy analysis and how missing data points in the primary efficacy analysis (for patients who exit early due to disease progression) will be handled; and

    c. immunization with an antigen to which the study population is immunologically

Exhibit B, 1

naive will be included, in order to evaluate the effect of prior Rituximab therapy on a primary immune response.

6. Submit, within 60 days, a protocol for evaluation of the effect of Rituximab therapy on the levels of preexisting serum titers against viral and/or bacterial antigens. In support of this protocol, data from two control groups from Protocol 102-09 which address the range of serologic titers at study entry and the number of patients needed to show whether clinically relevant change occurs in the months following Rituximab administration, will be submitted.

It is acknowledged that Genentech, Inc. will receive adverse experience reports and be responsible for submitting those reports to FDA in accordance with the adverse experience reporting requirements for licensed biological products (21 CFR 600.80) as well as distribution reports as described (21 CFR 600.81).

Please submit three copies of all final printed labeling at the time of use and include part II of the label transmittal form (FDA Form 2567) with completed implementation information. In addition, you may wish to submit draft copies of the proposed introductory advertising and promotional labeling with an FDA form 2567 to the Center for Biologics Evaluation and Research, Advertising and Promotional Labeling Staff, HFM-202, 1401 Rockville Pike, Rockville, MD 20852-1448. Final printed advertising and promotional labeling should be submitted at the time of initial dissemination, accompanied by an FDA form 2567. All promotional claims must be consistent with and not contrary to approved labeling. No comparative promotional claim or claim of superiority over other products should be made unless data to support such claims are submitted to and approved by the Center for Biologics Evaluation and Research.

Please acknowledge receipt of the enclosed biologics license to the Director, Division of Application Review and Policy (HFM-585), Center for Biologics Evaluation and Research.

Sincerely yours,
--- *signature* ---

Jay P. Siegel, M.D., FACP
Director
Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research

Last Updated: 1/15/2001

Back to Top Back to Index

Date created: September 25, 2003

Exhibit B,2

Product Approval Information - Licensing Action

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852-1448

February 19, 2002

Our STN: BL 103737/5005

Alice Wei
IDEC Pharmaceuticals Corporation
3030 Callan Road
San Diego, CA 92121

Dear Ms. Wei:

Your request to supplement your biologics license application for Rituximab to revise the dosage and administration section of the package insert to include information regarding the use of Rituximab as a component of the Zevalin therapeutic regimen has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 2567. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

This information will be included in your biologics license application file.

Sincerely yours,

--- signature ---

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design and Analysis

Exhibit C

Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research

Last Updated: 3/5/2002

Back to Top Back to Index

Date created: September 25, 2003

Exhibit C, 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103737/5023

OCT 0 9 2003

IDEC Pharmaceuticals Corporation
Attention: Linda Robertson, Ph.D.
Director, Regulatory Affairs
3030 Callan Road
San Diego, CA 92121

Dear Dr. Robertson:

Your request to supplement your biologics license application for Rituximab to revise the Adverse Reactions section of the package insert has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cber/transfer/transfer.htm and http://www.fda.gov/OHRMS/DOCKETS/98fr/03-16242.html. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Exhibit D

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Office of New Drugs
Center for Drug Evaluation and Research

Exhibit D, 1

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103737/5031

JUN 0 9 2004

IDEC Pharmaceuticals Corporation
Attention: Nadine Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
Biogen Idec, Incorporated
3030 Callan Road
San Diego, CA 92121

Dear Dr. Cohen:

Your request to supplement your biologics license application for Rituximab to revise the package insert to add a Hepatitis B Reactivation with Related Fulminant Hepatitis subsection to the WARNINGS section has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

The regulatory responsibility for review and continuing oversight for this product transferred from the Center for Biologics Evaluation and Research to the Center for Drug Evaluation and Research effective June 30, 2003. For further information about the transfer, please see http://www.fda.gov/cder/biologics/default.htm. Until further notice, however, all correspondence, except as provided elsewhere in this letter, should continue to be addressed to:

CBER Document Control Center
Attn: Office of Therapeutics Research and Review
Suite 200N (HFM-99)
1401 Rockville Pike
Rockville, Maryland 20852-1448

Exhibit E

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

Patricia Keegan, M.D.
Director
Division of Therapeutic Biological Oncology Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Package Insert Labeling

Exhibit E, 1

CONCURRENCE PAGE

Letter Type: LETTER: Approval (AP)
Summary Text: Clinical Supplmt. - Labeling Only
REVIEW COMPLETION REQUIRED BY: RIS

SS Data Check:

- **Place copy of Approval Ltr. with original signature concurrence page in Archival package behind the "Approval Materials" Tab after LAR (Licensing Action Recommendation).**

RIS Data Check:

- **Verify short summary - Ltr. & Submission screen should match.**
- **Check Letter for PMCs (if PMCs - add "PMCs - Approved With" special characteristic code.)**
- **Perform Review Completion Process**
- **Milestone: Confirm Approved Status**

cc: HFM-500/K. Weiss
HFM-585/E. Dye
HFM-570/P. Keegan
HFM-110/RIMs
DRMP BLA letter file
HFM-588/S. Sickafuse
HFM-570/H. Luksenburg
HFD-430/R. Pratt
HFD-430/S. Lu
HFD-013/Debbie Taub (ORP/DIDP)
HFD-013/Heidi Brubaker (ORP/DIDP)

Exhibit E, 2

History: Sickafuse:5-19-04:6-3-04:6-7-04:6-8-04: K. Townsend: 6.8.2004: 6.9.2004

File Name: (S:Sickafuse\Rituxan\labeling supplements\103737_5031\approval letter.doc)

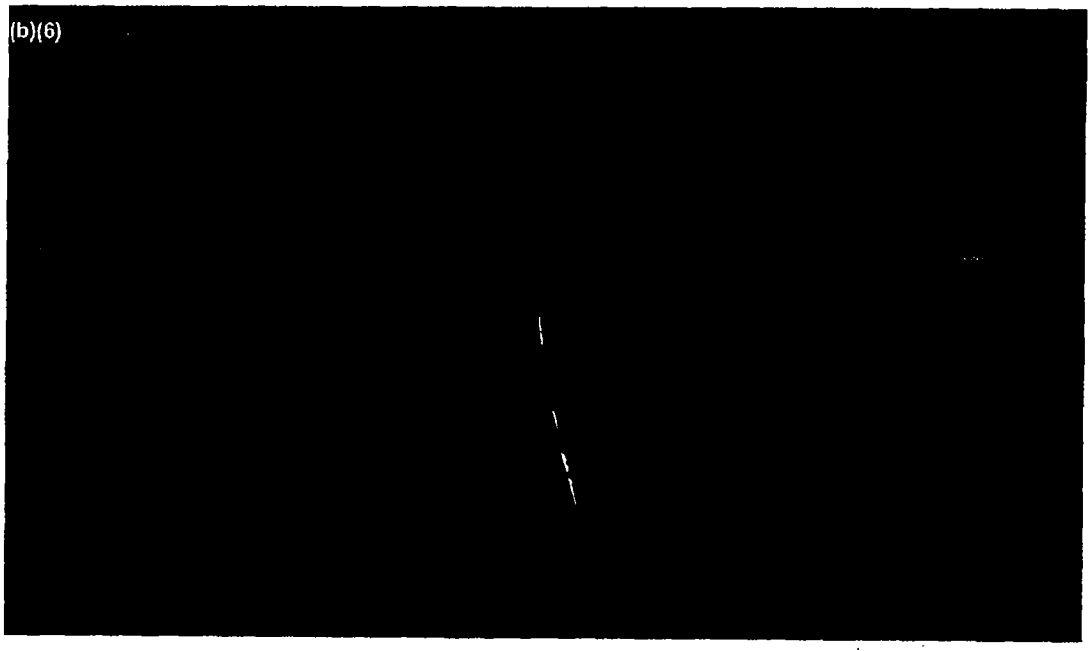


Exhibit E, 3

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 103737/5055

NOV 0 2 2004

IDEC Pharmaceuticals, Incorporated
Attention: Nadine D. Cohen, Ph.D.
Senior Vice President, Regulatory Affairs
5200 Research Place
San Diego, CA 92122

Dear Dr. Cohen:

Your request to supplement your biologics license application for Rituximab to revise the ADVERSE REACTIONS, Infectious Events section of the package insert to include information on fatal infections in patients with HIV-associated lymphoma has been approved.

Please submit all final printed labeling at the time of use and include implementation information on FDA Form 356h. Please provide a PDF-format electronic copy as well as original paper copies (ten for circulars and five for other labels).

Please refer to http://www.fda.gov/cder biologics/default.htm for important information regarding therapeutic biological products, including the address for submissions Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

Exhibit F

This information will be included in your biologics license application file.

Sincerely,

(b)(6)

(b)(6) Patricia Keegan, M.D.
Director
Division of Therapeutic Biologic Oncology Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Enclosure: Final Draft Labeling

Exhibit F, 1

DO NOT REMOVE STAPLES

ROBERT S. MUELLER, III
United States Attorney

ANDREW M. SCOBLE
Assistant United States Attorney

Attorneys for Plaintiff
UNITED STATES OF AMERICA

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA, Plaintiff, v. GENENTECH, INC., Defendant.	NO. CR. 99-0141 MJJ PLEA AGREEMENT

Defendant GENENTECH, INC. ("GENENTECH"), a Delaware corporation, by and through its counsel of record, as ratified by its Board of Directors, enters into this Plea Agreement with the United States Department of Justice, by the United States Attorney's Office for the Northern District of California (the "United States"), pursuant to Rule 11(e)(1)(C) of the Federal Rules of Criminal Procedure. This Agreement binds only the United States, as defined herein, not any state or local prosecuting authorities.

5

Exhibit G

DEFENDANT'S PLEA

1. GENENTECH agrees to waive indictment and plead guilty to a one count information charging the Introduction of a Misbranded Drug in Interstate Commerce, in violation of 21 U.S.C. §§ 331(a), 333(a)(2), and 352.

THE NATURE OF THE OFFENSE

2. GENENTECH understands that at any trial the government would be required to prove the following elements of the offense to which it is pleading guilty:

a. GENENTECH produced Protropin, which was a "New Drug" within the meaning of 21 U.S.C. §§ 321(g)(1) and (p).

b. A New Drug must be approved by the United States Food and Drug Administration ("FDA") before it may be introduced into interstate commerce for use in medical treatment.

c. The FDA may limit its approval of a New Drug to the treatment of one or more specific medical conditions. If a New Drug has been approved for use in treating a specific condition or conditions, it may not lawfully be promoted and introduced into interstate commerce for use in the treatment of other conditions for which FDA approval has not been granted.

d. Shipments of New Drugs in interstate commerce must be accompanied by adequate instructional labeling describing the intended medical uses for the drug.

e. In 1985, GENENTECH obtained FDA approval to promote and distribute Protropin for a single specified medical use: "the

Exhibit G, 1

long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion."

f. Despite the foregoing limitation, from October 1985 until June 1994, GENENTECH promoted and introduced Protropin in interstate commerce for use in treatment of other medical conditions, for which GENENTECH did not have FDA approval. Moreover, the labeling that accompanied shipments of Protropin contained no instructions for use of the drug in treatment of those other medical conditions.

g. In promoting Protropin for unapproved uses, and in distributing Protropin in interstate commerce without instructional labeling relating to those uses, GENENTECH acted with the intent to mislead the Food and Drug Administration.

THE MAXIMUM STATUTORY PENALTIES

3. GENENTECH understands that the maximum statutory penalties for the offense to which it is pleading guilty are:

a. Five years' probation;

b. Fine of the greater of $500,000 or twice the pecuniary gain to GENENTECH;

c. Mandatory special assessment of $400, which is to be paid at the time of sentencing;

d. Restitution as ordered by the Court.

FACTUAL BASIS

4. GENENTECH is guilty of the offense to which it will plead guilty, including all of the elements as set forth in Paragraph 2 above. GENENTECH agrees that the following facts are true:

Exhibit G, 2

a. GENENTECH produced Protropin, which was a drug within the meaning of 21 U.S.C. §§ 321(g)(i) and (p).

b. A New Drug must be approved by the United States Food and Drug Administration ("FDA") before it may be introduced into interstate commerce for use in medical treatment.

c. The FDA may limit its approval of a drug to use in the treatment of one or more specific medical conditions. If a drug has been approved for use in treating a specific condition, it may not lawfully be promoted and introduced into interstate commerce for use in the treatment of other conditions for which FDA approval has not been granted.

d. Shipments of FDA-approved drugs in interstate commerce must be accompanied by instructional labeling describing the FDA-approved uses for the drug.

e. In 1985, GENENTECH obtained FDA approval to promote Protropin for a single specified medical use: "the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion."

f. From October 1985 until June 1994, GENENTECH promoted and introduced Protropin in interstate commerce for use in treatment of other medical conditions, for which GENENTECH did not have FDA approval. Moreover, the labeling that accompanied shipments of Protropin contained no instructions for use of the drug in treatment of those other medical conditions.

g. In promoting Protropin for unapproved uses, and in distributing Protropin in interstate commerce without instructional

Exhibit G, 3

labeling relating to those uses, GENENTECH acted with the intent to mislead the Food and Drug Administration.

WAIVER OF RIGHTS

5. GENENTECH understands and agrees that by pleading guilty it is giving up the following rights which it would have if the case went to trial:

a. the rights to plead not guilty, to be presumed innocent, and to require the government to prove all of the elements of the crimes beyond a reasonable doubt;

b. the right to a speedy and public jury trial with the assistance of an attorney;

c. the right to a unanimous jury verdict;

d. the right to confront and cross-examine government witnesses;

e. the right to present evidence and/or witnesses on its own behalf, and to compulsory process;

f. the right not to present evidence or have adverse inferences drawn if it did not do so;

g. the rights to pursue any affirmative defenses, Fourth or Fifth Amendment claims, or any other claims presented or that could be presented in any pretrial or post-trial motion;

h. the rights to both appeal and collaterally attack, the guilty plea, the judgment of guilt, orders of the Court, and any part of the sentence imposed by the Court; and

i. the right to be indicted by a grand jury for the felony charge to which it is pleading guilty.

Exhibit 6,4

SENTENCING PROCEDURES AND FACTORS

6. If acceptable to the Court, the parties agree to waive the presentence investigation and report pursuant to Rule 32(c)(1) of the Federal Rules of Criminal Procedure and ask that the defendant be sentenced at the time the guilty plea is entered.

7. GENENTECH understands that, notwithstanding Paragraph 6 and Paragraph 9 below, its sentencing is governed by the United States Sentencing Guidelines.

8. The parties agree to the following Sentencing Guideline calculations (pursuant to the November 1, 1998 revision of the Sentencing Guidelines):

a. Pursuant to U.S.S.G. §§ 8C2.1 and 8C2.4(a)(2), and U.S.S.G. § 2F1.1, the base offense level is 22.

b. Pursuant to U.S.S.G. §§ 8C2.1 and 8C2.4(a)(2), and U.S.S.G. § 2F1.1, since the offense involved more than minimal planning, the adjusted offense level is 24.

c. Pursuant to U.S.S.G. § 8C2.5(a) and (b)(2), the culpability score is 9.

d. Pursuant to U.S.S.G. § 8C2.5(g)(2), the final culpability score is 7.

e. Pursuant to U.S.S.G. § 8C2.6, the minimum multiplier is 1.40 and the maximum multiplier is 2.80.

f. Pursuant to U.S.S.G. § 8C2.7, the Guidelines fine range falls between a minimum of $29,500,000 and a maximum of $57,800,000.

g. Pursuant to U.S.S.G. § 8B1.1(a)(1)(1991), the Court

Exhebet G, 5

may enter a restitution order in accordance with 18 U.S.C. §§ 3663-3664.

9. Pursuant to Rule 11(e)(1)(C) of the Federal Rules of Criminal Procedure, the parties agree that an appropriate disposition of this case is that GENENTECH receive the following sentence within the guidelines range:

a. ~~GENENTECH will not be placed on probation.~~

b. GENENTECH will pay a criminal fine of $30,000,000.

c. GENENTECH will pay restitution in the amount of $20,000,000 pursuant to a civil settlement agreement between the United States and GENENTECH, which will be entered into in conjunction with this Plea Agreement (the "Civil Settlement Agreement"). A copy of the Civil Settlement Agreement will be attached as Exhibit A to this Plea Agreement and incorporated by reference herein.

d. GENENTECH will pay a special assessment of $400.

10. The amounts listed in Paragraph 9(b) and (c) above shall be paid to the Financial Litigation Unit, United States Attorney's Office, Northern District of California, by FEDWIRE. Payment of all amounts described in Paragraph 9 above shall be made in full on the date of sentence.

11. GENENTECH understands that nothing in this agreement precludes any private party from pursuing any civil remedy against GENENTECH, and GENENTECH agrees that it will not raise this agreement or its guilty plea as a defense to any such civil action.

12. GENENTECH further understands that this agreement does not

Exhibit G, 6

bind the Internal Revenue Service ("IRS"). Further, GENENTECH understands that the United States takes no position as to the proper tax treatment of any of the payments made by GENENTECH pursuant to this Plea Agreement or the Civil Settlement Agreement.

13. GENENTECH understands that both the United States and GENENTECH retain the right to withdraw from this Agreement, and this Agreement will be null and void, if the Court rejects the Agreement and refuses to be bound by the sentence agreed to in Paragraph 9.

14. GENENTECH and the United States also both retain the right to withdraw from this Agreement, and this Agreement will be null and void, if the Civil Settlement Agreement is not executed by the date of acceptance of this Plea Agreement by the Court.

15. GENENTECH understands and agrees that, should it withdraw its plea in accordance with Paragraph 13 and/or Paragraph 14, it may thereafter be prosecuted for any criminal violation of which the government has knowledge, notwithstanding the expiration of any applicable statute of limitations following the signing of this agreement. GENENTECH agrees that it will not raise the expiration of any statute of limitations as a defense to any such prosecution, except to the extent that the statute of limitations would have been a defense pursuant to the terms of a Tolling Agreement between the parties dated October 9, 1998, and all subsequent extensions of that Tolling Agreement.

THE UNITED STATES' COMMITMENT

16. In exchange for GENENTECH's guilty plea and its performance

Exhibit G.7

of its other obligations under this Agreement as set forth above, the United States agrees to do the following:

a. It will not file any other criminal charges against GENENTECH, or its present or former officers, directors, or employees, for offenses relating to conduct in connection with the manufacture, marketing, sale or promotion of Protropin during the period October 1985 and June 1994; and,

b. It will agree, pursuant to Rule 11(e)(1)(C), to the sentence set forth in Paragraph 9 above.

MODIFICATION OF PLEA AGREEMENT

17. This Agreement sets forth all the terms of the plea agreement between GENENTECH and the United States. GENENTECH understands that no modifications of or additions to this Agreement shall be valid unless they are in writing and signed by the United States, GENENTECH's attorney, and a duly authorized representative of GENENTECH.

STATEMENT BY GENENTECH -- KNOWING AND VOLUNTARY PLEA

This Agreement has been authorized, following consultation with counsel, by the GENENTECH Board of Directors, by corporate resolution dated February 10, 1999. A certified copy of the corporate resolution is attached as Exhibit B to this agreement and incorporated herein. Except as set forth in this plea agreement, GENENTECH has received no promises or inducements to enter its guilty plea, nor has anyone threatened GENENTECH or any other person to cause it to enter its guilty plea.

Exhibit G, 8

Dated: May 7, 1999

Cynthia J. Ladd, Vice President,
Corporate Law, Legal Department,
GENENTECH, INC.

DEFENSE COUNSEL AFFIRMATION -- KNOWING AND VOLUNTARY PLEA

We have discussed with and fully explained to GENENTECH: the facts and circumstances of the case; all rights with respect to the offense charged in the Information; possible defenses to the offense charged in the Information; all rights with respect to the Sentencing Guidelines; and all of the consequences of entering into this plea agreement and entering guilty plea. We have reviewed the entire plea agreement with our client, through its authorized representatives. In our judgment, GENENTECH, through its authorized representatives, understands the terms and conditions of the plea agreement, and we believe GENENTECH's decision to sign the agreement is knowing and voluntary. GENENTECH's execution of and entry into the plea agreement is done with our consent.

DATED: May 7, 1999

DAVID P. KING
Hogan & Hartson, L.L.P.

DATED: May 7, 1999

THOMAS P. SULLIVAN
Jenner & Block

DATED: 5/7/99

WILLIAM M. GOODMAN
Topel & Goodman

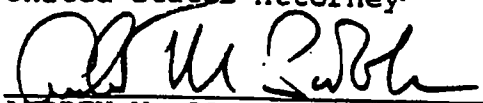
Counsel for Defendant GENENTECH, INC.

Exhibit G, 9

UNITED STATES' Signature

DATED: April 14, 1999

ROBERT S. MUELLER, III
United States Attorney



ANDREW M. SCOBLE
Assistant United States Attorney

Exhibit G, 10

EXHIBIT A

Exhibit G.11

SETTLEMENT AGREEMENT

I. PARTIES

This Settlement Agreement ("Agreement") is entered into between the United States of America ("United States"), acting through its Department of Justice and the United States Attorney's Office for the Northern District of California, and Genentech, Inc. ("Genentech") (sometimes collectively referred to as the "Parties").

II. PREAMBLE

As a preamble to this Agreement, the Parties agree to the following:

A. Genentech is a Delaware corporation that maintains its headquarters in South San Francisco, California. Genentech is a pharmaceutical company that develops, manufactures, and distributes prescription drugs.

B. Genentech is entering a plea of guilty to an Information alleging that it distributed a misbranded drug in interstate commerce in violation of 21 U.S.C. §§ 331(a), 333(a)(2), and 352, in a matter captioned United States of America v. Genentech, Inc., No. CR 99-0141 MJJ (filed in the Northern District of California, April 30, 1999);

C. During the relevant time period, Genentech manufactured and marketed Protropin, a human growth hormone.

D. In 1985, the United States Food and Drug Administration ("FDA") granted approval to Genentech to market and distribute Protropin for a single approved medical use, the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion.

Exhibit G, 12

E. On December 17, 1985, the FDA granted orphan drug status to Protropin under the Orphan Drug Act within the Food, Drug and Cosmetic Act, which granted Genentech seven years marketing exclusivity and certain tax benefits.

F. During the relevant time period, the FDA did not approve any additional uses for Protropin although it did approve Nutropin, a human growth hormone similar to Protropin, in 1993 for the treatment of growth failure due to a lack of adequate endogenous growth hormone secretion, and in 1994 for the treatment of chronic renal insufficiency.

G. Genentech marketed and sold Protropin for use by patients insured under state Medicaid programs, 42 U.S.C. §§ 1396 et seq., and claims for payment were submitted for Protropin to these Medicaid Programs and were paid by these Medicaid Programs. Similarly, Genentech marketed and sold Protropin for use by patients covered by the CHAMPUS/ TRICARE program and claims for payment were submitted to and paid by this program.

H. The United States contends that it has certain civil claims against Genentech under the False Claims Act, 31 U.S.C. §§ 3729-3733, and/or the common law theories of payment by mistake of fact, unjust enrichment, breach of contract and fraud (a) for the sale and promotion of Protropin in interstate commerce with the intent that it would be used in the treatment of medical conditions for which no FDA approval had been granted, in violation of federal law, during the period October 1985 through June 1994, which conduct is described more specifically and fully in paragraphs 2 and 4 of the Plea Agreement attached hereto as Exhibit A and the entirety of the Stipulated Statement of Facts attached hereto as Exhibit B, and (b) during the period October 1985 through June 1994 for causing the submission of false claims for Protropin to Medicaid Programs and/or CHAMPUS/TRICARE or making false statements to get a false or fraudulent claim for Protropin

Exhibit G, 13

paid by the Medicaid and CHAMPUS/TRICARE Programs to the extent that such claims were paid for by federal funds (collectively the "Covered Conduct").

I. Genentech denies the contentions of the United States as set forth in Preamble Paragraph H above.

J. To avoid the delay, uncertainty, inconvenience and expense of protracted litigation of these claims, the Parties reach a full and final settlement as set forth below.

III. TERMS AND CONDITIONS

NOW, THEREFORE, in consideration of the mutual promises, covenants, and obligations set forth below, and for good and valuable consideration as stated herein, the Parties agree as follows:

1. Genentech agrees to pay to the United States the sum of Twenty Million dollars ($20,000,000) (the "Settlement Amount"). Genentech will pay the Settlement Amount by electronic funds transfer pursuant to written instructions to be provided by the United States Attorney's Office for the Northern District of California. This Settlement Amount shall be paid to the United States on the date that the United States District Court for the Northern District of California imposes sentence on Genentech in accordance with the Plea Agreement between the United States and Genentech, a copy of which is attached hereto as Exhibit A.

2. Genentech releases the United States, and each of its agencies, officers, agents, employees, and contractors and their employees from any and all claims, causes of action, adjustments, and set-offs of any kind arising out of or pertaining to the Covered Conduct, including the investigation of the Covered Conduct and this Agreement.

Exhibit G, 14

3. Conditioned upon Genentech's payment in full of the Settlement Amount, the United States agrees to release Genentech, its predecessors, successors, assigns, and affiliates and any of their current or former directors, officers and employees in such capacity from any civil claim the United States has or may have under the False Claims Act, 31 U.S.C. §§ 3729-3733, or the common law theories of payment by mistake of fact, unjust enrichment, breach of contract and fraud for the Covered Conduct and to the extent, and only to the extent, that federal funds were used for payments by the Medicaid Programs (the "federal participation" in Medicaid) and/or the Civilian Health and Medical Program of the Uniformed Services ("CHAMPUS")/ TRICARE Programs. The United States expressly reserves any claims against any entities and individuals other than Genentech, its predecessors, successors, assigns, and affiliates and any of their current or former directors, officers and employees.

4. Notwithstanding any term of this Agreement, specifically reserved and excluded from the scope and terms of this Agreement as to any entity or person (including Genentech) are any and all of the following:

a. Any criminal, civil, or administrative liability that Genentech has or may have to any state Medicaid Program, or any other state or local program that paid for Protropin treatment and/or paid for the purchase of Protropin. This Agreement does not release any criminal, civil, or administrative claims whatsoever that any state, or agent or agency of a state, has or may have against Genentech.

b. Any civil, criminal or administrative claims arising under Title 26, U.S. Code (Internal Revenue Code);

c. Any criminal liability;

Exhibit G, 15

d. Any administrative liability, including mandatory or permissive exclusion from federal health care programs; suspension or debarment from federal contracts, and/or claims for defective pricing, price reductions, and/or pricing violations;

e. Any liability to the United States (or its agencies) for any conduct other than the Covered Conduct;

f. Any claims based upon such obligations as are created by this Agreement;

g. Any express or implied warranty claims or other claims for defective or deficient products or services, including quality of goods and services, provided by Genentech;

h. Any claims based on a failure to deliver items or services billed;

i. Any claims against any individuals, including current or former officers and employees who are criminally indicted or convicted of an offense or who enter a criminal plea related to the Covered Conduct, and

j. Any claims brought by any state.

5. This Settlement Agreement may be declared null and void by either the United States or Genentech if the United States District Court for the Northern District of California does not accept in its entirety the Plea of Guilty and Statement of Facts attached hereto as Exhibits A and B. In the event the United States or Genentech declares this Settlement Agreement null and void: (i) the United States shall, within a prompt manner after such declaration, return to Genentech any payment made to the United States under this Settlement Agreement, in the amount of the principal of such payment without any actual or imputed interest; and (ii) Genentech agrees that all applicable statutes of limitations shall be tolled from the date of this Settlement Agreement until the date on which this agreement is declared null and void, and the entire time period subject to such

Exhibit G.16

tolling shall not count in any proceeding brought by the United States against Genentech for purposes of any statutes of limitation, laches, or other time-based defenses.

6. Genentech waives and will not assert any defenses it may have to any criminal prosecution or administrative action relating to the Covered Conduct, which defenses may be based in whole or in part on a contention that, under the Double Jeopardy or Excessive Fines Clause of the Constitution, this settlement bars a remedy sought in such criminal prosecution or administrative action. Genentech agrees that this Settlement Agreement and Settlement Amount is not punitive in purpose or effect for purposes of the Double Jeopardy or Excessive Fines Clauses. Nothing in this paragraph or any other provision of this Agreement constitutes an agreement by the United States concerning the characterization of the Settlement Amount for purposes of the Internal Revenue Laws, Title 26 of the United States Code.

7. Genentech agrees that all costs (as defined in the Federal Acquisition Regulations ("FAR") § 31.205-47 and the regulations promulgated thereunder) incurred by or on behalf of Genentech in connection with: (1) the matters covered by this Agreement, (2) the Government's audit(s) and civil and any criminal investigation(s) of the matters covered by this Agreement, (3) Genentech's investigation, defense, and corrective actions undertaken in response to the Government's audit(s) and civil and any criminal investigation(s) in connection with the matters covered by this Agreement (including attorney's fees), (4) the negotiation of this Agreement, and (5) the payment made pursuant to this Agreement, are unallowable costs on any Government contracts including, but not limited to the Medicare Program, Medicaid Program, TRICARE Program, Veterans Affairs Program (VA), Federal Employee Health Benefits Program (FEHBP) and Railroad Retirement Board (RRB) (hereafter, "unallowable costs"). These unallowable costs

Exhibit 6, 17

will be separately estimated and accounted for by Genentech, and Genentech will not charge such unallowable costs directly or indirectly to any contracts with the United States or any state Medicaid program, or seek payment for such unallowable costs through any cost report, cost statement, information statement or payment request submitted by Genentech or any of its subsidiaries to a federally subsidized program such as the Medicare, Medicaid, TRICARE, VA, FEHBP and RRB programs.

8. This Agreement is intended to be for the benefit of the Parties only, and by this instrument the Parties do not release any claims against any other person or entity.

9. Genentech agrees that it will not seek payment for any of the health care billings covered by this Agreement from any health care beneficiaries or their parents or sponsors. Genentech waives any causes of action against these beneficiaries or their parents or sponsors based upon the claims for payment covered by this Agreement.

10. Each party to this Agreement will bear its own legal and other costs incurred in connection with this matter, including the preparation and performance of this Agreement.

11. Genentech represents that this Agreement is freely and voluntarily entered into without any degree of duress or compulsion whatsoever.

12. This Agreement is governed by the laws of the United States. The Parties agree that the exclusive jurisdiction and venue for any dispute arising between and among the Parties (but not any other persons or third-parties) under this Agreement will be the United States District Court for the Northern District of California.

Exhibit G, 18

13. This Agreement, including Exhibits A and B which are incorporated by reference, constitutes the complete agreement between the Parties. This Agreement may not be amended except by written consent of the Parties.

14. The undersigned individual signing this Agreement on behalf of Genentech represents and warrants that he is authorized pursuant to a resolution of the Board of Directors of Genentech, a copy of which is attached to the Plea Agreement, to execute this Agreement on behalf of Genentech. The undersigned United States signatories represent that they are signing this Agreement in their official capacities and that they are authorized to execute this Agreement.

15. This Agreement may be executed in counterparts, each of which constitutes an original and all of which constitute one and the same agreement.

16. The Parties agree that this Agreement does not constitute an admission by any person or entity with respect to any issue of law or fact.

15. This Agreement is effective on May 7, 1999.

THE UNITED STATES OF AMERICA

DAVID W. OGDEN
Acting Assistant Attorney General

ROBERT S. MUELLER, III
United States Attorney

Dated: May 7, 1999 By: _____ AUSA, fw
Joann M. Swanson
Assistant United States Attorney

GENENTECH, INC.

Dated: May 7, 1999 By: _____
Cynthia J. Ladd
Vice President, Corporate Law

Exhibit 6, 19

HOGAN & HARTSON, L.L.P.

Dated: May 7, 1999

By: _____
David P. King
Counsel for Genentech

Exhibit G, 20

EXHIBIT A

TO SETTLEMENT AGREEMENT

Exhibit 6, 21

ROBERT S. MUELLER, III
United States Attorney

ANDREW M. SCOBLE
Assistant United States Attorney

Attorneys for Plaintiff
UNITED STATES OF AMERICA

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA, Plaintiff, v. GENENTECH, INC., Defendant.	NO. CR. PLEA AGREEMENT

Defendant GENENTECH, INC. ("GENENTECH"), a Delaware corporation, by and through its counsel of record, as ratified by its Board of Directors, enters into this Plea Agreement with the United States Department of Justice, by the United States Attorney's Office for the Northern District of California (the "United States"), pursuant to Rule 11(e)(1)(C) of the Federal Rules of Criminal Procedure. This Agreement binds only the United States, as defined herein, not any state or local prosecuting authorities.

EXHIBIT A TO SETTLEMENT AGT.

Exhibit 6.22

DEFENDANT'S PLEA

1. GENENTECH agrees to waive indictment and plead guilty to a one count information charging the Introduction of a Misbranded Drug in Interstate Commerce, in violation of 21 U.S.C. §§ 331(a), 333(a)(2), and 352.

THE NATURE OF THE OFFENSE

2. GENENTECH understands that at any trial the government would be required to prove the following elements of the offense to which it is pleading guilty:

a. GENENTECH produced Protropin, which was a "New Drug" within the meaning of 21 U.S.C. §§ 321(g)(1) and (p).

b. A New Drug must be approved by the United States Food and Drug Administration ("FDA") before it may be introduced into interstate commerce for use in medical treatment.

c. The FDA may limit its approval of a New Drug to the treatment of one or more specific medical conditions. If a New Drug has been approved for use in treating a specific condition or conditions, it may not lawfully be promoted and introduced into interstate commerce for use in the treatment of other conditions for which FDA approval has not been granted.

d. Shipments of New Drugs in interstate commerce must be accompanied by adequate instructional labeling describing the intended medical uses for the drug.

e. In 1985, GENENTECH obtained FDA approval to promote and distribute Protropin for a single specified medical use: "the

Exhibit G, 23

long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion."

f. Despite the foregoing limitation, from October 1985 until June 1994, GENENTECH promoted and introduced Protropin in interstate commerce for use in treatment of other medical conditions, for which GENENTECH did not have FDA approval. Moreover, the labeling that accompanied shipments of Protropin contained no instructions for use of the drug in treatment of those other medical conditions.

g. In promoting Protropin for unapproved uses, and in distributing Protropin in interstate commerce without instructional labeling relating to those uses, GENENTECH acted with the intent to mislead the Food and Drug Administration.

THE MAXIMUM STATUTORY PENALTIES

3. GENENTECH understands that the maximum statutory penalties for the offense to which it is pleading guilty are:

a. Five years' probation;

b. Fine of the greater of $500,000 or twice the pecuniary gain to GENENTECH;

c. Mandatory special assessment of $400, which is to be paid at the time of sentencing;

d. Restitution as ordered by the Court.

FACTUAL BASIS

4. GENENTECH is guilty of the offense to which it will plead guilty, including all of the elements as set forth in Paragraph 2 above. GENENTECH agrees that the following facts are true:

Exhibit G, 24

a. GENENTECH produced Protropin, which was a drug within the meaning of 21 U.S.C. §§ 321(g)(1) and (p).

b. A New Drug must be approved by the United States Food and Drug Administration ("FDA") before it may be introduced into interstate commerce for use in medical treatment.

c. The FDA may limit its approval of a drug to use in the treatment of one or more specific medical conditions. If a drug has been approved for use in treating a specific condition, it may not lawfully be promoted and introduced into interstate commerce for use in the treatment of other conditions for which FDA approval has not been granted.

d. Shipments of FDA-approved drugs in interstate commerce must be accompanied by instructional labeling describing the FDA-approved uses for the drug.

e. In 1985, GENENTECH obtained FDA approval to promote Protropin for a single specified medical use: "the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion."

f. From October 1985 until June 1994, GENENTECH promoted and introduced Protropin in interstate commerce for use in treatment of other medical conditions, for which GENENTECH did not have FDA approval. Moreover, the labeling that accompanied shipments of Protropin contained no instructions for use of the drug in treatment of those other medical conditions.

g. In promoting Protropin for unapproved uses, and in distributing Protropin in interstate commerce without instructional

Exhibit G, 25

labeling relating to those uses, GENENTECH acted with the intent to mislead the Food and Drug Administration.

WAIVER OF RIGHTS

5. GENENTECH understands and agrees that by pleading guilty it is giving up the following rights which it would have if the case went to trial:

a. the rights to plead not guilty, to be presumed innocent, and to require the government to prove all of the elements of the crimes beyond a reasonable doubt;

b. the right to a speedy and public jury trial with the assistance of an attorney;

c. the right to a unanimous jury verdict;

d. the right to confront and cross-examine government witnesses;

e. the right to present evidence and/or witnesses on its own behalf, and to compulsory process;

f. the right not to present evidence or have adverse inferences drawn if it did not do so;

g. the rights to pursue any affirmative defenses, Fourth or Fifth Amendment claims, or any other claims presented or that could be presented in any pretrial or post-trial motion;

h. the rights to both appeal and collaterally attack, the guilty plea, the judgment of guilt, orders of the Court, and any part of the sentence imposed by the Court; and

i. the right to be indicted by a grand jury for the felony charge to which it is pleading guilty.

Exhibit G, 26

SENTENCING PROCEDURES AND FACTORS

6. If acceptable to the Court, the parties agree to waive the presentence investigation and report pursuant to Rule 32(c)(1) of the Federal Rules of Criminal Procedure and ask that the defendant be sentenced at the time the guilty plea is entered.

7. GENENTECH understands that, notwithstanding Paragraph 6 and Paragraph 9 below, its sentencing is governed by the United States Sentencing Guidelines.

8. The parties agree to the following Sentencing Guideline calculations (pursuant to the November 1, 1998 revision of the Sentencing Guidelines):

a. Pursuant to U.S.S.G. §§ 8C2.1 and 8C2.4(a)(2), and U.S.S.G. § 2F1.1, the base offense level is 22.

b. Pursuant to U.S.S.G. §§ 8C2.1 and 8C2.4(a)(2), and U.S.S.G. § 2F1.1, since the offense involved more than minimal planning, the adjusted offense level is 24.

c. Pursuant to U.S.S.G. § 8C2.5(a) and (b)(2), the culpability score is 9.

d. Pursuant to U.S.S.G. § 8C2.5(g)(2), the final culpability score is 7.

e. Pursuant to U.S.S.G. § 8C2.6, the minimum multiplier is 1.40 and the maximum multiplier is 2.80.

f. Pursuant to U.S.S.G. § 8C2.7, the Guidelines fine range falls between a minimum of $29,500,000 and a maximum of $57,800,000.

g. Pursuant to U.S.S.G. § 8B1.1(a)(1)(1991), the Court

Exhibit G, 27

may enter a restitution order in accordance with 18 U.S.C. §§ 3663-3664.

9. Pursuant to Rule 11(e)(1)(C) of the Federal Rules of Criminal Procedure, the parties agree that an appropriate disposition of this case is that GENENTECH receive the following sentence within the guidelines range:

a. GENENTECH will not be placed on probation.

b. GENENTECH will pay a criminal fine of $30,000,000.

c. GENENTECH will pay restitution in the amount of $20,000,000 pursuant to a civil settlement agreement between the United States and GENENTECH, which will be entered into in conjunction with this Plea Agreement (the "Civil Settlement Agreement"). A copy of the Civil Settlement Agreement will be attached as Exhibit A to this Plea Agreement and incorporated by reference herein.

d. GENENTECH will pay a special assessment of $400.

10. The amounts listed in Paragraph 9(b) and (c) above shall be paid to the Financial Litigation Unit, United States Attorney's Office, Northern District of California, by FEDWIRE. Payment of all amounts described in Paragraph 9 above shall be made in full on the date of sentence.

11. GENENTECH understands that nothing in this agreement precludes any private party from pursuing any civil remedy against GENENTECH, and GENENTECH agrees that it will not raise this agreement or its guilty plea as a defense to any such civil action.

12. GENENTECH further understands that this agreement does not

Exhibit G, 28

bind the Internal Revenue Service ("IRS"). Further, GENENTECH understands that the United States takes no position as to the proper tax treatment of any of the payments made by GENENTECH pursuant to this Plea Agreement or the Civil Settlement Agreement.

13. GENENTECH understands that both the United States and GENENTECH retain the right to withdraw from this Agreement, and this Agreement will be null and void, if the Court rejects the Agreement and refuses to be bound by the sentence agreed to in Paragraph 9.

14. GENENTECH and the United States also both retain the right to withdraw from this Agreement, and this Agreement will be null and void, if the Civil Settlement Agreement is not executed by the date of acceptance of this Plea Agreement by the Court.

15. GENENTECH understands and agrees that, should it withdraw its plea in accordance with Paragraph 13 and/or Paragraph 14, it may thereafter be prosecuted for any criminal violation of which the government has knowledge, notwithstanding the expiration of any applicable statute of limitations following the signing of this agreement. GENENTECH agrees that it will not raise the expiration of any statute of limitations as a defense to any such prosecution, except to the extent that the statute of limitations would have been a defense pursuant to the terms of a Tolling Agreement between the parties dated October 9, 1998, and all subsequent extensions of that Tolling Agreement.

THE UNITED STATES' COMMITMENT

16. In exchange for GENENTECH's guilty plea and its performance

Exhibit G, 29

of its other obligations under this Agreement as set forth above, the United States agrees to do the following:

a. It will not file any other criminal charges against GENENTECH, or its present or former officers, directors, or employees, for offenses relating to conduct in connection with the manufacture, marketing, sale or promotion of Protropin during the period October 1985 and June 1994; and,

b. It will agree, pursuant to Rule 11(e)(1)(C), to the sentence set forth in Paragraph 9 above.

MODIFICATION OF PLEA AGREEMENT

17. This Agreement sets forth all the terms of the plea agreement between GENENTECH and the United States. GENENTECH understands that no modifications of or additions to this Agreement shall be valid unless they are in writing and signed by the United States, GENENTECH's attorney, and a duly authorized representative of GENENTECH.

STATEMENT BY GENENTECH -- KNOWING AND VOLUNTARY PLEA

This Agreement has been authorized, following consultation with counsel, by the GENENTECH Board of Directors, by corporate resolution dated February 10, 1999. A certified copy of the corporate resolution is attached as Exhibit B to this agreement and incorporated herein. Except as set forth in this plea agreement, GENENTECH has received no promises or inducements to enter its guilty plea, nor has anyone threatened GENENTECH or any other person to cause it to enter its guilty plea.

Exhibit G, 30

Dated: May 7, 1999

Cynthia J. Ladd, Vice President,
Corporate Law, Legal Department,
GENENTECH, INC.

DEFENSE COUNSEL AFFIRMATION -- KNOWING AND VOLUNTARY PLEA

We have discussed with and fully explained to GENENTECH: the facts and circumstances of the case; all rights with respect to the offense charged in the Information; possible defenses to the offense charged in the Information; all rights with respect to the Sentencing Guidelines; and all of the consequences of entering into this plea agreement and entering guilty plea. We have reviewed the entire plea agreement with our client, through its authorized representatives. In our judgment, GENENTECH, through its authorized representatives, understands the terms and conditions of the plea agreement, and we believe GENENTECH's decision to sign the agreement is knowing and voluntary. GENENTECH's execution of and entry into the plea agreement is done with our consent.

DATED: May 7, 1999

DAVID P. KING
Hogan & Hartson, L.L.P.

DATED: May 7, 1999

THOMAS P. SULLIVAN
Jenner & Block

DATED: 5/7/99

WILLIAM M. GOODMAN
Topel & Goodman

Counsel for Defendant GENENTECH, INC.

Exhibit G, 31

UNITED STATES' Signature

DATED: April 14, 1999

ROBERT S. MUELLER, III
United States Attorney

ANDREW M. SCOBLE
Assistant United States Attorney

Exhibit G, 32

EXHIBIT B

TO SETTLEMENT ACT

Exhibit G, 33

ROBERT S. MUELLER, III
United States Attorney

ANDREW M. SCOBLE
Assistant United States Attorney

Attorneys for Plaintiff
UNITED STATES OF AMERICA

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

UNITED STATES OF AMERICA, Plaintiff, v. GENENTECH, INC., Defendant.	NO. CR. 99-141 (MJJ) STIPULATED STATEMENT OF FACTS

1. The defendant GENENTECH, INC. ("GENENTECH") is a Delaware corporation with its main office in South San Francisco, California. GENENTECH engages in, among other things, the development, manufacture, promotion, sale and interstate distribution of prescription drugs.

2. The United States Food and Drug Administration ("FDA") is the agency of the United States government responsible for protecting the health and safety of the American public by ensuring, among other things, that new prescription drug products ("New Drugs") are safe and effective for their intended medical uses. The FDA carries out its responsibilities, in part, by requiring drug

EXH. B TO SETTLEMENT AGT

Exhibit G, 34

companies and others seeking to market and distribute New Drugs to obtain FDA approval before doing so.

3. The FDA may limit its approval of a New Drug to the treatment of one or more specific medical conditions. If a New Drug has been approved for use in treating a specific medical condition or conditions, it may not lawfully be promoted and introduced into interstate commerce for use in the treatment of other conditions for which FDA approval has not been granted.

4. Shipments of FDA-approved New Drugs in interstate commerce must be accompanied by adequate instructional labeling describing the intended medical uses for the drug.

5. One drug that GENENTECH produced was Protropin, a synthetic growth hormone that was a "New Drug" within the meaning of 21 U.S.C. § 321(g)(1) and (p).

6. In October 1985, GENENTECH obtained FDA approval to promote and distribute Protropin for a single specified medical use: "the long-term treatment of children who have growth failure due to a lack of adequate endogenous growth hormone secretion."

7. Despite the foregoing limitation, from in or about October 1985 until June 1994, within the Northern District of California and elsewhere, the defendant GENENTECH promoted and introduced Protropin in interstate commerce with the intent that it would be used in the treatment of other medical conditions, for which GENENTECH did not have FDA approval. Moreover, the labeling that accompanied shipments of Protropin contained no instructions for use of the drug in treatment of those other medical conditions.

Exhibit G, 35

EXHIBIT B

TO PLEA AGREEMENT

Exhibit G, 36

8. In promoting Protropin for unapproved uses, and in distributing Protropin in interstate commerce without instructional labeling relating to those uses, GENENTECH acted with the intent to mislead the FDA.

DATED: May 7, 1999

DAVID P. KING
Hogan & Hartson, L.L.P.

DATED: May 7, 1999

Thomas P. Sullivan by dpk
THOMAS P. SULLIVAN
Jenner & Block

DATED: 5/7/99

WILLIAM M. GOODMAN
Topel & Goodman

Counsel for Defendant GENENTECH, INC.

UNITED STATES' Signature

DATED: 5/06/99

ROBERT S. MUELLER, III
United States Attorney

ANDREW M. SCOBLE
Assistant United States Attorney

Exhibit, 637

APPENDIX A

WHEREAS, the Company has been the target of a grand jury investigation conducted by the United States Department of Justice, the Food and Drug Administration ("FDA"), and the Attorney's Office for the Northern District of California;

WHEREAS, the investigation has focused on allegations that during the time period 1985 to June 1994, the Company promoted its human growth hormone products for uses beyond those approved the FDA;

WHEREAS, the Company has retained counsel and has engaged in an extensive review of the conduct alleged by the government investigation;

WHEREAS, both Company counsel and outside counsel have engaged in negotiations with the government agencies involved in the investigation;

WHEREAS, the Board of Directors formed a special committee to consider an appropriate resolution of the investigation and the special committee has been thoroughly briefed regarding the status of the investigation and the proposed resolution;

WHEREAS, the special committee has recommended in favor of resolution of the dispute in the manner described below; and

WHEREAS, the Board of Directors has this day carefully considered and thoroughly discussed the proposed resolution.

RESOLVED; that the Board determines it is in the best interests of the Company to resolve the investigation; and approves the resolution negotiated by Genentech's counsel and previously approved by the special committee, in which the Company will enter a plea of guilty to one count of promoting human growth hormone for an unlabeled use during the time frame 1985 to 1994, and make a payment to the United States in the amount of $50,000,000;

RESOLVED FURTHER, the officers of the Company and each of them are authorized to execute such documents, make such court appearances, and take such further actions as necessary to resolve this matter.

Exhibit G, 38

Secretary's Certificate

I, Cynthia J. Ladd, hereby certify that I am the duly elected and acting Assistant Secretary of Genentech, Inc. (the "Company") and that the attached hereto as Appendix "A" is a true and correct copy of a resolution adopted February 10, 1999 by the Genentech Board of Directors and that this resolution has not been rescinded or modified and remains in full force and effect.

Dated: May 6, 1999

Cynthia J. Ladd
Assistant Secretary

#61287.1

Exhibit, G 39

F I L E C O P Y

gdl

United States District Court
for the
Northern District of California
May 14, 1999

* * CERTIFICATE OF SERVICE * *

Case Number:3:99-cr-00141

USA

vs

Genentech, Inc.

I, the undersigned, hereby certify that I am an employee in the Office of the Clerk, U.S. District Court, Northern District of California.

That on May 14, 1999, I SERVED a true and correct copy(ies) of the attached, by placing said copy(ies) in a postage paid envelope addressed to the person(s) hereinafter listed, by depositing said envelope in the U.S. Mail, or by placing said copy(ies) into an inter-office delivery receptacle located in the Clerk's office.

Andrew M. Scoble, Esq.
U S Attorney's Office
Criminal Division
450 Golden Gate Ave
San Francisco, CA 94102

David King
111 S. Calvert Street
Baltimore, Maryland 21202

Thomas Sullivan
One IBM Plaza
Chicago, IL 60611

William Goodman
832 Sansome STreet, 4th Floor
San Francisco, CA 94111

Financial

Richard W. Wieking, Clerk

BY: _____
Deputy Clerk

Exhibit G, 40

RITUXAN™
Rituximab

DESCRIPTION

The RITUXAN (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG, kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures.

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for intravenous administration in 9.0 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Sterile Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1,2] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL)[3] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[4] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[3]

Pre-clinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[7] and antibody-dependent cellular cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[8]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B-lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in non-lymphoid tissues examined.

Human Pharmacokinetics/Pharmacodynamics

In patients given single doses at 10, 50, 100, 250 or 500 mg/m² as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose. In 9 patients given 375 mg/m² as an IV infusion for four doses, the mean serum half-life was 59.8 hours (range 11.1 to 104.6 hours) after the first infusion and 174 hours (range 26 to 442 hours) after the fourth infusion. The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20 positive (normal and malignant) B-cell populations upon repeated administrations.

Rituximab at a dose of 375 mg/m² was administered as an IV infusion at weekly intervals for four doses to 166 patients. The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20 positive B cells and measures of disease burden. Median steady-state serum levels were higher for responders compared to nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared to those with subtype A. Rituximab was detectable in the serum of patients three to six months after completion of treatment.

The pharmacokinetic profile of Rituximab when administered as six infusions of 375 mg/m² in combination with six cycles of CHOP chemotherapy was similar to that seen with Rituximab alone.

Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B-cells in seven of eight patients who had received single doses of Rituximab ≥100 mg/m². [9] Among the 166 patients in the pivotal study, circulating B-cells (measured as CD19+ cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients. One of the responding patients (1%), failed to show significant depletion of CD19+ cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately six months following completion of treatment. Median B-cell levels returned to normal by twelve months following completion of treatment.

There were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgG and/or IgM serum levels, resulting in values below the normal range.

CLINICAL STUDIES

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m² of RITUXAN given as an IV infusion weekly for four doses. Patients with tumor masses >10 cm or with >5,000 lymphocytes/μL in the peripheral blood were excluded from the study. The overall response rate (ORR) was 48% (80/166) with a 6% (10/166) complete response (CR) and a 42% (70/166) partial response (PR) rate. Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of those patients. The median time to onset of response was 50 days and the median duration of response is projected to be 10 to 12 months.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF A subtype (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm in greatest diameter (55% vs. 38%), and higher in patients with chemosensitive relapse as compared to chemoresistant (defined as duration of response <3 months) relapse (53% vs. 36%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following factors were not associated with a lower response rate: age ≥ 60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

In a second multicenter, multiple-dose study, 37 patients with relapsed or refractory B-cell NHL received 375 mg/m² of RITUXAN as an IV infusion once weekly for four doses.[10,11] The ORR was 46% with a median duration of response of 8.6 months (range 2.6 to 26.2+). Single doses of up to 500 mg/m² were well-tolerated.[9]

Twenty patients have received two courses and one patient has received three courses of RITUXAN as 4 weekly infusions of 375 mg/m² per infusion. The percentage of patients reporting adverse events upon retreatment was similar to that reported following the first course, although the incidence of specific adverse events differed (see ADVERSE EVENTS). All patients had obtained an objective clinical response (CR or PR) to the first course of RITUXAN™ (Rituximab); upon retreatment, 6 of 12 patients evaluable for response obtained a complete or partial remission.

Twenty-nine patients with relapsed or refractory, bulky (single lesion of >10 cm in diameter), low grade NHL received 375 mg/m² of RITUXAN as four weekly infusions. The overall incidence of adverse events and the incidence of Grade 3 and 4 adverse events was higher in patients with bulky disease than in patients with non-bulky disease (see ADVERSE EVENTS). Ten of 21 patients evaluable for response have obtained a complete or partial remission.

INDICATIONS AND USAGE

RITUXAN is indicated for the treatment of patients with relapsed or refractory low-grade or follicular, CD20 positive, B-cell non-Hodgkin's lymphoma.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known Type I hypersensitivity or anaphylactic reactions to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS

RITUXAN is associated with hypersensitivity reactions which may respond to adjustments in the infusion rate. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion as part of an infusion-related symptom complex. RITUXAN infusion should be interrupted for severe reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids should be available for immediate use in the event of a reaction during administration.

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

PRECAUTIONS

Laboratory Monitoring: Complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE EVENTS).

Drug/Laboratory Interactions: There have been no formal drug interaction studies performed with RITUXAN.

HAMA/HACA Formation: Human anti-murine antibody (HAMA) was not detected in 67 patients evaluated. Less than 1.0% (3/355) of patients evaluated for human anti-chimeric antibody (HACA) were positive. Patients who develop HAMA/HACA titers may have allergic or hypersensitivity reactions when treated with this or other murine or chimeric monoclonal antibodies.

Immunization: The safety of immunization with any vaccine, particularly live viral vaccines, following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to any vaccine has also not been studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility: No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C: Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use: The safety and effectiveness of RITUXAN in children have not been established.

ADVERSE REACTIONS

Safety data are based on 315 patients treated in five single-agent studies of RITUXAN. This includes patients with bulky disease (lesions >10 cm), those who have received more than one course of RITUXAN, and patients receiving 375 mg/m² for eight doses.

Infusion-Related Events: An infusion-related symptom complex consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion-related symptoms included nausea, urticaria, fatigue, headache, pruritus, bronchospasm, dyspnea, sensation of tongue or throat swelling (angioedema), rhinitis, vomiting, hypotension, flushing, and pain at disease sites. These reactions generally occurred within 30 minutes to 2 hours of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (IV saline, diphenhydramine, and acetaminophen). The incidence of infusion-related events decreased from 80% (7% Grade 3/4) during the first infusion to approximately 40% (5% to 10% Grade 3/4) with subsequent infusions. Mild to moderate hypotension requiring interruption of RITUXAN infusion with or without the administration of IV saline occurred in 32 (10%) patients. Isolated occurrences of severe reactions requiring epinephrine have been reported in patients receiving RITUXAN for other indications. Angioedema was reported in 41 (13%) patients and was serious in one patient. Bronchospasm occurred in 25 (8%) patients; one-quarter of these patients were treated with bronchodilators. A single report of bronchiolitis obliterans was noted.

Immunologic Events: RITUXAN induced B-cell depletion in 70 to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients. The incidence of infection does not appear to be increased. During the treatment period, 50 patients in the pivotal trial developed 68 infectious events; 6 (9%) were Grade 3 in severity and none were Grade 4 events. Of the

Exhibit H

6 serious infectious events, none were associated with neutropenia. The serious bacterial events included sepsis due to Listeria (n=1), Staphylococcal bacteremia (n=1) and polymicrobial sepsis (n=1). In the post-treatment period (30 days to 11 months following the last dose), bacterial infections included sepsis (n=1); significant viral infections included herpes simplex infections (n=2) and herpes zoster (n=3).

Retreatment Events: Twenty-one patients have received more than one course of RITUXAN™ (Rituximab). The percentage of patients reporting any adverse event upon retreatment was similar to the percentage of patients reporting adverse events upon initial exposure. The following adverse events were reported more frequently in retreated subjects: asthenia, throat irritation, flushing, tachycardia, anorexia, leukopenia, thrombocytopenia, anemia, peripheral edema, dizziness, depression, respiratory symptoms, night sweats, and pruritus.

Hematologic Events: During the treatment period (up to 30 days following last dose) severe thrombocytopenia occurred in 1.3% of patients, severe neutropenia occurred in 1.9% of patients, and severe anemia occurred in 1.0% of patients. A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported.

Cardiac Events: Four patients developed arrhythmias during RITUXAN infusion. One of the four discontinued treatment because of ventricular tachycardia and supraventricular tachycardias. The other three patients experienced trigeminy (1) and irregular pulse (2) and did not require discontinuation of therapy. Angina was reported during infusion and myocardial infarction occurred 4 days post-infusion in one subject with a prior history of myocardial infarction.

Table 1.

Adverse Events ≥5% of Patients (N=315)

	Incidence All Grades	
	N	%
Any Adverse Event	275	87
Body As A Whole		
Fever	154	49
Chills	102	32
Asthenia	49	16
Headache	43	14
Throat Irritation	19	6
Abdominal Pain	18	6
Cardiovascular System		
Hypotension	32	10
Digestive System		
Nausea	55	18
Vomiting	23	7
Hemic and Lymphatic System		
Leukopenia	33	11
Thrombocytopenia	25	8
Neutropenia	21	7
Metabolic and Nutritional System		
Angioedema	41	13
Musculo-Skeletal System		
Myalgia	21	7
Nervous System		
Dizziness	23	7
Respiratory System		
Rhinitis	25	8
Bronchospasm	24	8
Skin and Appendages		
Pruritus	32	10
Rash	31	10
Urticaria	24	8

Severe and life-threatening (Grade 3 and 4) events were reported in 10% (32/315) of patients. The following Grade 3 and 4 adverse events were reported: neutropenia (1.9%), chills (1.6%), leukopenia and thrombocytopenia (1.3% for each), hypotension, anemia, bronchospasm, and urticaria (1.0% for each), headache, abdominal pain, arrhythmia (0.6% for each), and asthenia, hypertension, nausea, vomiting, coagulation disorder, angioedema, arthralgia, pain, rhinitis, increased cough, dyspnea, bronchiolitis obliterans, hypoxia, asthma, pruritus, and rash (one patient each, 0.3%).

The following adverse events occurred in ≥1.0% but <5.0% of patients, in order of decreasing incidence: flushing, arthralgia, diarrhea, anemia, cough increase, hypertension, lacrimation disorder, pain, hyperglycemia, back pain, peripheral edema, paresthesia, dyspepsia, chest pain, anorexia, anxiety, malaise, tachycardia, agitation, insomnia, sinusitis, conjunctivitis, abdominal enlargement, postural hypotension, LDH increase, hypocalcemia, hypesthesia, respiratory disorder, tumor pain, pain at injection site, bradycardia, hypertonia, nervousness, bronchitis, and taste perversion.

The proportion of patients reporting any adverse event was similar in patients with bulky disease and those with lesions <10 cm in diameter. However, the incidence of dizziness, neutropenia, thrombocytopenia, myalgia, anemia and chest pain was higher in patients with lesions >10 cm. The incidence of any Grade 3 and 4 event was higher (31% vs. 13%) and the incidence of Grade 3 or 4 neutropenia, anemia, hypotension, and dyspnea was also higher in patients with bulky disease compared with patients with lesions <10 cm.

OVERDOSAGE

There has been no experience with overdosage in human clinical trials. Single doses higher than 500 mg/m² have not been tested.

DOSAGE AND ADMINISTRATION

Usual Dose:

The recommended dosage of RITUXAN is 375 mg/m² given as an IV infusion once weekly for four doses (days 1, 8, 15, and 22). RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration: Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride USP or 5% Dextrose in Water USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion are stable at 2° to 8°C (36° to 46°F) for 24 hours and at room temperature for an additional 12 hours. No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. Hypersensitivity reactions may occur (see WARNINGS). Premedication, consisting of acetaminophen and diphenhydramine, should be considered before each infusion of RITUXAN™ (Rituximab). Premedication may attenuate infusion-related events. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion: The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If hypersensitivity or an infusion-related event develops, the infusion should be temporarily slowed or interrupted (see WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions: Subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated.

Stability and Storage: RITUXAN vials are stable at 2° to 8°C (36° to 46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight.

HOW SUPPLIED

RITUXAN is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.
Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).
NDC 50242-051-21
Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).
NDC 50242-053-06

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Jointly Manufactured by:

IDEC Pharmaceuticals Corporation
11011 Torreyana Road
San Diego, CA 92121

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

G4K097-RII (5441)
November 1997

Exhibit H, 1

Rituxan®
Rituximab

WARNINGS

Fatal Infusion Reactions: Deaths within 24 hours of RITUXAN infusion have been reported. These fatal reactions followed an infusion reaction complex which included hypoxia, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation or cardiogenic shock. Approximately 80% of fatal infusion reactions occurred in association with the first infusion. (See WARNINGS and ADVERSE REACTIONS.)

Patients who develop severe infusion reactions should have RITUXAN infusion discontinued and receive medical treatment.

Tumor Lysis Syndrome (TLS): Acute renal failure requiring dialysis with instances of fatal outcome has been reported in the setting of TLS following treatment with RITUXAN. (See WARNINGS.)

Severe Mucocutaneous Reactions: Severe mucocutaneous reactions, some with fatal outcome, have been reported in association with RITUXAN treatment. (See WARNINGS and ADVERSE REACTIONS.)

DESCRIPTION

The RITUXAN® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG, kappa immunoglobulin containing murine light- and heavy-chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

The chimeric anti-CD20 antibody is produced by mammalian cell (Chinese Hamster Ovary) suspension culture in a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product. The anti-CD20 antibody is purified by affinity and ion exchange chromatography. The purification process includes specific viral inactivation and removal procedures. Rituximab drug product is manufactured from bulk drug substance manufactured by Genentech, Inc. (US License No. 1048).

RITUXAN is a sterile, clear, colorless, preservative-free liquid concentrate for intravenous (IV) administration. RITUXAN is supplied at a concentration of 10 mg/mL in either 100 mg (10 mL) or 500 mg (50 mL) single-use vials. The product is formulated for IV administration in 9 mg/mL sodium chloride, 7.35 mg/mL sodium citrate dihydrate, 0.7 mg/mL polysorbate 80, and Water for Injection. The pH is adjusted to 6.5.

CLINICAL PHARMACOLOGY

General

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes.[1] The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL),[2] but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues.[3] CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation,[4] and possibly functions as a calcium ion channel.[5] CD20 is not shed from the cell surface and does not internalize upon antibody binding.[6] Free CD20 antigen is not found in the circulation.[7]

Preclinical Pharmacology and Toxicology

Mechanism of Action: The Fab domain of Rituximab binds to the CD20 antigen on B lymphocytes, and the Fc domain recruits immune effector functions to mediate B-cell lysis *in vitro*. Possible mechanisms of cell lysis include complement-dependent cytotoxicity (CDC)[8] and antibody-dependent cell mediated cytotoxicity (ADCC). The antibody has been shown to induce apoptosis in the DHL-4 human B-cell lymphoma line.[9]

Normal Tissue Cross-reactivity: Rituximab binding was observed on lymphoid cells in the thymus, the white pulp of the spleen, and a majority of B lymphocytes in peripheral blood and lymph nodes. Little or no binding was observed in the non-lymphoid tissues examined.

Human Pharmacokinetics/Pharmacodynamics

In patients given single doses at 10, 50, 100, 250 or 500 mg/m^2 as an IV infusion, serum levels and the half-life of Rituximab were proportional to dose.[10] In 14 patients given 375 mg/m^2 as an IV infusion for 4 weekly doses, the mean serum half-life was 76.3 hours (range, 31.5 to 152.6 hours) after the first infusion and 205.8 hours (range, 83.9 to 407.0 hours) after the fourth infusion.[10,11] The wide range of half-lives may reflect the variable tumor burden among patients and the changes in CD20-positive (normal and malignant) B-cell populations upon repeated administrations.

RITUXAN at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 4 doses to 203 patients naive to RITUXAN.[10,11] The mean C_{max} following the fourth infusion was 486 µg/mL (range, 77.5 to 996.6 µg/mL). The peak and trough serum levels of Rituximab were inversely correlated with baseline values for the number of circulating CD20-positive B cells and measures of disease burden. Mean steady-state serum levels were higher for responders compared with nonresponders; however, no difference was found in the rate of elimination as measured by serum half-life. Serum levels were higher in patients with International Working Formulation (IWF) subtypes B, C, and D as compared with those with subtype A.[10,12] Rituximab was detectable in the serum of patients 3 to 6 months after completion of treatment.

RITUXAN at a dose of 375 mg/m^2 was administered as an IV infusion at weekly intervals for 8 doses to 37 patients.[10] The mean C_{max} after 8 infusions was 550 µg/mL (range, 171 to 1177 µg/mL). The mean C_{max} increased with each successive infusion through the eighth infusion (Table 1).

Table 1
Rituximab C_{max} Values

Infusion Number	Mean C_{max} µg/mL	Range µg/mL
1	242.6	16.1–581.9
2	357.5	106.8–948.6
3	381.3	110.5–731.2
4	460.0	138.0–835.8
5	475.3	156.0–929.1
6	515.4	152.7–865.2
7	544.6	107.0–936.8
8	550.0	170.6–1177.0

The pharmacokinetic profile of RITUXAN when administered as 6 infusions of 375 mg/m^2 in combination with 6 cycles of CHOP chemotherapy was similar to that seen with RITUXAN alone.[13]

Administration of RITUXAN resulted in a rapid and sustained depletion of circulating and tissue-based B cells. Lymph node biopsies performed 14 days after therapy showed a decrease in the percentage of B cells in seven of eight patients who had received single doses of Rituximab ≥100 mg/m^2.[9] Among the 166 patients in the pivotal study, circulating B cells (measured as CD19-positive cells) were depleted within the first three doses with sustained depletion for up to 6 to 9 months post-treatment in 83% of patients.[3] Of the responding patients assessed (n = 80), 1% failed to show significant depletion of CD19-positive cells after the third infusion of Rituximab as compared to 19% of the nonresponding patients. B-cell recovery began at approximately 6 months following completion of treatment. Median B-cell levels returned to normal by 12 months following completion of treatment.[14]

These were sustained and statistically significant reductions in both IgM and IgG serum levels observed from 5 through 11 months following Rituximab administration. However, only 14% of patients had reductions in IgM and/or IgG serum levels, resulting in values below the normal range.[15]

CLINICAL STUDIES

Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, NHL

RITUXAN regimens tested include treatment weekly for 4 doses and treatment weekly for 8 doses. Results for studies with a collective enrollment of 296 patients are summarized below (Table 2):

Table 2
Summary of RITUXAN Efficacy Data by Schedule and Clinical Setting
(See ADVERSE REACTIONS for Risk Factors Associated with Increased Rates of Adverse Events)

	Weekly x 4 N=166	Weekly x 8 N=37	Bulky disease, Weekly x 4 N=39[a]	Retreatment, Weekly x 4 N=60
Overall Response Rate	48%	57%	36%	38%
Complete Response Rate	6%	14%	3%	10%
Median Duration of Response[b,c,d] (Months) [Range]	11.2 [1.9 to 42.1+]	13.4 [2.5 to 36.5+]	6.9 [2.8 to 25.0+]	15.0 [3.0 to 25.1+]

a Six of these patients are included in the first column. Thus, data from 296 intent to treat patients are provided in this table.
b Kaplan-Meier projected with observed range
c "+" indicates an ongoing response.
d Duration of response: interval from the onset of response to disease progression.

Weekly for 4 Doses

A multicenter, open-label, single-arm study was conducted in 166 patients with relapsed or refractory low-grade or follicular B-cell NHL who received 375 mg/m^2 of RITUXAN given as an IV infusion weekly for 4 doses.[3] Patients with tumor masses >10 cm or with >5,000 lymphocytes/µL in the peripheral blood were excluded from the study. Results are summarized in Table 2. The median time to onset of response was 50 days and the median duration of response was 11.2 months (range, 1.9 to 42.1+). Disease-related signs and symptoms (including B-symptoms) were present in 23% (39/166) of patients at study entry and resolved in 64% (25/39) of these patients.

In a multivariate analysis, the ORR was higher in patients with IWF B, C, and D histologic subtypes as compared to IWF subtype A (58% vs. 12%), higher in patients whose largest lesion was <5 cm vs. >7 cm (maximum, 21 cm) in greatest diameter (53% vs. 38%), and higher in patients with chemosensitive relapse as compared with chemoresistant (defined as duration of response <3 months) relapse (53% vs. 35%). ORR in patients previously treated with autologous bone marrow transplant was 78% (18/23). The following adverse prognostic factors were *not* associated with a lower response rate: age ≥60 years, extranodal disease, prior anthracycline therapy, and bone marrow involvement.

Weekly for 8 Doses

In a multicenter, single-arm study, 37 patients with relapsed or refractory, low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 8 doses. Results are summarized in Table 2. (see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Bulky Disease, Weekly for 4 Doses

In pooled data from multiple studies of RITUXAN, 39 patients with relapsed or refractory, bulky disease (single lesion >10 cm in diameter), low-grade NHL received 375 mg/m^2 of RITUXAN weekly for 4 doses. Results are summarized in Table 2.[3,16] (For information on the higher incidence of Grade 3 and 4 adverse events, see ADVERSE REACTIONS, Risk Factors Associated with Increased Rates of Adverse Events.)

Retreatment Weekly for 4 Doses

In a multi-center, single-arm study, 60 patients received 375 mg/m^2 of RITUXAN weekly for 4 doses.[17] All patients had relapsed or refractory, low-grade or follicular B-cell NHL and had achieved an objective clinical response to RITUXAN administered 3.8–35.6 months (median 14.5 months) prior to retreatment with RITUXAN. Of these 60 patients, 55 received their second course of RITUXAN, 3 patients received their third course and 2 patients received their second and third courses of RITUXAN in this study. Results are summarized in Table 2.

Diffuse, Large B-Cell, NHL

The safety and effectiveness of RITUXAN were evaluated in three, randomized, active-controlled, open-label, multicenter studies with a collective enrollment of 1854 patients. Patients with previously untreated diffuse, large B-cell, NHL received RITUXAN in combination with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) or other anthracycline-based chemotherapy regimens.

Study 1

A total of 632 patients aged ≥60 years with either B-cell NHL Grade F, G, or H by the International Working Formulation classification or DLBCL (including primary mediastinal B-cell lymphoma) in the REAL classification were randomized in a 1:1 ratio to treatment with CHOP or R-CHOP. Patients were given 8 or 8, 21 day cycles of CHOP. Patients in the R-CHOP arm also received 4 or 5 doses of RITUXAN 375 mg/m^2 on Days −7 and −3 (prior to Cycle 1), and 48 to 72 hours pre-Cycle 3, pre-Cycle 5, and pre-Cycle 7 for patients receiving 8 cycles of CHOP induction. The main outcome measure of the study was progression-free survival (PFS), defined as the time from randomization to the first of progression, relapse or death. Responding patients underwent a second randomization to receive RITUXAN or no further therapy.

Among all enrolled patients, 62% had centrally confirmed DLBCL histology, 73% had Stage III-IV disease, 56% had IPI scores ≥2, 85% had ECOG performance status of <2, 57% had elevated LDH levels, and 30% had two or more extranodal disease sites involved. Efficacy results are presented in Table 3. These results reflect a statistical approach which allows for an evaluation of RITUXAN administered in the induction setting that excludes any potential impact of RITUXAN given after the second randomization.

Analysis of results after the second randomization in Study 1 demonstrates that for patients randomized to R-CHOP, additional RITUXAN exposure beyond induction was not associated with further improvements in progression free survival or overall survival.

Study 2

A total of 399 patients with DLBCL, aged ≥60 years, were randomized in a 1:1 ratio to receive CHOP or R-CHOP induction. All patients received up to 8, 3-week cycles of CHOP induction; patients in the R-CHOP arm received RITUXAN 375 mg/m^2 on Day 1 of each cycle. The main outcome measure of the study was event free survival (EFS), defined as the time from randomization to relapse, progression, change in therapy or death from any cause. Among all enrolled patients, 80% had stage III or IV disease, 60% of patients had an age-adjusted IPI ≥2, 80% had ECOG performance status scores <2, 66% had elevated LDH levels, and 52% had extranodal involvement in at least two sites. Efficacy results are presented in Table 3.

Study 3

A total of 823 patients with DLBCL, aged 18–60 years, were randomized in a 1:1 ratio to receive an anthracycline-containing chemotherapy alone or in combination with RITUXAN. The main outcome measure of the study was time to treatment failure (TTF), defined as time from randomization to the earliest of progressive disease, failure to achieve a complete response, relapse or death. Among all enrolled patients, 28% had Stage III-IV disease, 100% had IPI scores of ≤1, 99% had ECOG performance status of <2, 29% had elevated LDH levels, 49% had bulky disease and 34% had extranodal involvement. Efficacy results are presented in Table 3.

Table 3
Efficacy Results in Studies 1, 2, and 3

	Study 1 (n=632)		Study 2 (n=399)		Study 3 (n=823)	
	CHOP	R-CHOP	CHOP	R-CHOP	Chemo	R-Chemo
Main outcome	Progression-free survival (years)		Event-free survival (years)		Time to treatment failure (years)	
Median of main outcome measure	1.6	3.1	1.1	2.0	NE[b]	NE
Hazard ratio	0.69		0.60[c]		0.45[c]	
Overall survival at 2 years	63%	74%	58%	69%	86%	95%
Hazard ratio	0.72		0.68[c]		0.40[c]	

a Significant at $p<0.05$, 2-sided
b NE=Not reliably estimable.
c Kaplan-Meier estimates
d R-CHOP vs. CHOP

In Study 2, overall survival estimates at 5 years were 58% vs. 46% for R-CHOP and CHOP, respectively.

INDICATIONS AND USAGE

RITUXAN® (Rituximab) is indicated for the treatment of patients with relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, non-Hodgkin's lymphoma.

RITUXAN® (Rituximab) is indicated for the first-line treatment of diffuse large B-cell, CD20-positive, non-Hodgkin's lymphoma in combination with CHOP or other anthracycline-based chemotherapy regimens.

CONTRAINDICATIONS

RITUXAN is contraindicated in patients with known anaphylaxis or IgE-mediated hypersensitivity to murine proteins or to any component of this product. (See WARNINGS.)

WARNINGS (See BOXED WARNINGS.)

Severe Infusion Reactions (see BOXED WARNINGS, ADVERSE REACTIONS, and Hypersensitivity Reactions)

RITUXAN has caused severe infusion reactions. In some cases, these reactions were fatal. These severe reactions typically occurred during the first infusion with time to onset of 30 to 120 minutes. Signs and symptoms of severe infusion reactions may include hypotension, angioedema, hypoxia or bronchospasm, and may require interruption of RITUXAN administration. The most severe manifestations and sequelae include pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, and cardiogenic shock. In the reported cases, the following factors were more frequently associated with fatal outcomes: female gender, pulmonary infiltrates, and chronic lymphocytic leukemia or mantle cell lymphoma.

Management of severe infusion reactions: The RITUXAN infusion should be interrupted for severe reactions and supportive care measures instituted as medically indicated (e.g., intravenous fluids, vasopressors, oxygen, bronchodilators, diphenhydramine, and acetaminophen). In most cases, the infusion can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Patients requiring close monitoring during first and all subsequent infusions include those with pre-existing cardiac and pulmonary conditions, those with prior clinically significant cardiopulmonary adverse events and those with high numbers of circulating malignant cells (≥25,000/mm^3) with or without evidence of high tumor burden.

Tumor Lysis Syndrome (TLS) (See BOXED WARNINGS and ADVERSE REACTIONS)

Rapid reduction in tumor volume followed by acute renal failure, hyperkalemia, hypocalcemia, hyperuricemia, or hyperphosphatasemia, have been reported within 12 to 24 hours after the first RITUXAN infusion. Rare instances of fatal outcome have been reported in the setting of TLS following treatment with RITUXAN. The risks of TLS appear to be greater in patients with high numbers of circulating malignant cells (≥25,000/mm^3) or high tumor burden. Prophylaxis for TLS should be considered for patients at high risk. Correction of electrolyte abnormalities, monitoring of renal function and fluid balance, and administration of supportive care, including dialysis, should be initiated as indicated. Following complete resolution of the complications of TLS, RITUXAN has been tolerated when re-administered in conjunction with prophylactic therapy for TLS in a limited number of cases.

Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections

Hepatitis B virus (HBV) reactivation with fulminant hepatitis, hepatic failure, and death has been reported in some patients with hematologic malignancies treated with RITUXAN. The majority of patients received RITUXAN in combination with chemotherapy. The median time to the diagnosis of hepatitis was approximately 4 months after the initiation of RITUXAN and approximately one month after the last dose.

Persons at high risk of HBV infection should be screened before initiation of RITUXAN. Carriers of hepatitis B should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following RITUXAN therapy. In patients who develop viral hepatitis, RITUXAN and any concomitant chemotherapy should be discontinued and appropriate treatment including antiviral therapy initiated. There are insufficient data regarding the safety of resuming RITUXAN therapy in patients who develop hepatitis subsequent to HBV reactivation.

The following additional serious viral infections, either new, reactivated or exacerbated, have been identified in clinical studies or postmarketing reports. The majority of patients received RITUXAN in combination with chemotherapy or as part of a hematopoietic stem cell transplant. These viral infections included JC virus [progressive multifocal leukoencephalopathy (PML)], cytomegalovirus, herpes simplex virus, parvovirus B19, varicella zoster virus, West Nile virus, and hepatitis C. In some cases, the viral infections occurred up to one year following discontinuation of RITUXAN and have resulted in death.

Hypersensitivity Reactions

RITUXAN has been associated with hypersensitivity reactions (non-IgE-mediated reactions) which may respond to adjustments in the infusion rate and in medical management. Hypotension, bronchospasm, and angioedema have occurred in association with RITUXAN infusion (see Severe Infusion Reactions). RITUXAN infusion should be interrupted for severe hypersensitivity reactions and can be resumed at a 50% reduction in rate (e.g., from 100 mg/hr to 50 mg/hr) when symptoms have completely resolved. Treatment of these symptoms with diphenhydramine and acetaminophen is recommended; additional treatment with bronchodilators or IV saline may be indicated. In most cases, patients who have experienced non-life-threatening hypersensitivity reactions have been able to complete the full course of therapy. (See DOSAGE and ADMINISTRATION.) Medications for the treatment of hypersensitivity reactions, e.g., epinephrine, antihistamines and corticosteroids, should be available for immediate use in the event of a reaction during administration.

Cardiovascular

Infusions should be discontinued in the event of serious or life-threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of RITUXAN. Patients with pre-existing cardiac conditions (including arrhythmias and angina) have had recurrences of those events during RITUXAN therapy and should be monitored throughout the infusion and immediate post-infusion period.

Renal (See BOXED WARNINGS: Tumor Lysis Syndrome [TLS] and ADVERSE REACTIONS)

RITUXAN administration has been associated with severe renal toxicity including acute renal failure requiring dialysis and in some cases, has led to a fatal outcome. Renal toxicity has occurred in patients with high numbers of circulating malignant cells (>25,000/mm^3) or high tumor burden who experience tumor lysis syndrome and in patients administered concomitant cisplatin therapy during clinical trials. The combination of cisplatin and RITUXAN is not an approved treatment regimen. If this combination is used in clinical trials *extreme caution* should be exercised; patients should be monitored closely for signs of renal failure. Discontinuation of RITUXAN should be considered for those with rising serum creatinine or oliguria.

Severe Mucocutaneous Reactions (See BOXED WARNINGS)

Mucocutaneous reactions, some with fatal outcome, have been reported in patients treated with RITUXAN. These reports include paraneoplastic pemphigus (an uncommon disorder which is a manifestation of the patient's underlying malignancy),[18] Stevens-Johnson syndrome, lichenoid dermatitis, vesiculobullous dermatitis, and toxic epidermal necrolysis. The onset of the reaction in the reported cases has varied from 1 to 13 weeks following RITUXAN exposure. Patients experiencing a severe mucocutaneous reaction should not receive any further infusions and seek prompt medical evaluation. Skin biopsy may help to distinguish among different mucocutaneous reactions and guide subsequent treatment. The safety of readministration of RITUXAN to patients with any of these mucocutaneous reactions has not been determined.

Bowel Obstruction and Perforation

Abdominal pain, bowel obstruction and perforation, in some cases leading to death, were observed in patients receiving RITUXAN in combination with chemotherapy for DLBCL. In post-marketing reports, which include both patients with low-grade or follicular NHL and DLBCL, the mean time to onset of symptoms was 6 days (range 1–77) in patients with documented gastro-intestinal perforation. Complaints of abdominal pain, especially early in the course of treatment, should prompt a thorough diagnostic evaluation and appropriate treatment.

PRECAUTIONS

Laboratory Monitoring

Because RITUXAN targets all CD20-positive B lymphocytes, malignant and nonmalignant, complete blood counts (CBC) and platelet counts should be obtained at regular intervals during RITUXAN therapy and more frequently in patients who develop cytopenias (see ADVERSE REACTIONS). The duration of cytopenias caused by RITUXAN can extend well beyond the treatment period.

Drug/Laboratory Interactions

There have been no formal drug interaction studies performed with RITUXAN. However, renal toxicity was seen with this drug in combination with cisplatin in clinical trials. (See WARNINGS, Renal.)

Exhibit I

Immunization
The safety of immunization with live viral vaccines following RITUXAN therapy has not been studied. The ability to generate a primary or anamnestic humoral response to vaccination is currently being studied.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term animal studies have been performed to establish the carcinogenic or mutagenic potential of RITUXAN, or to determine its effects on fertility in males or females. Individuals of childbearing potential should use effective contraceptive methods during treatment and for up to 12 months following RITUXAN therapy.

Pregnancy Category C
Animal reproduction studies have not been conducted with RITUXAN. It is not known whether RITUXAN can cause fetal harm when administered to a pregnant woman or whether it can affect reproductive capacity. Human IgG is known to pass the placental barrier, and thus may potentially cause fetal B-cell depletion; therefore, RITUXAN should be given to a pregnant woman only if clearly needed.

Nursing Mothers
It is not known whether RITUXAN is excreted in human milk. Because human IgG is excreted in human milk and the potential for absorption and immunosuppression in the infant is unknown, women should be advised to discontinue nursing until circulating drug levels are no longer detectable. (See CLINICAL PHARMACOLOGY.)

Pediatric Use
The safety and effectiveness of RITUXAN in pediatric patients have not been established.

Geriatric Use
Among patients with DLBCL in three randomized, active-controlled trials, 927 patients received RITUXAN in combination with chemotherapy. Of these, 396 (43%) were age 65 or greater and 123 (13%) were age 75 or greater. No overall differences in effectiveness were observed between these subjects and younger subjects. However, elderly patients were more likely to experience cardiac adverse events, mostly supraventricular arrhythmias. Serious pulmonary adverse events were also more common among the elderly, including pneumonia and pneumonitis.

Among the 331 patients with low-grade or follicular lymphoma enrolled in clinical studies of single agent RITUXAN, 24% were 65 to 75 years old and 5% were 75 years old and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

ADVERSE REACTIONS
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates.

The overall safety database for RITUXAN is based on clinical trial data from 1283 patients with NHL, who received RITUXAN either as a single agent or in combination with chemotherapy. Additional safety information was obtained from post-marketing safety surveillance. The most common adverse reactions were infusion reactions (see INFUSION REACTIONS below).

The following serious adverse reactions, some with fatal outcomes, have been reported in patients treated with RITUXAN (see BOXED WARNINGS and WARNINGS): severe or fatal infusion reactions, tumor lysis syndrome, severe mucocutaneous reactions, hepatitis B reactivation with fulminant hepatitis, other viral infections, hypersensitivity reactions, cardiac arrhythmias, renal toxicity, bowel obstruction and perforation.

Except as noted, adverse events described below occurred in the setting of relapsed or refractory, low-grade or follicular, CD20-positive, B-cell, NHL and are based on 356 patients treated in nonrandomized, single-arm studies of RITUXAN administered as a single agent. Most patients received RITUXAN 375 mg/m² weekly for 4 doses.

Infusion Reactions (See BOXED WARNINGS and WARNINGS)
Mild to moderate infusion reactions consisting of fever and chills/rigors occurred in the majority of patients during the first RITUXAN infusion. Other frequent infusion reaction symptoms included nausea, pruritus, angioedema, asthenia, hypotension, headache, bronchospasm, throat irritation, rhinitis, urticaria, rash, vomiting, myalgia, dizziness, and hypertension. These reactions generally occurred within 30 to 120 minutes of beginning the first infusion, and resolved with slowing or interruption of the RITUXAN infusion and with supportive care (diphenhydramine, acetaminophen, IV saline, and vasopressors). The incidence of infusion reactions was highest during the first infusion (77%) and decreased with each subsequent infusion (30% with fourth infusion and 14% with eighth infusion). Injection site pain was reported in less than 5% of patients.

Infectious Events (See WARNINGS: Hepatitis B Reactivation with Related Fulminant Hepatitis and Other Viral Infections)
RITUXAN-induced B cell depletion in 70% to 80% of patients and was associated with decreased serum immunoglobulins in a minority of patients; the lymphopenia lasted a median of 14 days (range, 1 to 588 days). Infectious events occurred in 31% of patients: 19% of patients had bacterial infections, 10% had viral infections, 1% had fungal infections, and 6% were unknown infections. Incidence is not additive because a single patient may have had more than one type of infection. Serious infectious events (Grade 3 or 4), including sepsis, occurred in 2% of patients.

Hematologic Events
Grade 3 and 4 cytopenias were reported in 46% of patients treated with RITUXAN; these include: lymphopenia (40%), neutropenia (6%), leukopenia (4%), anemia (3%), and thrombocytopenia (2%). The median duration of lymphopenia was 14 days (range, 1 to 588 days) and of neutropenia was 13 days (range, 2 to 116 days). A single occurrence of transient aplastic anemia (pure red cell aplasia) and two occurrences of hemolytic anemia following RITUXAN therapy were reported.

Pulmonary Events
135 patients (38%) experienced pulmonary events in clinical trials. The most common respiratory system adverse events experienced were increased cough, rhinitis, bronchospasm, dyspnea, and sinusitis. In both clinical studies and post-marketing surveillance, there have been a limited number of reports of bronchiolitis obliterans presenting up to 6 months post-RITUXAN infusion and a limited number of reports of pneumonitis (including interstitial pneumonitis) presenting up to 3 months post-RITUXAN infusion, some of which resulted in fatal outcomes. The safety of reinjection or continued administration of RITUXAN in patients with pneumonitis or bronchiolitis obliterans is unknown.

Immunogenicity
The observed incidence of antibody positivity in an assay is highly dependent on the sensitivity and specificity of the assay and may be influenced by several factors including sample handling, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to RITUXAN with the incidence of antibodies to other products may be misleading.

In clinical studies of patients with low-grade or follicular NHL receiving single-agent RITUXAN, human antichimeric antibody (HACA) was detected in 4 of 356 (1.1%) patients and 3 had an objective clinical response. These data reflect the percentage of patients whose test results were considered positive for antibodies to RITUXAN using an enzyme-linked immunosorbent assay (limit of detection = 7 ng/mL).

Single Agent RITUXAN for Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, NHL
Study subjects ranged from 22 to 81 years of age. Sixty percent were male; 93% were Caucasian, 1% were African American, 2% were Hispanic, 2% were Asian, and 2% were from other racial groups.

Table 4 lists the most common, as well as Grade 3 and 4, adverse events observed.

Table 4
Incidence of Adverse Events in ≥ 5% of Patients with Relapsed or Refractory, Low-Grade or Follicular NHL, Receiving Single-agent RITUXAN (N=356)[a]

	All Grades (%)	Grade 3 and 4 (%)
Any Adverse Events	99	57
Body as a Whole	86	10
Fever	53	1
Chills	33	3
Infection	31	4
Asthenia	26	1
Headache	19	1
Abdominal Pain	14	1
Pain	12	1
Back Pain	10	1
Throat Irritation	9	0
Flushing	5	0
Cardiovascular System	25	3
Hypotension	10	1
Hypertension	6	1
Digestive System	37	2
Nausea	23	1
Diarrhea	10	1
Vomiting	10	1
Hemic and Lymphatic System	67	48
Lymphopenia	48	40
Leukopenia	14	4
Neutropenia	14	6
Thrombocytopenia	12	2
Anemia	8	3
Metabolic and Nutritional Disorders	38	3
Angioedema	11	1
Hyperglycemia	9	1
Peripheral Edema	8	0
LDH Increase	7	0
Musculoskeletal System	26	3
Myalgia	10	1
Arthralgia	10	1
Nervous System	32	1
Dizziness	10	1
Anxiety	5	1
Respiratory System	38	4
Increased Cough	17	1
Rhinitis	12	1
Bronchospasm	8	1
Dyspnea	7	1
Sinusitis	6	0
Skin and Appendages	44	2
Night Sweats	15	1
Rash	15	1
Pruritus	14	1
Urticaria	8	1

a Adverse Events observed up to 12 months following RITUXAN
b Adverse Events graded for severity by NCI-CTC criteria.[19]

Risk Factors Associated with Increased Rates of Adverse Events
Administration of RITUXAN weekly for 8 doses resulted in higher rates of Grade 3 and 4 adverse events[b] overall (70%) compared with administration weekly for 4 doses (57%). The incidence of Grade 3 or 4 adverse events was similar in patients retreated with RITUXAN compared with initial treatment (58% and 57%, respectively). The incidence of the following clinically significant adverse events was higher in patients with bulky disease (lesions ≥10 cm) (N=39) versus patients with lesions < 10 cm (N=195): abdominal pain, anemia, dyspnea, hypotension, and neutropenia.

RITUXAN in Combination with Chemotherapy for DLBCL
Except as noted, adverse events described in the setting of DLBCL are based on three randomized, active-controlled clinical trials in which 927 patients received RITUXAN in combination with chemotherapy and 802 received chemotherapy alone. Detailed safety data collection was primarily limited to Grade 3 and 4 adverse events and serious adverse events.

The population varied from 18 to 92 years of age and 55% were male; racial distribution was collected only for Study 1 (see CLINICAL STUDIES section) where 90% of patients were Caucasian, 5% were African American, 3% were Hispanic and 2% were from other racial groups. Patients received 4 - 8 doses of RITUXAN at 375 mg/m².

The following adverse events, regardless of severity, were reported more frequently (≥5%) in patients age ≥60 years receiving R-CHOP as compared to CHOP alone: cardiac disorder (28% vs. 21%), pyrexia (56% vs. 46%), chills (13% vs. 4%) and lung disorder (31% vs. 24%). In one of these studies (Study 2), more detailed assessment of cardiac toxicity revealed that supraventricular arrhythmias or tachycardia accounted for most of the difference in cardiac disorders, with 4.5% vs. 1.0% incidences for R-CHOP and CHOP, respectively.

The following Grade 3 or 4 adverse events were reported more frequently among patients in the R-CHOP arm compared with those in the CHOP arm: thrombocytopenia (9% vs. 7%) and lung disorder (6% vs. 3%). Other severe adverse events reported more commonly among patients receiving R-CHOP in one or more studies were viral infection, neutropenia and anemia.

Post-Marketing Reports
The following adverse reactions have been identified during post-approval use of RITUXAN. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Decisions to include these reactions in labeling are typically based on one or more of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connection to RITUXAN.

Hematologic: prolonged pancytopenia, marrow hypoplasia, and late onset neutropenia.

Hyperviscosity syndrome in Waldenstrom's macroglobulinemia.

Cardiac: fatal cardiac failure.

Immune/Autoimmune Events: uveitis, optic neuritis, systemic vasculitis, pleuritis, lupus-like syndrome, serum sickness, polyarticular arthritis and vasculitis with rash.

Infection: increased in fatal infections in HIV associated lymphoma.

Skin: severe mucocutaneous reactions.

Gastrointestinal: bowel obstruction and perforation.

OVERDOSAGE
There has been no experience with overdosage in human clinical trials. Single doses of up to 500 mg/m² have been given in dose-escalating clinical trials.[a]

DOSAGE AND ADMINISTRATION
Relapsed or Refractory, Low-Grade or Follicular, CD20-Positive, B-Cell, Non-Hodgkin's Lymphoma
The recommended dose of RITUXAN is 375 mg/m² IV infusion once weekly for 4 or 8 doses.

Retreatment Therapy
The recommended dose of RITUXAN is 375 mg/m² IV infusion once weekly for 4 doses in responding patients who develop progressive disease after previous RITUXAN therapy. Currently there are limited data concerning more than 2 courses.

Diffuse Large B-Cell NHL
The recommended dose of RITUXAN is 375 mg/m² IV per infusion given on Day 1 of each cycle of chemotherapy for up to 8 infusions.

RITUXAN as a Component of Zevalin™ (Ibritumomab Tiuxetan) Therapeutic Regimen
As a required component of the Zevalin therapeutic regimen, RITUXAN 250 mg/m² should be infused within 4 hours prior to the administration of Indium-111- (In-111-) Zevalin and within 4 hours prior to the administration of Yttrium90- (Y-90-) Zevalin. Administration of RITUXAN and In-111-Zevalin should precede RITUXAN and Y-90-Zevalin by 7–9 days. Refer to the Zevalin package insert for full prescribing information regarding the Zevalin therapeutic regimen.

RITUXAN may be administered in an outpatient setting. **DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS. (See Administration.)**

Instructions for Administration

Preparation for Administration
Use appropriate aseptic technique. Withdraw the necessary amount of RITUXAN and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride, USP, or 5% Dextrose in Water, USP. Gently invert the bag to mix the solution. Discard any unused portion left in the vial. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

RITUXAN solutions for infusion may be stored at 2–8°C (36–46°F) for 24 hours. RITUXAN solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since RITUXAN solutions do not contain a preservative, diluted solutions should be stored refrigerated (2–8°C). No incompatibilities between RITUXAN and polyvinylchloride or polyethylene bags have been observed.

Administration: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS
Infusion and hypersensitivity reactions may occur (see BOXED WARNINGS, WARNINGS, and ADVERSE REACTIONS). Premedication consisting of acetaminophen and diphenhydramine should be considered before each infusion of RITUXAN. Premedication may attenuate infusion reactions. Since transient hypotension may occur during RITUXAN infusion, consideration should be given to withholding antihypertensive medications 12 hours prior to RITUXAN infusion.

First Infusion
The RITUXAN solution for infusion should be administered intravenously at an initial rate of 50 mg/hr. RITUXAN should not be mixed or diluted with other drugs. If hypersensitivity or infusion reactions do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 400 mg/hr. If a hypersensitivity (non-IgE-mediated) or an infusion reaction develops, the infusion should be temporarily slowed or interrupted (see BOXED WARNINGS and WARNINGS). The infusion can continue at one-half the previous rate upon improvement of patient symptoms.

Subsequent Infusions
If the patient tolerated the first infusion well, subsequent RITUXAN infusions can be administered at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30-minute intervals, to a maximum of 400 mg/hr as tolerated. If the patient did not tolerate the first infusion well, follow the guidelines under First Infusion.

Stability and Storage
RITUXAN vials are stable at 2–8°C (36–46°F). Do not use beyond expiration date stamped on carton. RITUXAN vials should be protected from direct sunlight. Do not freeze or shake. Refer to the "Preparation for Administration" section for information on the stability and storage of solutions of RITUXAN diluted for infusion.

HOW SUPPLIED
RITUXAN® (Rituximab) is supplied as 100 mg and 500 mg of sterile, preservative-free, single-use vials.

Single unit 100 mg carton: Contains one 10 mL vial of RITUXAN (10 mg/mL).

NDC 50242-051-21

Single unit 500 mg carton: Contains one 50 mL vial of RITUXAN (10 mg/mL).

NDC 50242-053-06

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Jointly Marketed by: Biogen Idec Inc., and Genentech, Inc.

RITUXAN® (Rituximab)

Manufactured by:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990

7141412 1J1188
FDA Approval Date February 2006

Exhibit I, 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: September 30, 2008
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
TELEPHONE NO. *(Include Area Code)*	FACSIMILE (FAX) Number *(Include Area Code)*
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)*

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:

(PROPOSED) INDICATION(S) FOR USE:

APPLICATION INFORMATION

APPLICATION TYPE *(check one)*
☐ NEW DRUG APPLICATION (NDA, 21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (BLA, 21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug | Holder of Approved Application

TYPE OF SUBMISSION *(check one)*
☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☐ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED | THIS APPLICATION IS ☐ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

Exhibit J

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
	☐ A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	☐ B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	☐ C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

FORM FDA 356h (10/05)

Exhibit J.1

INSTRUCTIONS FOR FILLING OUT FORM FDA 356h

APPLICANT INFORMATION This section should include the name, street address, telephone, and facsimile numbers of the legal person or entity submitting the application in the appropriate areas. Note that, in the case of biological products, this is the name of the legal entity or person to whom the license will be issued. The name, street address and telephone number of the legal person or entity authorized to represent a non-U.S. applicant should be entered in the indicated area. Only one person should sign the form.

PRODUCT DESCRIPTION This section should include all of the information necessary to identify the product that is the subject of this submission. For new applications, the proposed indication should be given. For supplements to an approved application, please give the approved indications for use.

APPLICATION INFORMATION If this submission is an ANDA or 505(b)(2), this section should include the name of the approved drug that is the basis of the application and identify the holder of the approved application in the indicated areas.

TYPE OF SUBMISSION should be indicated by checking the appropriate box:

Original Application = a complete new application that has never before been submitted;

Amendment to a Pending Application = all submissions to pending original applications, or pending supplements to approved applications, including responses to Information Request Letters;

Resubmission = a complete response to an action letter, or submission of an application that has been the subject of a withdrawal or a refusal to file action;

Presubmission = information submitted prior to the submission of a complete new application;

Annual Report = periodic reports for licensed biological products (for NDAs Form FDA-2252 should be used as required in 21 CFR 314.81 (b)(2));

Establishment Description Supplement = supplements to the information contained in the Establishment Description section (#15) for biological products;

Efficacy Supplement = submissions for such changes as a new indication or dosage regimen for an approved product, a comparative efficacy claim naming another product, or a significant alteration in the patient population; e.g., prescription to Over-The-Counter switch;

Labeling Supplement = all label change supplements required under 21 CFR 314.70 and 21 CFR 601.12 that do not qualify as efficacy supplements;

Chemistry, Manufacturing, and Controls Supplement = manufacturing change supplement submissions as provided in 21 CFR 314.70, 21 CFR 314.71, 21 CFR 314.72 and 21 CFR 601.12;

Other = any submission that does not fit in one of the other categories (e.g., Phase IV response). If this box is checked the type of submission can be explained in the **REASON FOR SUBMISSION** block.

Submission of Partial Application Letter date of agreement to partial submission should be provided. Also, provide copy of scheduled plan.

CBE "Supplement-Changes Being Effected" supplement submission for certain moderate changes for which distribution can occur when FDA receives the supplement as provided in 21 CFR 314.70 and 21 CFR 601.12.

Exhibit J, 2

CBE-30 "Supplement-Changes Being Effected in 30 Days" supplement submission for certain moderate changes for which FDA receives at least 30 days before the distribution of the product made using the change as provided in 21 CFR 314.70 and 21 CFR 601.12.

Prior Approval (PA) "Prior Approval Supplements" supplement submission for a major change for which distribution of the product made using the change cannot occur prior to FDA approval as provided in 21 CFR 314.70 and 21 CFR 601.12.

REASON FOR SUBMISSION This section should contain a brief explanation of the submission, e.g., "manufacturing change from roller bottle to cell factory" or "response to Information Request Letter of 1/9/97" or "Pediatric exclusivity determination request" or "to satisfy a subpart H postmarketing commitment".

NUMBER OF VOLUMES SUBMITTED Please enter the number of volumes, including and identifying electronic media, contained in the archival copy of this submission.

This application is
☐ Paper ☐ Paper and Electronic ☐ Electronic
Please check the appropriate box to indicate whether this submission contains only paper, both paper and electronic media, or only electronic media.

ESTABLISHMENT INFORMATION This section should include information on the locations of all manufacturing, packaging and control sites for both drug substance and drug product. If continuation sheets are used, please indicate where in the submission they may be found. For each site please include the name, address, telephone number, registration number (Central File Number), Drug Master File (DMF) number, and the name of a contact at the site. The manufacturing steps and/or type of testing (e.g. final dosage form, stability testing) conducted at the site should also be included. Please indicate whether the site is ready for inspection or, if not, when it will be ready. Please note that, when applicable, the complete establishment description is requested under item 15.

CROSS REFERENCES This section should contain a list of all License Applications, Investigational New Drug Applications (INDs), NDAs, Premarket Approval Applications (PMAs), Premarket Notifications (510(k)s), Investigational Device Exemptions (IDEs), Biological Master Files (BMFs) and DMFs that are referenced in the current application.

Items 1 through 20 on the reverse side of the form constitute a check list that should be used to indicate the types of information contained within a particular submission. Please check all that apply. The numbering of the items on the checklist is not intended to specify a particular order for the inclusion of those sections into the submission. The applicant may include sections in any order, but the location of those sections within the submission should be clearly indicated in the Index. It is therefore recommended that, particularly for large submissions, the Index immediately follows the Form FDA 356h and, if applicable, the User Fee Cover Sheet (Form FDA 3397).

The CFR references are provided for most items in order to indicate what type of information should be submitted in each section. For further information, the applicant may consult the guidance documents that are available from the Agency.

Signature The form must be signed and dated. Ordinarily only one person should sign the form, i.e., the applicant, or the applicant's attorney, agent, or other authorized official. However, if the person signing the application does not reside or have a place of business within the United States, the application should be countersigned by an attorney, agent, or other authorized official who resides or maintains a place of business within the United States.

Exhibit J.3