CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125019/0

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: BLA STN No. 125019/0

From: Deborah Trout, HFM-675

Subject: Categorical exclusion under 21 CFR 25.31 (c)

Date: February 19, 2002

I have reviewed pertinent sections of the Biologics License Application (STN number 125019/0) from IDEC Pharmaceuticals Corp., and ——— for the manufacture, formulation, fill and packaging of Zevalin™, and find that their request for a categorical exclusion from an environmental assessment under 21 CFR 25.31 (c) is justified as the product is composed of naturally occurring substances, and that no extraordinary circumstances exist.

D. Trout 2.19.02

Deborah Trout Date
Committee Member
Division of Manufacturing Product Quality

Concurrence:

John A. Eltermann 2/19/02

John A. Eltermann, Jr., R.Ph.,M.S. Date
Director
Division of Manufacturing Product Quality

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Compliance and Biologics Quality
Division of Manufacturing and Product Quality

To: File, STN No. 125019/0

From: Deborah Trout, OCBQ, DMPQ, HFM-675

Subject: Review of IDEC's biologics license application for the treatment of patients with relapsed or refractory low grade follicular or CD20+ transformed B-cell non-Hodgkin's lymphoma and Rituximab refractory follicular NHL

Date: December 8, 2001

I have completed my review of all submissions relating to STN number 125019/0, and have found the information and data submitted to be adequate to determine that this application be approved at this time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: November 20, 2001

To: STN BL 125019/0 File

From: Michael A. Noska, M.S., Regulatory Project Manager MAN
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Teleconference with IDEC Pharmaceuticals Corporation

November 20, 2001, 15:00

Location: WOC I/DCTDA Conference Room

MEETING OBJECTIVES

The purpose of this teleconference was to discuss the proposed Phase 4 confirmatory trials for Zevalin and other post-marketing commitments.

DISCUSSION

The agenda for this discussion focused on three issues: the status of follow-up for survival and progression in the 106-04 trial; the confirmation of efficacy of Zevalin in low-grade follicular non-Hodgkin's lymphoma (NHL), and; confirmation in the transformed sub-population.

Follow-up for survival and progression in Study 106-04

The sponsor reported that no difference has been observed in overall survival and that they have never seen a survival advantage. The sponsor also noted that the Center has seen the data for progression. CBER requested that the sponsor submit a proposal for the final time-to-progression (TTP) analysis and a revised analytical plan. The sponsor stated that they would provide a proposal for the analysis and a timeline for the conduct of the analysis and submission of a final report. They will send this as an amendment to the protocol.

Confirmatory trial in low-grade follicular NHL

The sponsor proposed to compare Zevalin to Zevalin followed by Rituxan for follicular patients

only. They would exclude transformed and IWF-A histologies. They would not exclude prior Rituxan therapy but would exclude patients who are refractory to Rituxan. CBER inquired as to how this would assess the efficacy of Zevalin alone. The sponsor proposed that this could be done by comparing Rituxan alone to Zevalin plus Rituxan. They would stratify for prior Rituxan therapy. CBER noted that this is different from the –04 population but still is in the spirit of accelerated approval. The sponsor stated that the primary endpoint would be event-free survival. This was defined in the past as TTP, however, events could be defined as death, progression or new therapy without progression. CBER noted that time-to-next-therapy (TNT) could be a function of cytopenia which could introduce bias. It would be desirable for the endpoint to be defined as close to the Chesson criteria as possible.

The sponsor asked whether TTP should be separated from TNT. CBER noted that TTP is less subject to bias than TNT, which can be influenced by any delays in treatment caused by an intervening toxicity assessment. Event-free survival would be acceptable if it were driven by progression rather than next therapy. Response rate, duration and survival should be the secondary endpoints. The study should be powered on the primary endpoint. However, for the secondary endpoints, the sponsor should describe what differences would be detectable, even if the study is not powered for this analysis.

The sponsor stated that they were planning a LEXCOR analysis for the primary endpoint. CBER stated that this might not be necessary but that case report form (CRF) documentation is important. In response to the sponsor's question, CBER replied that success in the Rituxan versus Zevalin-Rituxan study could support a change in labeling. The sponsor stated that they would propose the study without a LEXCOR panel, but would make (digital) CT scans available if requested by the Center.

The sponsor estimated that they would enroll approximately 50 sites to study 500 patients. CBER suggested that the sponsor could use cooperative groups to help accelerate the trial, so long as the groups inform the company whenever changes are made to the protocol. The sponsor committed to submitting a timeline for discussing the protocol with the NCI and submitting the protocol to the Center. CBER stated that it would like to review the draft protocol at the same time as the NCI. The sponsor committed to conducting the trial if the cooperative groups delayed for any reason.

CBER advised the sponsor not to exclude for HACA and to continue to look for altered biodistribution and related adverse events. The company stated that they would propose to exclude for HAMA and study this separately. CBER stated that it would be acceptable not to wait for HAMA/HACA results. The sponsor also confirmed that they intend to follow cytogenetics.

In summary, the sponsor stated that they would conduct a trial of Rituxan versus Zevalin followed by Rituxan for patients with follicular NHL. They will obtain HAMAs and stratify for patients with prior Rituxan therapy. The secondary endpoints will be similar to the –04 trial and

the primary endpoint will be powered for an alpha of 0.05 at the 80% confidence level. CBER stated that the study might need to be more robust depending on the results from the –04 trial.

Confirmatory trial in transformed sub-population

For the transformed group, the sponsor proposed a single arm, 50 patient Phase 2 study of Zevalin followed by Rituxan, to be carried out by a cooperative group. The proposed primary endpoint would be event-free survival and the secondary endpoints would be the same as in the follicular, low-grade confirmatory study (above). CBER stated that event-free survival is only suitable for controlled trials. The sponsor replied that, in such a small population, it is difficult to have a control arm and to randomize patients. CBER suggested that it might be necessary to utilize objective responses rather than event-free survival, such as a primary endpoint of overall response rate, with secondary endpoints of TTP, duration or event-free survival. The sponsor will need to clearly define the patient population for the transformed group and should consider asking the cooperative group for a definition of tranformation, both pathological and clinical. CBER inquired as to the existing data for the use of Rituxan in transformed patients. The sponsor noted that there are only four patients from the randomized Zevalin trial. CBER recommended that the sponsor seek additional data on this treatment regimen from the cooperative group and stated that the Center is not committed to the proposed study at this time.

The sponsor stated that it would submit an outline of the proposed trials by November 30th.

Participants:

Agency	Sponsor
Philippe Bishop, M.D., CBER/OTRR/DCTDA	Brian Leigh
George Mills, M.D., CBER/OTRR/DCTDA	Leslie Shelly
Patricia Keegan, M.D., CBER/OTRR/DCTDA	Alice Wei
Michael Noska, M.S., CBER/OTRR/DARP	Rick Landin
	Paul Grint
	Dave Shin
	Christine White

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

Memorandum

From: **Bradley J. Glasscock, Pharm.D.**

Subject: **Imaging format**

Sponsor: **IDEC**

Product: **ibritumomab (STN 125019/0)**

Date, Location, & Time of Meeting: **July 2, 2001**
WOC-1, Conference Room 350 N
2:30 – 3:30 p.m. (EST)

IDEC Representatives: **Daniel Kim, Diane Shanahan, Brian Lee, Leslie Shelly, David Chen**

FDA Representatives: **George Mills, Rick Sparks, Michael Fauntleroy, Bradley Glasscock**

Summary:

The Agency informed IDEC that their recent submission to their BLA containing a response to our May 3, 2001 CR letter is not considered complete and the review clock has not started since the imaging component of the submission is not reviewable as provided. The Agency stated that the following items need to be submitted in order to allow the review of the dosimetry data:

1) Raw images provided in a standard format (i.e., DICOM)
2) Images with ROIs for side-by-side comparison. These images may be submitted in TIF format, although this is not Center standard and should be avoided in the future.

The data provided should allow the Agency to recreate the calculations and outputs

provided by IDEC regarding the dosimetry study. 3 copies of this material will be required. IDEC assured the Agency that this material would be submitted by the end of next week (July 13, 2001). The call was concluded.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE June 20, 2001

FROM Mary Andrich
Bioresearch Monitoring
HFM-664

TO Patricia Keegan
HFM-573

SUBJECT Bioresearch Monitoring Inspection Results
BLA: STN-125019
Product: Zevalin™ (IDEC-Y2B8; ^{90}Yttrium-IDEC-2B8-MX-DTPA; Ibritumomab tiuxetan)
Sponsor: IDEC Pharmaceuticals Corporation

PROTOCOLS/ TITLES

106-03: A Phase I/II Clinical Trial to Evaluate the Safety and Clinical Activity of IDEC-Y2B8 Administered to Patients with B-Cell Lymphoma

106-04: A Randomized, Phase III Multi-Center, Controlled Trial to Evaluate the Efficacy and Safety of IDEC-Y2B8 Radioimmunotherapy Compared to Rituxan™ Immunotherapy of Relapsed or Refractory Low-Grade or Follicular B-Cell Non-Hodgkin's Lymphoma

IND REFERENCES
B[redacted])

SUMMARY STATEMENT

The results of bioresearch monitoring inspections of three clinical sites indicate that the deviations made by the clinical investigators are not substantive, with the exceptions noted, and that the submitted data can be considered reliable and accurate.

BACKGROUND

Inspections of three clinical investigators were performed in support of the subject BLA. The inspections were conducted in with CPGM with 7348.811, the Inspection Program for Clinical Investigators.

Specific questions concerning the studies were included. Data audits were performed at the following three sites:

Site	Protocol(s)	Investigator(s)	Form 483	Classification
Mayo Clinic	106-03, 04	Witzig, Wiseman	No	NAI
Northwestern University	106-03, 04	Gordon	No	NAI
Sidney Kimmel Cancer Center	106-03,04	Saleh	Yes	VAI

INSPECTIONAL FINDINGS

A Form FDA 483 was issued to Dr. Saleh. Inspection of the sites revealed the following:

Northwestern University / Dr. Gordon

Three subjects (212, 311, and 317) were given doses of IDEC-Y2B8 that were higher than specified by Protocol 106-03. Dr. Gordon said that this occurred because the doses were calculated at 0.4 mCi/kg in the Nuclear Medicine Department without taking into account the maximum dose of 32 mCi in the protocol. He promised correction of this problem.

Sidney Kimmel Cancer Center / Dr. Saleh

Although all subjects signed consent forms at enrollment, versions that were revised while on study were missing for subjects 107 and 301. Another subject, 310, who was enroled on 6/24/97, did not sign an 8/20/97 version of the consent form until 1/8/99.

If you have any questions or comments about the contents of this memorandum, or any aspect of the Bioresearch Monitoring Program, please contact me at (301) 827-6335.

Mary Andrich

cc:

HFM-99
HFM-99
HFM-99 STN-125019
HFM-573 George Mills
HFM-573 Philippe Bishop
HFM-664 Mary Andrich
HFM-664 Joseph Salewski
HFM-664 Access/CHRON

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125019/0

MAR 23 2001

Ms. Alice M. Wei
IDEC Pharmaceuticals Corp.
3030 Callan Road
San Diego, CA 92121

Dear Ms. Wei:

This letter is in regard to your biologics license application (BLA) for Ibritumomab tiuxetan (Zevalin™) submitted under section 351 of the Public Health Service Act. Reference is also made to the telephone conversations of January 5, 2001 and February 2, 2001, between representatives of your organization and this office.

Your BLA is for a kit for the preparation of radiolabeled Zevalin™. The therapeutic dose is prepared by radiolabeling the antibody with Yttrium-90. As discussed on January 5, 2001, the Center for Biologics Evaluation and Research (CBER) has determined that information related to the manufacturing of Yttrium-90 chloride sterile solution should be submitted to and reviewed under a Type II Drug Master File instead of a New Drug Application (NDA). The reason for this decision is that Yttrium-90 has no approved indications as a stand-alone product and would be granted approval only as part of the license application for Zevalin™. This decision also is consistent with the Center for Drug Evaluation and Research's (CDER) policy of reviewing radionuclides as a drug substance when used solely for labeling of a final drug product. In this instance, the drug substance is reviewed in a drug master file rather than a NDA for separate marketing approval. We acknowledge that this represents a change from the advice communicated during the October 28, 1999 meeting between CBER and representatives of IDEC Pharmaceuticals Corporation and MDS Nordion, Incorporated. We want to assure you that this administrative change will not disrupt or delay the ongoing review process for Zevalin.

1. As a result of this change, you will need to submit a letter of cross-reference from MDS Nordion so that we may review their Type II Master File in support of your BLA.

2. Please submit a revised draft package insert for your product that incorporates information regarding Yttrium-90.

As discussed during the telephone conversation of February 2, 2001, we also have the following comments and requests for information:

3. Regarding the Yttrium-90:

   a. Please submit a letter of cross-reference from Amersham that gives the FDA authority to review their Master File for the Yttrium-90 Chloride used in the clinical trials in support of your BLA.

   b. Please amend your BLA to list the MDS Nordion manufacturing location as one of your contract facilities and include a complete description of the responsibilities of IDEC and Nordion regarding the manufacturing, testing, and distribution of Yttrium-90 Chloride sterile solution. Please provide a list of all standard operating procedures applicable to the contract arrangement. The description should include information regarding how IDEC will exercise control over the ordering and distribution of Yttrium-90 Chloride sterile solution to ensure it is only used as described in your product's labeling. IDEC should ensure that MDS Nordion fully informs IDEC of all deviations, complaints, and adverse events, as well as the results of all tests and investigations regarding or possibly impacting the Yttrium-90. IDEC also should ensure that MDS Nordion informs IDEC of all important proposed changes to production and facilities (including introduction of new products) and updates their master file accordingly. IDEC must notify CBER regarding proposed changes in the manufacture, testing, or specifications of the kit components including the Yttrium-90, in accordance with 21 CFR 601.12 (you may cross-reference the MDS Nordion master file, as applicable).

4. Consistent with the clinical studies, it is necessary to incorporate Indium-111-Zevalin biodistribution imaging into the overall treatment along with Yttrium-90-Zevalin and Rituximab:

   a. Please amend your BLA with additional product manufacturing information and revised package labeling to accommodate the Indium-111-Zevalin dose. Please submit a proposal with justification for the kit packaging configuration and shipping arrangements.

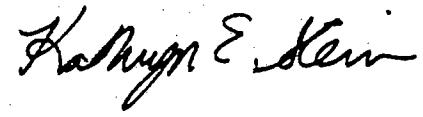
   b. Please submit a revised draft package insert that reflects the Indium dose and biodistribution imaging.

   c. For use of a currently FDA-approved source of Indium-111 Chloride Sterile Solution, please submit letters of cross-reference authorizing CBER to review the manufacturer's file in support of your BLA. The Indium-111 manufacturer will also need a letter of cross-reference to your BLA to support a supplement to revise their labeling.

d. Please amend your BLA to include a description of agreements to ensure that the Indium manufacturer will inform you of all important proposed changes to production and facilities.

Should you need additional information or have any questions concerning administrative or procedural matters please contact the Regulatory Project Manager, Mr. Michael Noska, in the Division of Application Review and Policy at (301) 827-5101.

Sincerely yours,



Kathryn E. Stein, Ph.D.
Division of Monoclonal Antibodies
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: HFM-561/M.Shapiro
HFM-585/L.Epps
HFM-579/Martin D. Green
HFM-573/P.Bishop
HFM-573/G.Mills
HFM-215/S.Misra
HFM-664/M.Andrich
HFM-675/D.Trout
HFM-675/K.O'Brien
HFM-588/M.Noska
HFM-555/K.Webber
HFM-555/K.Stein
HFM-573/R.Steffen
HFM-570/P.Keegan
HFM-570/K.Weiss
HFM-675/J.Lukas
HFM-675/J.Elterman
HFM-500/B.Goldman
HFM-500/S.Risso
HFM-500/Jay Siegel
HFM-110/R.Eastep
HFM-10/R.Yetter

CBER:DARP:Noska:1/25/01:mn:1/26/01:mn:2/7/01:Mildred:2.09.01:mn:2-13-01:mn:3-22-01:mn:3-23-01:amw:3-23-01
(S:\Noska\Letters\License\IDEC_NDA_Wdl.doc)

LETTER: Other (OT)

Division	Name/Signature	Date
OMA	Stein	3/23/01
DARP	[illegible]	3/23/01
DMA	Marjorie A. Shapiro	3/23/01
DARP	Annette Williams	3/23/01

MEMORANDUM OF TELECON

Date: February 2, 2001, 14:00

To: BLA File (STN 125019/0)

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes from telecon with IDEC regarding additional review issues

CBER Participants: Phillipe Bishop
George Mills
Michael Noska
Leon Epps
Debbie Trout
Marjorie Shapiro
Keith Webber
Patricia Keegan

IDEC Participants: Alice Wei
Christine White
Daniel Kim
John Leonard

IDEC was informed that the information on Yttrium-90 would need to be reviewed as a master file and not an NDA. MDS Nordion will be considered a contract manufacturer. IDEC will need to amend the BLA to demonstrate how responsibilities will be distributed for assuring GMPs, purity, potency. Any changes made by Nordion would need to be reported in their master file and to IDEC for possible inclusion in the BLA. Final release specifications will need to be established for the radiopharmacies.

IDEC will need to obtain a letter of cross reference for the Nordion master file.

IDEC needs to provide a letter of cross reference for information regarding Amersham's Yttrium-90.

IDEC must include In-111-2B8 in the BLA for biodistribution imaging as there is no trial which supports not using it. Indium-111 is not needed for dosimetry or dose-setting, but rather to assess the potential for altered biodistribution, which could lead to adverse events. Also, there are no data to rule out a possible contribution to the therapeutic efficacy from the antibody dose associated with In-111 imaging.

IDEC needs to provide a plan for coordinating the distribution of antibody and Yttrium-90 to clinical sites.

If IDEC is to use currently licensed sources of Indium-111, the NDA holders will need to amend their licenses to include their use with IDEC's product.

IDEC was informed that they would not be able to market product which was made in the ——— vials at ——————————. IDEC acknowledged that they would not release this product commercially and that it would only be used in stability studies or perhaps pre-clinical studies. IDEC clarified that there were no ———, in real time stability tests, only in the accelerated stability studies. There were no changes in biochemical or biophysical parameters.

MEMORANDUM

Date: January 30, 2001, 9:30-12:30

To: BLA File (STN BL 125019/0)

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes of Mid-cycle Meeting for IDEC BLA for Zevalin (Ibritumomab tiuxetan)

Participants: Mary Andrich, Philippe Bishop, Leon Epps, Bette Goldman, Dave Green, Shyam Gupta, Glen Jones, Patricia Keegan, Julia Lukas, George Mills, Satish Misra, Michael Noska, Kevin O'Brien, Sharon Risso, Marjorie Shapiro, Jay Siegel, Richard Steffen, Kathryn Stein, Debbie Trout, Keith Webber, Karen Weiss

Mr. Noska opened the meeting by reviewing the milestones of the BLA review. He also discussed the decision to administratively change the handling of information on Yttrium-90 from an NDA to a master file.

Dr. Bishop summarized the clinical section of the BLA, discussing adverse events, problems with some missing hematologic data, difficulties in reading HAMA/HACA data and an overview of labeling issues. Dr. Siegel noted that it would be necessary for the package insert for Rituxan to be revised to be consistent with the use of Zevalin.

Dr. Mills addressed the need for Indium-111-Zevalin imaging to be included in the BLA for the purposes of assessing dosimetry and altered biodistribution. He also discussed the need for additional radiation dose modeling.

Dr. Misra briefly discussed statistical problems with the Quality of Life data.

Dr. Andrich reported that three bioresearch monitoring inspections had been assigned but not yet completed.

Dr. Green reported some difficulties verifying in the electronic document room that the Y-90 comparability study was submitted.

Dr. Shapiro reported no issues with the review of drug substance.

Dr. Epps discussed the problem of pH ——————which was addressed with the company.

Ms. Trout discussed the results of the inspection at IDEC. There were 19 items on the 483, the most significant of which was the failure to identify organisms from open environmental

excursions. This represents a problem with quality assurance and the company will not be able to release this material without resolving the inspectional findings. Ms. Trout reported that the inspection a[redacted] would take place in three weeks.

Action items:

- Notify IDEC of change in handling of Y-90 application from NDA to master file
- Notify company that In-111-Zevalin needs to be included in overall treatment plan
- Inform company of need to revise labeling for Rituxan
- Arrange to change kit configuration to include In-111-Zevalin
- Address release of product affected by pH [redacted]
- Clarify method and responsibilities for distribution of kit and Y-90
- Inform sponsor of need for cross reference for Amersham's Y-90

MEMORANDUM OF TELECON

Date: January 30, 2001, 15:30

To: BLA File (STN 125019/0)

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes from telecon with IDEC regarding review issues

CBER Participants: Phillipe Bishop
George Mills
Michael Noska

IDEC Participants: Alice Wei
Leslie Shelley
Christine White
Paul Grint
Antonio Grillo-Lopez

CBER called the sponsor to provide an update on review issues after the mid-cycle meeting.

CBER informed the company that it would not be possible to compile all the information needed in time for the March ODAC meeting, particularly since some materials would need to be redacted.

CBER indicated that it would be asking for the following information in a complete response letter:

- The sponsor will need to submit additional dosimetry data including results from theoretical models of obstructed urinary outflow and colloid formation
- The sponsor will need to provide safety information from the 106-98 trial to address neutropenias and thrombocytopenias and their possible relationship to bleeding events; also to look at the risk from prior treatments such as fludarabine
- The potential relationship between GI toxicity and GI tract activity seen on biodistribution imaging
- The sponsor will need to document or provide values for missing data, apparent lack of follow-up
- The sponsor will need to submit case report forms for the 106-05 trial
- The sponsor will need to provide explanations for hospitalizations, HAMA/HACA
- The sponsor will need to explain the differences in evaluation of Complete Remissions between the LEXCOR panel and onsite investigators

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 23, 2001

From: Leon Epps

Subject: Reported pH Changes for Ibritumomab tiuxetan (ZevalinTM) as Described in FAX of January 10, 2001 and is Relevant to IDEC's BLA 125019/0

To: File

CC: Mary Andrich
Keith Webber
Kathryn Stein
Marjorie Shapiro
Debra Trout
M. David Green
Philippe Bishop
George Mills
Patricia Keegan
Richard Steffen
Satish Misra
Kevin O'Brien
Michael Noska
Glen Jones

SUMMARY:

On January 5, 2001, IDEC advised Drs. Shapiro and Webber of the agency that its contract manufacturer (——— has determined that the commercial lots of Ibritumomab tiuxetan (Zevalin™) exceed the current stability pH specification of 8.0. The Zevalin™ drug product is stored in a 3 cc — glass vial with a ——— stopper and aluminum overseal and contains 3.2 mg of Ibritumomab tiuxetan and 17.6 mg sodium chloride in 2 mL of Water for Injection. The drug product is chemically modified monoclonal antibody (IDEC 2B8-MX-DTPA) dissolved in a normal saline solution designed to minimize Zevalin™ pH buffering capacity and allow for it be efficiently radiolabeled with yttrium-90. Based on the data available at the time of filling, the pH range of 6.0-8.0 was set as lot release and stability specification. Stability data from clinical development lots (in treated vials) demonstrate that the drug product meets this pH specification both at release and over the entire shelf life (up to ——— . The pH drift observed in the commercial lots was not observed in the historical

data produced with the clinical development lots (see Tables 1, 3, 4, 5 and 6 in the Attachment).

Stability data generalized from the [redacted] commercial lots indicate that this pH range may be acceptable for release but will not be acceptable over the proposed [redacted] shelf life. The upward pH trend of commercial lots on stability at the recommended storage temperature [redacted] is apparent and more pronounced at the accelerated temperature [redacted] (see Tables 3 and 4 for details).

[redacted]

Table 8 provides a summary of the proposed experiments.

RECOMMENDATIONS:

1. [redacted]

2. Add HPLC assay for evaluating the Y-90 radiolabeled Zevalin™ product to your proposal.

3. Your proposed studies on Zevalin™ in the [redacted] should proceed as soon as possible.

4. Modify your pH specification after your validation studies on Zevalin™ are completed.

5. Provide stability data on three lots of Zevalin™ drug product.

ATTACHMENT

Table 1

Drug Product	Storage Condition	pH Range Observed	
		Release Testing	Stability Studies
Proposed Commercial Process	[redacted]		
Clinical Process			

5 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Administrative- 1

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 10, 2001

From: Leon Epps LAE

Subject: January 8, 2001 Teleconference to Advise MDS Nordion Inc. that NDA — — Submitted for Yttrium Y-90 Chloride Sterile Solution in Support of IDEC's BLA 125019/0 for Ibritumomab tiuxetan (Zevalin ™) is being Reviewed as a BB-MF

CBER: Leon Epps, Ph.D., Marjorie Shapiro, Ph.D. and Keith Webber, Ph.D.

MDS Nordion's Regulatory Representative: Timothy F. Nason, Ph.D.
613-592-2790

To: File

CC:
Mary Andrich
Keith Webber
Kathryn Stein
Marjorie Shapiro
Debra Trout
M. David Green
Philippe Bishop
George Mills
Patricia Keegan
Richard Steffen
Satish Misra
Kevin O'Brien
Michael Noska
Glen Jones

BACKGROUND:

Nordion's NDA ——— for yttrium Y-90 chloride sterile solution was submitted to support IDEC's BLA for Zevalin ™ and is cross-referenced to BB-MF — and to IDEC's BLA (STN#125019\0\0). The submission describes the chemistry, manufacturing and control information on the production of yttrium Y-90 chloride sterile solution. On January 5, 2001, Drs. Shapiro and Webber advised IDEC that CBER's review committee would review Nordion's NDA as a BB-MF.

SUMMARY:

On January 8, 2001 at 4:15 P.M., we called Dr. — the regulatory representative for MDS Nordion, Inc., to advise him that CBER changed the policy on reviewing NDAs that do not contain data to support an independent clinical use for the radionuclide. The change means that these NDAs will be reviewed as BB-MFs. Yttrium Y-90 chloride sterile solution is a radionuclide with no independent clinical use and is considered a drug substance; thus, it is best reviewed under the BB-MF. We emphasized that CBER's current policy is consistent with CDER's recently approved radiopharmaceutical rule that considers a radiopharmaceutical to be the radionuclide plus the ligand (21CFR315.3).

AGREEMENTS:

1. We agreed to send Nordion and IDEC specific guidance on the new policy and procedures after they are finalized.

2. We agreed to have additional discussions as necessary. Requests for future discussions would be handled through the project manager.

000360822

DEC 2 9 2000

Our STN: BL 125019/0

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

Dear Ms. Wei:

This letter is in regard to your biologics license application submitted under Section 351 of the Public Health Service Act.

The Center for Biologics Evaluation and Research has completed an initial review of your application dated November 1, 2000 for Ibritumomab tiuxetan (Zevalin™) to determine its acceptability for filing. In accordance with 21 CFR 601.2(a) the application is considered to be filed effective today's date.

This acknowledgment of filing does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you need additional information or have any questions concerning administrative or procedural matters, please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5101.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CBER:DARP:M.Noska:12-27-00:Dixon:12/27/00:12/29/00
(S:\Noska\Letters\License\Filing_IDEC_125019.doc)

MILESTONE - COMMUNICATION TYPE:
LETTER: FILING NOTIFICATION (FL)

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTEE/DARP	M. Noska	12/29/00	DARP	Dixon	12/29/00			
DARP	[illegible] for [illegible]	12/29/00						

MEMORANDUM

Date: December 12, 2000, 15:40-16:50

To: BLA File (STN 125019/0))

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes of Filing Meeting for IDEC BLA Submission for Y-90-Ibritumomab tiuxetan (2B8-MX-DTPA Murine Monoclonal Antibody [Zevalin™] for non-Hodgkin's Lymphoma)

Participants:

Deborah Trout	Glen Jones
George Mills	Ghanshyam Gupta
Philippe Bishop	Richard Steffen
Kevin O'Brien	Patricia Keegan
Leon Epps	Keith Webber
Marjorie Shapiro (Chair)	Kathryn Stein
Mary Andrich	Sharon Risso
Satish Misra	Michael Noska

Dr. Mills stated that the company is expected to submit original source data for radiation dosimetry but that it has not yet arrived at the Center. These data are required for filing. It was agreed that the sponsor would be given a deadline for submitting these data. [N.B. Immediately after this filing meeting, it was learned that the documents had been received by the Center, removing this as a filing issue.] Dr. Mills also noted that In-111-Zevalin would likely be required as part of the overall treatment regimen but that the application contains sufficient clinical information to support this.

Drs. Mills and Bishop stated that there are no other filing issues from the clinical perspective.

Drs. Epps and Shapiro reported that there are no product-related filing issues.

Dr. Andrich stated that a table listing the clinical sites for the pivotal studies contained an error and that the sponsor was supposed to submit a corrected version. [This information was submitted along with the dosimetry data sited above.]

Dr. Misra noted that he was having difficulties accessing files in the electronic BLA, however, this is not a problem with the submission and therefore, he concluded that the BLA could be filed.

Ms. Trout and Mr. O'Brien briefly discussed the timing of manufacturing site inspections and stated that there are no CMC filing issues.

The committee briefly discussed the decision to review the manufacturing information from MDS Nordion for Y-90-chloride as a master file instead of a NDA. Nordion will be asked to withdraw the NDA and submit letters of cross-reference to the IDEC BLA. Information from the Y-90 package insert will need to be incorporated into the IDEC labeling.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

MEMORANDUM

Date: November 27, 2000

To: IDEC BLA File (STN BL 125019/0)

From: Michael A. Noska, M.S., Regulatory Project Manager MAN
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Teleconference with IDEC Pharmaceuticals Corporation regarding its biologics license application for Y-90-labeled Ibritumomab tiuxetan (IDEC-Y2B8) murine monoclonal antibody to CD20 for the treatment of non-Hodgkin's lymphoma

November 21, 2000, 14:45-16:25

Location: WOC I/Room 200 South

MEETING OBJECTIVES

The Agency initiated this teleconference to discuss several issues related to the sponsor's BLA for Yttrium-90 radiolabeled Zevalin. Ms. Alice Wei, from IDEC's regulatory affairs group, was present in the room for the teleconference, as she was already on site for another meeting. Other IDEC representatives who participated by phone are listed at the end of this memorandum.

DISCUSSION

The first item which was discussed was an IND submitted by the National Cancer Institute for the use of Y-90-Zevalin in which the product would be administered twice to patients. (IDEC's IND —— was cross-referenced by the NCI for product information.) This raised some concern within the Agency because the sponsor had previously stated that the product would not be re-administered and that the BLA and proposed package insert (PI) would specifically exclude re-administration. Therefore, Dr. Mills wanted to discuss the implications of this protocol for the review of the BLA. He pointed out that any potential for adverse events which might be reported during the review of the BLA would need to be reflected in the PI. Further, it might be necessary to conduct a study of the safety of re-administration of Y-90-Zevalin. The sponsor noted that it would perhaps be two years before any data accrued from the NCI's study and therefore, the impact on the BLA was uncertain. However, Dr. Bishop pointed out that any expedited adverse

events reported from IND —— during the BLA review would need to considered in the PI, particularly since the oncology community would be likely to want to attempt re-administration of Zevalin for those patients who did not respond to the first treatment. The sponsor stated that they would take this under advisement and respond back to the Agency.

Drs. Mills and Bishop noted that the BLA does not contain data on the subset of 41 patients for which the Agency asked the sponsor to submit CT films. They asked the sponsor to provide a SAS data set for this subset of patients which includes efficacy parameters from both the LEXCOR and Principal Investigator assessments of response. The sponsor thought they would be able to provide this data readily.

Dr. Mills informed the sponsor that the CDs which were sent to Dr. Richard Sparks for his dosimetry review did not contain time-activity data for organs or tissues. The sponsor stated that they would investigate this and respond to the Agency.

Dr. Mills asked the sponsor whether they included information in the BLA regarding which specific antibody product (by manufacturer) was given to each patient. This had previously been requested by the Agency and it was recalled that the data was submitted to IND —— However, IDEC representatives could not immediately identify the location of this data in the BLA, although they were reasonably certain that it had been included. Therefore, they stated that they would respond to the Agency with this information.

Finally, Drs. Mills and Bishop noted that data on the use of Indium-111-Zevalin (2B8) could not be found in the BLA. The sponsor indicated that they did not consider it to be necessary since they were proposing to license only Y-90-Zevalin without the use of In-111 for dosimetry imaging. However, the Agency stated that, while the topic of dosimetry imaging is perhaps open to discussion, the current issue is the contribution of the antibody from In-111-Zevalin to the overall efficacy of the treatment regimen. Dr. Mills noted that there are no data from a controlled clinical study to show that there is no contribution to the treatment effect from In-111-Zevalin. In the absence of such data, the application is deficient due to the lack of information on chemistry, manufacturing and controls (CMC) and package insert data for In-111. The sponsor was informed that this is a filing issue. The sponsor was also informed that, if they have data on In-111, it should be submitted to the BLA as soon as possible so that this filing issue can be removed from consideration. The sponsor stated that they would discuss this internally and respond to the Agency.

The call was concluded at 16:25.

Participants:

Agency	Sponsor
Philippe Bishop, M.D., CBER/OTRR/DCTDA	Ken Fite
George Mills, M.D., CBER/OTRR/DCTDA	Rick Landin
Michael Noska, M.S., CBER/OTRR/DARP	Christine White, M.D.
	Alice Wei

11/27/00
S:\Noska\Meetings\Tcon_11-21-00_IDEC.doc

Division of Manufacturing and Product Quality
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research
Food and Drug Administration

MEMORANDUM

TELEPHONE CONVERSATION RECORD

Date: Novermber 27, 2000

CBER Representative: Deborah Trout, OCBQ/DMPQ/HFM-675

Organization Representatives: Alice Wei

Organization: IDEC Pharmaceuticals Corp.

Subject: Request additional information be submitted to the BLA for completeness of the application.

STN/Ref No: 125019/0

Following my initial review for filing adequacy of the BLA, I noted that information required for filing of the application was reference in the Contract Manufacturer's Drug Master File (DMF). I called Ms. Wei to inform her that the application will not be considered filed until the following data from their Contract Manufacturer has been received:

A. Room numbers were manufacturing equipment is located.

B. Data resulting from media fill validation using the same container closure system and filling procedure used for their product. These data should be obtained using the same filling line(s) that are used for their product. In addition, the following information should be submitted for each media fill run:

1.
2.
3.
4.
5.
6.

7.
8.
9.
10.

C. Verification that sterilization validations referenced in the DMF are applicable to their container closure system.

I stated that the information must be submitted to the Center prior to December 12, 2000 for BLA filing acceptability.

cc: Noska HFM-588
electronic cc: Lukas HFM-675
electronic cc: Shapiro HFM-561

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NOV 21 2000

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

Dear Ms. Wei:

SUBMISSION TRACKING NUMBER (STN) BL 125019/0 has been assigned to your recent submission of your biologics license application, received on November 1, 2000, for Ibritumomab tiuxetan for the treatment of patients with relapsed or refractory low grade follicular or CD20+ transformed B-cell non-Hodgkin's lymphoma and Rituximab refractory follicular non-Hodgkin's lymphoma.

All future correspondence, supportive data, or labeling relating to this application should be submitted in triplicate and should bear the above STN and be addressed to the Director, Division of Application Review and Policy, HFM-585, Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448.

This acknowledgement does not mean that a license has been issued nor does it represent any evaluation of the adequacy of the data submitted. Following a review of the application, we shall advise you in writing as to what action has been taken and request additional information if needed.

Should you have the need to discuss any technical aspects of the application, you may obtain the name of the chairperson of the licensing review committee by contacting this office at 301-827-5101. Any questions concerning administrative or procedural matters should also be directed to this office.

Sincerely yours,

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. Kahn	11/21/00	DARP	A Williams	11-21-00			
DARP	Jorgase	11/21/00						
DARP	D. Jones	11/21/00						

bcc: STN File
Director, Product Release Staff, HFM-672
Red Folder
Michael Noska

OTRR/DARP:amw:11-9-00:11-21-00
(S:\STN 2000/125019.0.app.doc)
STN ASSIGNMENT – APPLICATION
CORR: ACKNOWLEDGMENT LETTER

MEMORANDUM OF TELECON

Date: November 20, 2000, 15:00

To: BLA File (STN 125019/0)

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes from telecon with IDEC regarding formatting of electronic datasets

CBER Participants:	George Mills Philippe Bishop Michael Fauntleroy Michael Noska	**IDEC Participants:**	Ken Fite Rick Landon Daniel Kim Alice Wei Leslie Shelley

This call was initiated by the Agency to discuss the formatting of electronic datasets submitted in the BLA for Y-90-Zevalin.

Dr. Mills informed the company that the datasets, as submitted, are in a vertical format by lab test, whereas the Center needs to have them in a horizontal format with lab test results displayed horizontally and study visits presented vertically. This format is needed for both the safety and efficacy analyses for the 106-04 and –06 trials. It is not needed for the Phase 1 or dosimetry studies.

Dr. Mills asked the sponsor when they would be able to provide this information. The company responded that this would be difficult to do for adverse events. Dr. Mills stated that the Center could accept datasets for everything except adverse events at this time and then correct the AEs later.

Dr. Mills suggested that the company submit a draft format for review. Mr. Fauntleroy asked whether the company could send this draft by e-mail as a zip file with a secure password. IDEC agreed to do this and submit the draft by close of business Wednesday, November 22, 2000.

The call was completed.

MEMORANDUM

Date: November 20, 2000, 15:30

To: BLA File (STN 125019/0))

From: Michael A. Noska, M.S., Regulatory Project Manager, DARP MAN

Subject: Minutes of First Committee Meeting for IDEC BLA Submission for Y-90-Ibritumomab tiuxetan (2B8-MX-DTPA Murine Monoclonal Antibody [Zevalin™] for non-Hodgkin's Lymphoma)

Participants: Deborah Trout
George Mills
Philippe Bishop
Kevin O'Brien
M. David Green
Marjorie Shapiro (Chair)
Mary Andrich
Satish Misra
Leon Epps
Michael Noska
Glen Jones

After introductions of the team members, Mr. Noska reviewed the milestones for the review cycle. The application has been assigned priority review status (6 month cycle). The filing date is December 31, 2000 and a filing meeting has been scheduled for December 12, 2000. The mid-cycle meeting with Dr. Siegel is scheduled for January 30, 2001. The final action due date is May 3, 2001. Oncology Drug Advisory Committee meetings are currently scheduled for March 14-15 and June 6-7, 2001.

Ms. Trout suggested that inspections of the manufacturing sites might be conducted toward the end of January.

Dr. Mills noted that a call was made to the sponsor to try to correct a problem with the formatting of the electronic datasets. Dr. Andrich also commented on difficulties accessing the electronic CRTs which are slowing the scheduling of clinical site inspections.

Dr. Mills noted that the company still needs to submit the list of 41 patients who were randomly selected to compare on-site reviewer response data to that of LEXCOR.

Dr. Jones queried whether it might be necessary to revise the Rituxan package insert to reflect the new dosage used in the Zevalin therapy regimen.

The meeting was adjourned at 16:30.

ARCHIVAL

ORIGINAL

IDEC Pharmaceuticals Corporation

3030 Callan Road
San Diego, California 92121
858/431-8500 • Fax 858/431-8887

November 1, 2000

NOV 1 2000
L34534
DCC

Glen D. Jones, Ph.D.
Director
Division of Application Review and Policy
Office of Therapeutics Research and Review (OTRR)
Center for Biologics Evaluation and Research
Food and Drug Administration
Document Control Center (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

000801903

RE: **Original Biologics Licensing Application**
ZEVALIN™ (ibritumomab tiuxetan)

Dear Dr. Jones:

Pursuant to 21 CFR 601, we hereby submit an original Biologics License Application (BLA). This submission supports the use of ZEVALIN™ (ibritumomab tiuxetan), also identified as IDEC-Y2B8, for the treatment of patients with relapsed or refractory low grade, follicular or CD20+ transformed B cell Non-Hodgkin's lymphoma (NHL), and rituximab refractory follicular NHL. We believe ibritumomab tiuxetan to be a safe and effective treatment for this patient population. On June 4, 2000, ibritumomab tiuxetan was granted Fast Track designation pursuant to Section 506 of the Food, Drug and Cosmetic Act.

The following agreements were made with the Agency regarding the ZEVALIN BLA.

CMC:

- The submission includes comparability testing for product manufactured at ——— used in the Phase III pivotal trials and the new proposed commercial material produced at IDEC. ———

- As recommended by members of the Division of Manufacturing and Product Quality (FDA) in a teleconference on April 11, 2000, information required for a change from single-product to a multi-product manufacturing facility is included within the BLA.

- is a contract manufacturer for IDEC and is responsible fo. In discussions with Drs. Gorman (DMPQ) and Brunswick (DMA) on July 14, 1999, the following arrangement for the information within the filing was agreed upon. Non-product specific and proprietary information with respect to these procedures is found in a type V master file submitted by on October 28, 1999. Product specific information with respect to these processes is located within the ZEVALIN BLA.

- Biochemical testing of IDEC-Y2B8 to demonstrate that ^{90}Y from Amersham and MDS Nordion are comparable is included in the BLA.

- The application will be supplemented with stability information supporting the proposed product expiration date during the review period.

Human Pharmacokinetic Section:

- Validation of the HAMA assay is provided in the BLA.

- A pharmacokinetic analysis of IDEC-Y2B8 (^{90}Y-ZEVALIN) to characterize the pharmacokinetic profile of IDEC-Y2B8 compounded with ^{90}Y from Amersham and ^{90}Y supplied by MDS Nordion has been included in the BLA.

Clinical and Statistical Section:

- The proposed indication for ZEVALIN is for the treatment of patients with relapsed or refractory low grade, follicular or CD20+ transformed B cell Non-Hodgkin's lymphoma (NHL), and rituximab refractory follicular NHL. IDEC notes the concern

expressed by FDA in the July 18, 2000 pre-BLA meeting minutes with respect to the inclusion of transformed patients in the indication.

- The Zevalin BLA includes the following Phase III pivotal studies for this filing:

  A Phase III, multicenter, prospectively randomized, controlled comparison study in patients with relapsed or refractory, low-grade, follicular, or CD20+ transformed B-cell NHL (IDEC Study 106-04).

  A Phase III, multicenter, nonrandomized controlled study of IDEC-Y2B8 in rituximab-refractory NHL patients (IDEC Study 106-06).

- Protocol 106-06 includes a reference group for comparison with 106-06 patients. IDEC has included the data with respect to the reference group in the 106-06 clinical study report; although we recognize there are some limitations associated with these data.

- In reference to the statistical portion of the BLA submission, intent-to-treat populations have been included in all analyses. In some cases, additional analyses were performed on evaluable patients.

- The BLA submission includes data from all patients enrolled in studies 106-01, -02, -03, -04, -05, -06 and the pharmacokinetic study for comparison of yttrium-[90] (^{90}Y) sources. As agreed at the July 18, 2000 meeting, safety data would be included in the 120 day update, for patients on the 106-98 open label trial who have completed a minimum of 13 weeks on the trial.

- The BLA includes compatible SAS programs, including macros, codes and data sets for all patients in the 106-03, -04, -05 and -06 trials. In addition, compatible SAS data sets containing data from all patients for all trials are submitted in the Integrated Summaries of Efficacy (ISE) , Safety (ISS) and Dosimetry (ISD).

- Kaplan-Meier analyses are included for duration-of-response and time to progression data.

- All LEXCOR lesion measurements of any size are included within the BLA. However, all analyses were performed with the —— lesion measurement prospectively defined protocol criteria.

- Quality of Life assessments are included within the BLA as supportive measures for evaluation of overall patient benefit from the product. IDEC acknowledges the concern raised by FDA at the July 18, 2000 pre-BLA meeting with respect to the Quality of Life assessment and use of a validated instrument.

- A description of each manufacturing scheme, and the product lot administered to each patient have been included in the Clinical and CMC sections of the BLA.

- Financial disclosure information for clinical investigators (including members of the LEXCOR panel) has been included in the BLA submission.

- The ISS contains safety data from all patients including the six patients from group 1 of trial 106-03 who did not receive ^{90}Y-ZEVALIN.

- Hematologic toxicity data has been included in the safety section of the BLA.

- As agreed at the July 18, 2000 meeting, IDEC has surveyed study sites to evaluate the availability of the CT films that have established the duration of response for the pivotal trials. This information was submitted to the IND on October 27, 2000 (submission #224).

- Digitized CT scans for a selected group of 41 patients identified by FDA (August 18, 2000) for trials 106-04 and 106-06 are included in the application.

- IDEC has submitted correlation analyses comparing the onsite investigator assessment for response with the LEXCOR assessments for response.

- Electronic nuclear medicine images for all available patients treated in the 106-03, 106-04 and 106-06 trials are included in the application. As the pharmacokinetic study to compare yttrium-90 sources was restricted to blood and urine analysis of yttrium-90, there are no nuclear medicine images for these patients.

- A separate dosimetry package for analysis by the Agency's dosimetry consultant is included in the submission.

- ^{111}In dosimetry is no longer required prior to IDEC-Y2B8 treatment for this defined patient population.

- The 120 day update will include safety data from all trials, as well as TTP and DR for trials 106-04 and 106-06. In addition, as agreed at the July 18, 2000 meeting, the update will include safety data from patients on the 106-98 open label trial who have completed a minimum of 13 weeks on the trial, as well as interim safety data for patients enrolled in the pharmacokinetic analysis for comparability of ^{90}Y sources. Note all patients in the latter analysis will be included, whether or not they have completed the 13 week minimum.

Case Report Forms:

- Case Report Forms (CRF) are included in the application specifically for all patients treated in the pivotal trials 106-04 and 106-06, all patients who died, dropped out or experienced a serious adverse event in any study. In response to a request by FDA after the July 18, 2000 meeting, CRFs for trial 106-03 are also included.

With the exception of the NDA for ^{90}Y chloride sterile solution (MDS Nordion), the ZEVALIN BLA will be an entirely electronic,

The Zevalin BLA is presented on 30 CDs, seven contain the BLA, and 23 comprising the imaging section of the application. As requested by Michael Fauntleroy, we have also enclosed desk copies of relevant sections of the BLA on 10 CDs for each review team member. Two copies, one archival and one original, of all 40 CDs are included in the submission. The size of the application is approximately 3.0 gigabytes, not including the imaging section. The electronic submission is free from computer viruses, and IDEC has not installed any computer software that will monitor user activity. Inoculan for Windows NT 4.00 build 373, virus signature 4.24, manufactured by Computer Associates was utilized to check the electronic submission for computer viruses.

BLA Binder	CD Label	Contents
1	1–5	Main body of application, to be loaded on CBER server
1	6–7	Statistical Review CDs
1	IDEC_001–IDEC_023 (23 CDs)	Imaging section, including CT and dosimetry images, Cheshire software, imaging database, and user manual
2-7	Desk Copies (various, 10 CDs)	Various, for individual (clinical, nonclinical/human pharmacokinetic, DPMQ, CMC, BRM and Oakridge) reviewers

The following individuals should be contacted for any questions or comments regarding this electronic submission:

Regulatory Contact	**Technical Contact**
Alice Wei	Daniel Kim
Senior Director, Regulatory Affairs	Senior Supervisor, Regulatory Affairs
IDEC Pharmaceuticals Corporation	IDEC Pharmaceuticals Corporation
Telephone: 858-431-8920	Telephone: 858-431-8977
Facsimile: 858-431-8895	Facsimile: 858-431-8895
Pager: 858-919-1188	

We hereby request exclusion from an application fee for this orphan drug product in accordance with Section 736(a)(1) of the FD&C Act. This original application is for the treatment of a rare disease or condition that has already received designation pursuant to Section 526. Attached with the User fee cover sheet is a copy of the FDA letter designating ibritumomab tiuxetan as an Orphan Drug for the treatment of non-Hodgkin's lymphoma.

We look forward to working with you in obtaining a timely review and approval for this important new therapy. If there are any questions, please contact me by telephone 858-431-8920 or by facsimile 858-431-8895.

Sincerely,

Alice M. Wei
Senior Director, Regulatory Affairs

IDEC
Pharmaceuticals Corporation

3030 Callan Road
San Diego, California 92121
858/431-8500 • Fax 858/431-8887

October 16, 2000

Jay Siegel, M.D.
Director, Office of Therapeutics Research and Review
Center for Biologics Evaluation and Research
Document Control Room (HFM-99)
Woodmont Office Center, Suite 200N
1401 Rockville Pike
Rockville, MD 20852-1448

RE: Zevalin™ (ibritumomab tiuxetan)
Letter Authorizing Cross-Reference

Dear Dr. Siegel:

By this letter we hereby authorize access to the complete information contained in the Biologics License Application entiled "Original Biologics License Application for Zevalin™ (ibritumomab tiuxetan)".

The sponsor of the BLA is IDEC Pharmaceuticals Corporation and cross reference is provided to allow review of non-clinical, clinical, and manufacturing information regarding the testing, release and use of the monoclonal antibody termed IDEC-Y2B8 (ibritumomab tiuxetan).

This authorization is provided for use in the management and review of a New Drug Application (NDA) for the supply of Yttrium 90 submitted by MDS Nordion of Kanata, Canada.

MDS Nordion is also requesting to be excluded from an application fee for their New Drug Application being submitted for Yttrium-90 which is the radioisotope component of the orphan drug product Zevalin™, (ibritumomab tiuxetan) in accordance with Section 736(a)(1) of the FD&C Act. This original application is for the treatment of a rare disease or condition that has already received orphan drug designation pursuant to Section 526.

Please refer to the IDEC sponsored BLA for additional information regarding the orphan drug status of Zevalin™.

If there are any questions or comments regarding information contained in this submission, please contact me by telephone at (858) 431-8920 or by facsimile at (858) 431-8895.

Sincerely,

Alice M. Wei
Senior Director, Regulatory Affairs