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

Memorandum

Date of Telecon: February 19, 2003

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: BLA 125011/0 file
Corixa Corporation
Tositumomab and Iodine I 131 Tositumomab

Subject: FDA Review Comments; Labeling

PARTICIPANTS:
CBER/OTRR: Karen D. Jones, RPM, DARP

Corixa Corporation: Monica Krieger and Jill Henrich, Regulatory Affairs

Corixa representatives called on February 19, 2003 to ask if the FDA review letter will issue this week. I responded that the letter will not issue this week and committed to faxing the letter as soon as it is signed-off. Dr. Krieger expressed Corixa's desire to respond as rapidly as possible to any FDA concerns. I indicated FDA's appreciation of Corixa's willingness to work with the agency. The call concluded.

Later this same date, Jill Henrich phoned to provide contact information if the letter issues next week. Deborah Del Chiaro is authorized to receive the letter in the absence of Dr. Krieger or Ms. Henrich. She asked if FDA could possibly provide a written decision regarding the proposed proprietary name of BEXXAR when the review letter issues. I responded that that letter will issue under the IND, BB-IND 3323. We briefly discussed the package and vial labeling. I indicated that it is still under review, but that one potential issue may be the inkjet printed vial labels for the radiolabeled product. The call concluded.

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

Memorandum

Date of Telecon: January 30, 2003

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: BLA 125011/0 file
Corixa Corporation
Tositumomab and Iodine I 131 Tositumomab

Subject: Timing of FDA Review Comments

PARTICIPANTS:
CBER/OTRR: Karen D. Jones, RPM, DARP

Corixa Corporation: Jill Henrich, Regulatory Affairs

Jill Henrich called on January 30, 2003 to learn the intended date that FDA will provide written comment on the submissions Corixa has made to the file since the last CR letter was issued in March 2002. She noted that Dr. George Mills had recently indicated that a letter would be forthcoming. I responded that I would have to check with the review team. The call concluded.

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

Memorandum

Date of Telecon: January 6, 2003

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: BLA 125011/0 file
Corixa Corporation
Tositumomab and iodine I 131 Tositumomab

Subject: November 14, 2002 Resubmission Acknowledgement Letter

PARTICIPANTS:
CBER/OTRR: Karen D. Jones, RPM, DARP

Corixa Corporation: Jill Henrich, Regulatory Affairs

Jill Henrich called on January 6, 2003 to inform me that Corixa has not yet received the hard copy of the November 14, 2002 Resubmisison Acknowledgement Letter. I agreed to send a second copy to her at the 600 Gateway Blvd., South San Francisco address. The call concluded.

RECORD OF TELEPHONE CONVERSATION: BLA 125011 Corixa Corp. BEXXAR

DATE: 11/19/02

PARTICIPANTS: FDA: Terrye Zaremba, Ph.D., DMA
Corixa: Jill Henrich, Mike Buckley, David Colcher
GSK: Marcia Frederici, Doug Nesta

PURPOSE: To request additional information regarding their Oct 30, 2002 submission to the BLA. The submission contained responses to CMC items 9 to 16 of the CBER CR letter dated March 12, 2002.

b(4)

Corixa indicated that while the 1st in Appendix A was from BI Pharma and the 2nd in Appendix C was from Corixa, the 2 should be identical.

b(4)

Corixa stated that they thought these errors were due to the translation from German. They will contact BI Pharma and have them modify the SOP to be the same as the SOP in Appendix C. They also agreed to

b(4)

In their response to item 9, Corixa indicated that the validation information and testing results for this method would be available upon inspection. However, I informed them that we probably will not do a PAI at BI Pharma since both biennial inspections in 2000 and 2002 were VAI & no major problems were found. We would inspect them only if we suspected that there were problems with their manufacturing & controls. Therefore, Corixa will need to submit this information to their BLA as soon as it is available. This also applies to the SDS-PAGE silver staining method, which was also to be available at the time of inspection.

b(4)

Corixa stated that they will obtain data during stability studies for these tests so that they can set specifications.

Corixa agreed to provide time-lines for data submission and will submit a copy of the corrected SOP for BI Pharma to CBER for review prior to beginning the testing. They hope to provide all of the data by March 2003.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

NOV 14 2002

Monica Krieger, Ph.D
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

We acknowledge receipt on October 31, 2002 of your October 30, 2002 resubmission to your license application for Tositumomab (B1) and Iodine-131-Tositumomab (Bexxar®).

This resubmission contains chemistry, manufacturing and control information (responses to items 9-19 of the March 12, 2002 complete response letter) and cross references the September 5, 2002 amendment requesting that the complete response be submitted in two parts and the October 4, 2002 amendment containing clinical information (responses to items 1-8), submitted in response to our March 12, 2002 complete response letter.

We consider this October 30, 2002 submission, together with the September 5, 2002 and October 4, 2002 submissions, to be a complete, class 2 response to our action letter. CBER intends to review these submissions and take action on them by May 2, 2003.

If you have any questions, please contact the Regulatory Project Manager, Karen D. Jones, at (301) 827-5101.

Sincerely yours,

Carl Dyke

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

CONCURRENCE PAGE

cc: DARP BLA file, HFM-588
HFM-594/T.Zaremba
HFM-555/K.Webber

CBER:DARP:K.Jones:K.Townsend:11.13.2002:11.14.2002
(S:\Jonesk\125011-0 Tositumomab\ResubmissionAck)

COMMUNICATION TYPE:

LETTER: Resubmission Acknowledgment Letter (RAC)
Summary Text: Class 2 Resubmission (6 mos)

SS & RIS Data Check:
- **Communication**
- **Milestone: Receipt Date In Ltr. & Milestone (Response To CR) Should Match**

RIS Data Check:
- **Confirm New Action Due Date**

Division	Name/Signature	Date
OTRR/DARP	Karen D Jones	11/14/02
DARP	[signature]	11/14/02
DARP	Dge Ea Jones	11-14-02
DARP	Kelly Townsend	11-14-02

Memorandum

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

Date: November 14, 2002

To: File STN 125011/0

From: Deborah Trout, BLA Committee Member, HFM-675

Through: Cynthia Kelley, Branch Chief, Branch 1, HFM-675

Subject: Review of Complete Review Letter responses submitted October 30, 2002.

Question 16: The firm's response appears adequate. The firm has submitted two-years of accelerated aging and one year of real time data for package integrity of the ———— bags. The firm commits to submitting the two-year real time data, available December 2002.

b(4)

Question 17: The firm's response appears adequate. A r ———— limit of < — CFU/mL has been established for the intermediate drug product.

Question 18: The firm's response is incomplete. The firm plans to verify the sensitivity of the microbial challenge test by introducing capillaries specifically bored into the glass and stoppers thus introducing defects of known diameter. Using this approach, the sensitivity of the microbial test would be verified directly. The microbial challenge test would be performed at GSK laboratories using this method. The firm indicates results of this study would be available for review at the time of the pre-approval inspection. The microbial challenge test results should be submitted to file for review in that container closure integrity testing is a review issue as per our CMC guidance.

Question 19: The firm's response appears adequate.

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: November 8, 2002

From: Leon Epps
Regulatory Review Officer, DMA/OTRR

Subject: Review of Response Dated October 30, 2002 to Corixa Corporation's BLA (STN# 125011\0\046): BEXXAR™ (Tositumomab, Iodine I 131 Tositumomab) Complete Review Letter of March 12, 2002

To: File

Through: Patrick Swann 11-18-02

CC: Keith Webber
Terrye Zaremba
George Mills
Stephen Litwin
M. David Green
Satish Misra
Deborah Trout
Karen Jones

Comments on Responses to CR Letter: Questions 16 and 19 Answered

QUESTION 16
Your response to item 15 remains incomplete in that the one year real-time results of your package integrity study in support of a 2-year shelf life for ——— bags containing seals, which was slated for completion in December 2001, have not been submitted for review. Please submit the first year study results. If you wish to claim a 2-year shelf life, please submit real-time data to support this claim.

Company Response to Question 16

The package integrity study was initiated in December 2000 in support of a two-year shelf life. Table 1 contains the one-year and two-year accelerated aging and one year real time data for the [redacted] bags. Two-year real time data will be available in December 2002 and will be provided at that time. [redacted] Porosity testing was only performed at Time 0 as specified by the protocol.

COMMENT: Review of data supports the claim of package integrity and adequately addresses our concerns.

QUESTION 19

Please note that successful pre-license inspections of the following facilities are required prior to approval of this application: Corixa Corporation, located at South San Francisco, California; McKesson BioServices, located at Rockville, Maryland; and MDS Nordion, Inc., located at Kanata, Canada.

Company Response to Question 19

Pre-licensure inspection plans are noted and understood.

COMMENT: Corixa Corporation's response is adequate.

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

MEMORANDUM

Revision Date: October 22, 2002

Date: August 23, 2002

To: STN BL 125011/0 File

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

Subject: Meeting with Corixa Corporation to discuss the outstanding CMC issues from the March 12, 2002 complete review letter

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MEETING OBJECTIVE

The sponsor requested this meeting to discuss the chemistry, manufacturing and controls issues which were raised in the Center's March 12, 2002 complete review letter for the biologics license application for Tositumomab and Iodine-131-Tositumomab (Bexxar®).

DISCUSSION

The sponsor presented their proposed strategy for addressing the issues raised in the CR letter as shown in the attached slides and the briefing document.

[redacted] b(4)

1 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 22

Keith Sibbert, MDS Nordion
Kristina Kopp, BI Pharma KG
Uwe Buecheler, BI Pharma KG

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our Reference: BL 125011/0

OCT 29 2002

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger

Please refer to your September 13, 2002 submission to your biologics license application for Tositumomab (Anti B1) and Iodine-131-Tositumomab (Bexxar®) submitted under section 351 of the Public Health Service Act, regarding the August 23, 2002 meeting summary of the Type A meeting held on July 24, 2002 between representatives of your firm and this Agency. We have the following comment:

1. We have revised paragraph 8 of the DISCUSSION section of the August 23, 2002 meeting summary to clarify agreements regarding the SDS-PAGE silver staining method. This paragraph now states, "The sponsor agreed to redevelop the SDS-PAGE silver staining method to improve consistency and performance. [redacted] It was agreed that densitometric scanning of silver stained gels was not necessary." b(4)

In reviewing the meeting minutes, we have also made changes to paragraphs 2, 4, 5, and 7 to improve clarity. Please refer to the enclosed, revised meeting summary for these changes.

This supersedes the meeting summary provided to you on August 23, 2002. If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Karen D. Jones

Karen D. Jones
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Revised Meeting Summary: 10-22-02

CONCURRENCE PAGE

OTRR:DARP:K.Jones:10-22-02:K.Townsend:10.23.2002:10.29.2002
(S:\Jonesk\125011-0 Tositumomab/Ltr-Other-Revised Mtg Minutes-7-24-02.doc)

COMMUNICATION TYPE:
LETTER: OTHER (OT)
Summary Text: Revised summary for 7-24-02 meeting

SS Data Check:
- **Communication**

Division	Name/Signature	Date
DARP	Kelly Townsend	10/29/02

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

Memorandum

Date of Telecon: October 8, 2002

From: Karen D. Jones, CBER/OTRR/DARP, HFM-588

To: BLA 125011/0 file
Corixa Corporation
Tositumomab and iodine I 131 Tositumomab

Subject: Submission 043

PARTICIPANTS:
CBER/OTRR: Karen D. Jones, RPM, DARP

Corixa Corporation: Jill Henrich, Regulatory Affairs

Jill Henrich called on October 8, 2003 in reference to the BLA amendment submission (Corixa # 043) submitted September 5, 2002 requesting permission to submit the response to the March 12 CR letter in two parts. She noted that the first part was submitted October 4, 2003 containing the response to the clinical questions. The CMC response will be submitted at the end of October.
I noted that the October 4, 2002 submission will be characterized as an incomplete response to the complete response letter.
The call concluded.

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

MEMORANDUM

Date: **September 19, 2002**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Proprietary Name

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Monica Krieger

DISCUSSION:

I placed a call to Corixa and spoke with Monica Krieger regarding the proposed proprietary name Bexxar for the company's Tositumomab product, currently under BLA review. I informed her that Corixa should resubmit the formal request for proprietary name review, in accordance with SOPP 8061.4, 90-100 days prior to the action due date for the BLA for a final review. Dr. Krieger committed to resubmission of the request.

The call concluded.

Jones, Karen

From: Henrich, Jill [Jill_Henrich@corixa.com]
Sent: Friday, September 13, 2002 12:48 PM
To: Satish Misra (E-mail); Karen Jones (E-mail)
Subject: FW: Agenda for telecon 9/13 at 3:30PM EDT


Proposal for Integration of MP...


Dataset Questions for Dr. Misr...

I am forwarding this to you for today's teleconference (I didn't have your email addresses yesterday).

Regards,
Jill Henrich

> -----Original Message-----
> From: Henrich, Jill
> Sent: Thursday, September 12, 2002 10:51 PM
> To: George Mills (E-mail); Stephen Litwin (E-mail);
> 'misras@cber.fda.gov'
> Cc: Krieger, Monica; Jacobs, Cindy; Henrich, Jill
> Subject: Agenda for telecon 9/13 at 3:30PM EDT
>
> For the teleconference to be held tomorrow, attached please find a
> proposal for the integration of recently obtained MIRROR Panel data
> (Proposal for Integration of MP data.doc). In addition, I am also
> attaching a copy of the document that Stew Kroll sent to Dr. Misra on Wed.
> (9/11), clarifying items and requesting feedback (Dataset Questions for
> Dr. Misra.doc).
>
> After receiving feedback on the datasets to be submitted in support of the
> ISS from Dr. Misra tomorrow, we will formally submit all of the revised
> datasets in our response to the Complete Review letter (Questions 1-4
> regarding safety issues) (Item 11/CRT). We will not be resubmitting the
> updated ISS as part of this submission, but will incorporate it by
> reference as part of our response (as directed in the CR letter).
>
> The dial-in information is as follows:
> (877) 895-6183
> Part. code 754-5729
>
> We look forward to speaking with you at 3:30PM.
> Best Regards,
> Jill
>
> <<Proposal for Integration of MP data.doc>> <<Dataset Questions for Dr.
> Misra.doc>>

Dear Dr. Mills:

Preliminary results are available for the MIRROR panel review of 37 selected patients from Bexxar studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004 and CP-97-012 (MIRROR2 – carried out under new charter) and of 15 patients, whose outcomes were censored in the previous analysis, from CP-97-012 (MIRROR1 – carried out under the existing charter).

These reviews, in general, confirm the results of previous MIRROR reviews.

In the MIRROR2 review, thirty-three of thirty-seven long-term durable responder patients were determined to have a time to progression (TTP) of at least 12 months. One patient previously classified as a long-term durable responder was determined to have progressed prior to one year (Patient 012-037-004). The three remaining patients had no baseline 2 x 2 lesions and were not assessed for response under the MIRROR2 charter (see below).

In the CP-97-012 review, four patients who had censored times to progression of <12 months, now have times to progression of at least 12 months.

Three issues arose during the conduct of these MIRROR reviews. In order to complete the analyses and successfully integrate the new data into planned submissions we need clarity regarding the treatment of these three different situations:

1. Six patients had a locked Formal Joint Review Assessment (FJRA) of progressive disease (PD) which the reviewers later believed to be in error. The nature of the error was documented and the expert reviewers then classified the patient in response (partial response [PR] or clinical complete response [CCR]) at the later visits.

    - Patient 000-002-013: Declared as PD on study day 916 with a >25% increase in SPD based on density increase in lesion in the (R) external iliac lymph node chain. The lesion was previously noted to have cystic necrosis. Without additional treatment the lesion again became cystic. The MIRROR Panel classified the patient as a continued PR at later visits. Based on the later visits the revised TTP would be 1476 days.

    - Patient 000-002-020: Declared as PD on study day 530 with two intrathoracic lymph nodes noted – 2.5 x 2.0 cm and 2.0 x 1.1 cm. These findings were associated with "fuzzy" pulmonary infiltrates and bilateral pleural effusions. Relevant clinical history included cough and wheezing and cardiomyopathy documented with markedly diminished ejection fraction. The lymph nodes resolved. Subsequent Joint Review commentary indicates the most likely explanation for nodes was intercurrent infection. Without additional anti-lymphoma therapy, the patient was classified as a CCR at later visits. Based on the later visits the revised TTP would be 2917+ days.

- Patient 000-002-030: The patient was classified as PD on study day 1835 with a 3.5 x 2.6 cm lung lesion. Clinical history was consistent with pneumonia. The lung lesion resolved. Without additional anti-lymphoma therapy, the patient was classified as a CCR at later visits. Based on the later visits the revised TTP would be 2590+ days.

- Patient 000-002-059: The patient was classified as PD on study day 433 when a previously undetected lytic bone lesion in the (L) ilium was noted (4.0 x 2.0 cm). Without further therapy for lymphoma, the lesion became BDL x BDL over 2+ years. The patient was later assessed as CCR. Based on the later visits the revised TTP would be 2065+ days. Review of patient notes revealed an explanation for this unusual lesion. The patient was involved in a motor vehicle accident. He required stabilization of his thoracolumbar spine that was accomplished with rods and bone grafting. The donor site was the iliac wing, resulting in the CAT scan finding.

- Patient 001-007-002: The patient was classified as PD on study day 467 on the basis of an ill-defined inguinal mass. Biopsy was planned; however, no lesion could be defined for biopsy and later radiographs demonstrated no evidence of mass or lymphadenopathy. Without further anti-lymphoma therapy, the patient was classified as a CCR at later visits. Based on these later visits the revised TTP would be 1826+ days.

- Patient 001-008-001: Patient was classified as PD on study day 1757 based on inguinal lymphadenopathy and an occipital mass. A biopsy of the inguinal lymph node disclosed a reactive node without evidence of lymphoma. The occipital mass was never again mentioned. The patient was classified at the next visit as a CCR. Based on the later visit the revised TTP would be 1890+ days.

Corixa believes that in each of these cases, the clinical course and outcome of the patient are best described by the revised opinion of the independent experts. We propose that designations of PD, which were later believed by the independent experts to have been in error, be removed from the database and the subsequent assessments of response be used for the purposes of determining response and duration measures.

2. Three patients were considered not assessable by the MIRROR2 panel because, at baseline, they had no lesion greater than 4.0 cm^2 (2 x 2 cm). However, these patients conformed to the protocols' inclusion criteria in effect at the time of their enrollments. These protocols required only evaluable bi-dimensionally measurable disease.

   - Patient 001-005-008: Patient had bilateral cervical lymphadenopathy with palpable nodes measuring 2 x 1 cm, 1.5 x 1 cm, and 1 x 1 cm. At baseline the MIRROR Panel radiologist documented five evaluable lesions. All five

lesions became BDL at the first response assessment and remained BDL x BDL at the last assessment on study day 1079.

- Patient 002-011-009: Patient had documented rapidly enlarging inguinal adenopathy that was subjected to excisional biopsy prior to study entry. At the time of study entry the patient had a 2.5 x 2.0 cm submandibular lymph node on physical exam. At baseline the MIRROR Panel radiologist documented a 2.2 x 1.6 cm infraparotid lymph node mass and a jugular node of 1.4 x 0.8 cm. All lesions became BDL x BDL at the first response assessment and remained BDL x BDL at the last assessment on study day 370.

- Patient 002-011-915: Patient received Bexxar following documented progression (> 25% increase in SPD from nadir) on the tositumomab arm of Study RIT-II-002. At study re-entry (cross-over) the MIRROR Panel radiologist documented 10 lesions, the greatest of which was a 2.3 x 1.7 cm (L) supraclavicular node. All lesions became BDL x BDL at the first response assessment. Progression would be documented (based on new measurable disease) on study day 652.

Because these patients conformed to the entry criteria of the studies in which they participated, Corixa proposes that these patients remain in the populations described by the statistical analyses. We propose that the responses for these patients be classified as PR at the first visit for which all lesions were BDL, CCR if the lesions remained BDL for 6 months, and PD per charter definitions.

3. One patient (Patient 000-002-057) was called PD on study day 1284 on the basis of two lesions that changed from 0 x 0 to BDL x BDL. Per charter, this was PD. The initial radiology assessment was that this did not represent progression. A query has been generated. Over the ensuing two years, without additional therapy, these lesions never became measurable (i.e. ≥ 4.0 cm^2). Based on later visits the revised TTP would be 2004+ days.

Corixa proposes that this patient be reported with a TTP of 2004+ days.

Summary

The preliminary results of the recent MIRROR Panel re-review of selected durable responders confirmed, to a great extent, the results of the original MIRROR Panel reviews. Three issues were identified during the recent MIRROR panel reviews. Corixa seeks guidance regarding the integration of the recent MIRROR panel evaluations into the existing study-specific and subpopulation data sets. We propose that the recently acquired data (MIRROR2 and extended MIRROR1) be integrated into all analyses (Integrated Summary of Efficacy and revised Final Study Report for Study CP-

97-012 to be submitted October 7, 2002) using preferentially, where available, MIRROR2 data; and otherwise the results from MIRROR1 (extended, where available; then original).

MEMORANDUM OF TELECONFERENCE

DATE: September 13, 2002

FROM: Karen D. Jones
Regulatory Project Manager
CBER/OTRR/DARP

SUBJECT: Corixa Corporation
Tositumomab (Bexxar)
BLA, STN 125011/0
Updated Safety Information

PARTICIPANTS: CBER/OTRR: George Mills, Stephen Litwin, Satish Misra, Patricia Keegan, Karen D. Jones
OC/OSI: Patricia Delaney, Jennifer Petrie (student intern), Jennifer Legan (student intern)

Corixa Corporation: Jill Henrich, Stewart Kroll, Stanford Stewart, Cindy Jacobs, Patricia Stewart

GSK: Meg Martin

This teleconference was held in follow-up to the September 10, 2002 teleconference regarding the safety database for the BLA file. In preparation for the teleconference, the sponsor provided an email containing preliminary results available from the MIRROR2 panel review of 37 selected subjects from studies RIT-I-000, RIT-II-001, RIT-II-002, RIT-II-004 and CP-97-012 and of 15 subjects from CP-97-012 whose outcomes were censored in the previous analysis.

Discussion Issues:

1. **Dr. Keegan asked Corixa to explain why data from 77 subjects previously excluded from the safety database were not included in the sponsor's March 2002 safety update submission.**
   - Corixa: Safety data was submitted for 620 subjects in 12/01. An update for these subjects, as per previous agreement with FDA, was submitted in 03/02. Another update is scheduled for 3/03.
     - **CBER: The purpose of a safety update is to provide all information newly available since the last report. Generally, such submissions are expected quarterly. Corixa should submit an updated report of all adverse events reported through the closure of the expanded access trial. What is the number of subjects treated under expanded access?**

Action Item: Corixa will submit narrative summaries for each serious adverse event from the expanded access program, not previously reported, in their complete response to the CR letter in early October. The submission will be in the form of a narrative summary and will contain laboratory values. The number of subjects enrolled in the expanded access trial is between 750 and 800.

2. **Are the data from subjects enrolled on study RIT003 in the ISS or another database? Since a number of subjects from this trial have a unique HAMA profile, CBER would like to see that a dataset includes profiles of each subject registered.**
    - Corixa: The data for all of these subjects can be found in datasets associated with the individual study, but that data is not included in the ISS and ISE databases because of exclusion criteria. As agreed to during the 9/10/02 teleconference, single patients are not included in the ISE.

3. **Which dataset includes data from those subjects who did not receive study drug?**
    - Corixa: These subjects will be included in the revised ISS to be submitted in October 2002.

4. **Regarding demographics in the ISS, please employ numerous index variables.**
    - Corixa: Currently, there are 7 individual variables employed in the ISS dataset, but they will include others that CBER requests.

5. **Study 002 enrolled 78 subjects; of these, 19 were crossover subjects. Please provide a breakdown of the numbers of subjects that received "cold" product and "hot" product initially.**
    - Corixa: They will do so.

6. **Please include efficacy fields for confirmed response in the ptout database for purposes of comparison. Specifically, include MIRROR2 evaluation of confirmed response and confirmed duration of response.**
    - Corixa: They will do so.

Regarding Corixa's September 12, 2002 email:

CBER's responses:

Item #1: CBER agrees with Corixa's proposal, as per the recommendation of the independent experts, to remove the PD designation for 6 subjects that had a locked Formal Joint Review Assessment classification of progressive disease and to reassess them in terms of response and duration.

Item #2: CBER agrees that Corixa may continue to include the 3 subjects that MIRROR panel2 considered not assessable because these subjects conformed to the protocols' inclusion criteria at the time they were enrolled, but cautions that CBER is very concerned that these subjects may not have had truly refractory disease. If they are included, Corixa should also provide convincing evidence that these subjects did have progressive non-Hodgkin's lymphoma as opposed to an infection process at the time they were evaluated for enrollment, since the proposed indication is refractory disease.

- Corixa will re-evaluate these cases. If they decide to include them in the database, they will provide a defense as to why they are included.

Item #3: Regarding Corixa's proposal that subject 000-002-057 be reported as having a time to progression of 2004+ days, CBER will require that Corixa provide the radiologist's interpretation and will rely on that assessment.

Based on items 1-3 discussed above, the Long-Term Responder database will have a total of 78 subjects unless the 3 subjects in #2 above are deleted. Corixa should replace the original MIRROR panel data with the MIRROR2 panel data. Study 012 should be updated with MIRROR2 data also.

Please submit 1 revised efficacy database and 1 revised safety database.

- Corixa will lock the database On September 13-14, 2002 and will rerun all analyses in the ISE in order to include MIRROR2 data. The ISS cannot be revised in time to be submitted with their complete response. They hope to resubmit this information in January or February 2003. However, they will include the SAEs as previously discussed in the October resubmission.

Regarding logistics: The dataset should include one column with the initial assessment of duration of response and one column with the final (MIRROR2) assessment of duration of response. Case report forms should simply note further review results; original assessments should not be altered.

Corixa plans to submit the complete response on October 4, 2002 and is in preparation for the December ODAC meeting.

The call concluded.

Attachment: Corixa (Jill Henrich) email 9/12/02
9/24/02; finalized 10/7/02.

MEMORANDUM OF TELECONFERENCE

DATE: September 10, 2002

FROM: Karen D. Jones
Regulatory Project Manager
CBER/OTRR/DARP

SUBJECT: Corixa Corporation
Tositumomab (Bexxar)
BLA, STN 125011/0
Updated Safety Information

PARTICIPANTS: CBER/OTRR: George Mills, M.D., Stephen Litwin, M.D., Ghanshyam Gupta, Ph.D., Satish Misra, Ph.D., Karen D. JonesDARP

Corixa Corporation: Jill Henrich, Stewart Kroll, Stanford Stewart, Cindy Jacobs, Patricia Stewart

GSK: Meg Martin, Michael Hamilton, Jean Viallet

FDA requested this teleconference to discuss updating of the safety database for the BLA file.

1. Regarding the ISE, CBER asked the sponsor to explain why (a) one patient with Mantle Cell NHL in the study RIT-II-004 was excluded from the safety database, and why (b) the safety database also excludes 77 patients on Expanded Access Study (CP-98-020) due to less than 13 weeks of follow-up as of the data cutoff date of August 31, 2001. Since the last data cutoff date, more than a year has elapsed and these patients should have adequate follow-up to be included in both the safety and efficacy database. It is CBER's expectation that additional follow-up data should be available to be included in the safety evaluation.
   - Corixa Response: (a)The mantle cell patient was excluded based upon a previous discussion with CBER (b) The intent is to use the March 2002 safety database as the basis for the appeal that is to be heard at the December ODAC meeting. The next planned safety update is March 2003 with an additional 77 subjects. Information has been collected since March 2002, but is not yet integrated into the database.
     - ACTION ITEM: CBER will discuss this further internally and then respond to the sponsor. For now, the sponsor should proceed as they have planned.

2. CBER also commented that the July 2 dataset was well organized. CBER asked for clarification of the number of subjects included in this dataset: is it 307, 303 or 250? What is the number of subjects in the effoutm dataset?

- Corixa Response: The total number of subjects is N=303 from studies 000, 001, 002, 004 and 0012. The integrated efficacy population number is N=250. The sponsor will have to check the number for effoutm.
    - ACTION ITEM: Provide a dataset that begins with 303 (or 307, as some of the data indicates) so that CBER reviewers can analyze the data, working back to 250. The responses by the independent panel should be included for the statisticians to work with as well. Use indicator variables to identify patients with MIRROR evaluation. Also include the mCi dose administered to each subject as a variable in the ptout dataset. Corixa will include other variables that CBER requests.

3. Regarding the ISS database, CBER would like Corixa to provide baseline demographic prognostic factors for all subjects.
    - Corixa Response: They have provided the progout dataset which had all prognostic factors and some demographic variables.
        - ACTION ITEM: At CBER's request Corixa will provide to Dr. Misra (ASAP via email) a similar dataset for the 754 subjects from studies 000, 001, 002, 004, 012, 98-020 and single patients with proper indicator variables to identify ISS, ISE, etc.

4. CBER inquired as to how the independent re-read is proceeding.
    - Corixa Response: The plan is to freeze the database by the close of this week. The reviews are completed and the analysis is in the query stage. The question is how to integrate this with the original datasets because the definition of response is different and there is also concern about PD.
        - ACTION ITEM: Please propose within 1-2 days how the independent analysis may be integrated into the original dataset; then CBER can provide comment. CBER is prepared to work with Corixa on the PD question. CR and CCR can be grouped together because the differences between those two in this case are small. Other minor issues can be dealt with on a subject-by-subject basis.

5. CBER asked Corixa to resubmit the July 2, 2002 ISS dataset for all 754 subjects with additional indicator variables.
    - Corixa Response: They will resubmit all datasets.

6. For ptout and progout datasets, please break down the maximum unidimensional lesion as measured in cm at baseline variable into 4 groups:
   0 to <5, 5 to <7, 7 to <10 and $\geq$10
    - Corixa Response: They will do as requested.

CBER asked that the information requested above be submitted via email to Dr. Misra and also be included in the October resubmission. It was agreed to further discuss this data during a follow-up discussion later in the week.

The call concluded.

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

MEMORANDUM

Date: **September 6, 2002**

To: STN BL 125011/0 File

From: Karen D. Jones, Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics Research and Review

Subject: Preparation for 9/10/02 Teleconference

Participants: **FDA/CBER/OTRR**: Karen D. Jones
Corixa: Jill Henrich

DISCUSSION:

A brief discussion was held with Jill Henrich of Corixa regarding the Corixa BLA STN 125011/0 and the teleconference scheduled for September 10, 2002 in order to discuss an updated safety database. Ms. Henrich mentioned that Corixa has just submitted an amendment to the BLA on September 5, 2002 that contains several proposals regarding how to move forward with the BLA review as well as a request to discuss outstanding issues. Ms. Henrich asked if the FDA is planning to discuss this submission during the September 10 telephone call. I responded that it is likely that the reviewers have not yet had an opportunity to review the September 5, submission and thus, it is not likely to be an agenda item for the Tuesday teleconference.

The call concluded.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

AUG 23 2002

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

Please refer to your **Biologics License Application (BLA)** for Tositumomab and Iodine-131-Tositumomab and to the meeting held on July 24, 2002, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Michael A. Noska, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Meeting Summary

CONCURRENCE PAGE

OTRR:DARP:Noska:8-20-02:K.Townsend:8.22.2002
(S:\Noska\Letters\License\MS_Corixa_7-24-02.doc)

MEETING SUMMARY ENCLOSED (MS)

Division	Name/Signature	Date
DARP	Michael C. Noska	8/23/02
DARP	K. Townsend	8/27/02

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

MEMORANDUM

Date: August 15, 2002

To: STN BL 125011/0 File

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

Subject: Return of CT films to Corixa Corporation

The purpose of this memorandum is to document the return of archival CT scans related to the BLA for Iodine-131-Tositumomab (Bexxar) to Corixa Corporation (STN BL 125011/0). The contents of each box was confirmed against the list provided in Item 20 of the original submission.

I acknowledge receipt of all CT films related to STN BL 125011/0.

Jill Henrich
Corixa Corporation

I acknowledge the return of all CT films related to STN BL 125011/0.

Michael A. Noska
Regulatory Project Manager
CBER/OTRR/DARP

Jules Meisler
Supervisor
CBER Document Control Center

Noska, Michael

From: Siegel, Jay
Sent: Thursday, August 01, 2002 3:41 PM
To: Keegan, Patricia; Mills, George; Noska, Michael; Risso, Sharon; Webber, Keith
Cc: Lard, Sherry
Subject: Telecon with Steve Gillis, Corixa

August 1, 3:15 p.m., initiated by Jay Siegel, in response to a call from Dr. Gillis on July 29.

Dr. Gillis expressed his understanding of the current situation. Given that Dr. Mills has ongoing requests and Corixa wishes to respond, Corixa would prefer to go to ODAC in December than in September with areas of disagreement. Corixa does not want to withdraw their dispute resolution request for fear they would not wind up at ODAC at all this year.

I explained that the materials submitted to date and those to come might constitute a CR and we could then go to ODAC without a dispute. He expressed concern that they might not constitute a CR, especially since our letter requested additional clinical studies.

I also noted that the indication for rituxan refractory patients was not, in my mind, a matter of dispute as it had not been requested nor rejected. He understood and also understood that the rituxan-refractory indication for Zevalin was not an accelerated approval.

I reassured him that, while nothing was scheduled nor should be announced, I felt strongly, given the Corixa decision not to go in September, this product should come to ODAC in December, one way or the other. I suggested that we keep open the dispute resolution, but, if CBER determined that a CR had been received, we would contact Corixa and decide together whether to change the December ODAC discussion to a routine consultation rather than a dispute resolution. He was happy with this course of action and said his staff would be pleased.

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

MEMORANDUM

Date: July 31, 2002

To: STN BL 125011/0 File

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

Subject: Teleconference with Corixa Corporation to discuss the status of dispute resolution and presentation to the Oncologic Drugs Advisory Committee

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DISCUSSION

Corixa opened the discussion by reporting that Mr. Gillis of Corixa had spoken with Ms. Sharon Risso of CBER and planned to follow up with Dr. Jay Siegel to discuss a potential third option for proceeding with the BLA which is to move toward a December 2002 ODAC meeting under the paradigm of dispute resolution. If this is not acceptable, they would likely proceed to the September 2002 ODAC meeting with information they submit by the August 1st cutoff.

Dr. Mills then provided descriptions of several of the discrepancies he had noted to date in his review of the long term responder dataset. Dr. Mills pointed out that, as noted in a footnote to Table B, the data from many patients do not include the MIRROR panel evaluation on the primary assessment (i.e., baseline) and are based only on investigator-assessed responses, including two investigators who are conflicted due to patent involvement. Corixa responded that this footnote only applied to duration-of-response assessments, however, Dr. Mills pointed out that all data need to be reviewed by the independent panel. Corixa stated that they apparently misunderstood CBER's request for the MIRROR panel to evaluate the last two timepoints for long term durable response. Dr. Mills pointed out that this assessment was needed for proof-of-concept but that the MIRROR panel needed to evaluate all timepoints, as per the protocol, due to the long time course of follow up and variations in the disease over time. Corixa noted that all timepoints were assessed by the investigators.

Dr. Mills then provided examples from long term follow-up contact forms which showed that some only referenced telephone contacts with family members of patients without any physical exam while others contained unclear information as to the nature of the follow-up. Corixa suggested that it would be more appropriate to look at case report forms (CRFs) for follow-up information.

Corixa stated that it does not appear that they could submit the necessary information to correct the database in time for the September ODAC meeting, however, they would still continue to provide information to support the analysis of the 75 patients as proof of long term response with Bexxar beyond 12 months. Corixa noted that they had audited the sites for all 75 patients including CRFs and would be able to provide source documentation which would include copies of original notes from the sites but would not include original CRFs. Dr. Mills asked if the company had audited the sites for conformance to eligibility criteria, to which Corixa replied that they had. However, Dr. Mills provided examples where patients did not seem to meet the entrance criteria for bone marrow cellularity.

Dr. Mills provided another example of an inconsistency with the MIRROR panel assessment vis-à-vis their charter, where a new lesion was apparently identified which hadn't been previously imaged, which forced an assessment of disease progression, although the patient was listed as a responder. (George, is this a correct description??)

Dr. Mills stated that CBER does not want to discourage Corixa from pursuing this application, but feels that it is important to point out that the data need to be reconciled. Dr. Mills also stated that he believed the data could be cleaned up over time.

Corixa stated that they wish to continue working with the Center to improve the database and move forward toward approval.

On another related item, Corixa asked for guidance on the timing of submission of their –049 Phase 3 trial, which CBER asked them to submit as a Special Protocol. Dr. Mills recommended that the company submit it before the ODAC meeting. Corixa indicated that they plan to submit the protocol in the second or third week of August.

The call was concluded with an agreement that Dr. Mills would contact Mr. Kroll to discuss further issues with the database.

Participants:

Agency	Sponsor
George Mills, CBER/OTRR/DCTDA	Monica Krieger, Corixa
Stephen Litwin, CBER/OTRR/DCTDA	Jill Henrich, Corixa
Michael Noska, CBER/OTRR/DARP	Cindy Jacobs, Corixa
	Stewart Kroll, Corixa
	Stanford Stewart, Corixa

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

MEMORANDUM

Date: July 26, 2002

To: STN BL 125011/0 File

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

Subject: Teleconference with Corixa Corporation to discuss the status of dispute resolution and presentation to the Oncologic Drugs Advisory Committee

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DISCUSSION

As a follow-up to previous discussions on July 19 and July 23, 2002, Dr. Keegan presented Corixa with two options for proceeding with the BLA for Bexxar® (Iodine-131-Tositumomab). The first option would be to continue with the request for dispute resolution and proceed to the September 2002 meeting of the Oncologic Drugs Advisory Committee (ODAC) with data submitted to CBER through July 12, 2002 plus any other supportive information that had been requested by Dr. George Mills, to be submitted by August 1, 2002. The second option would be to withdraw the request for dispute resolution and proceed on the basis of a response to CBER's March 12, 2002 complete response letter. The second option would allow for the submission of additional information with the goal of a possible December 2002 ODAC presentation. Since the Federal Register notice for the September meeting must issue soon, a decision is needed from Corixa by next week as to which way they wish to proceed.

Corixa stated that they would prefer to resolve the issues on all 75 patients in the database for long term responders and acknowledged that this would be difficult to do by August 1st. Corixa asked whether the September ODAC meeting is the only option under dispute resolution. Dr. Keegan responded that this would be the only option as the Center's actions could be called into question if the dispute resolution was allowed to linger without timely resolution. Corixa asked whether they could still submit additional information to the BLA if they chose to respond to the complete response letter. Dr. Keegan replied that they could submit additional supportive information. Corixa inquired as to what assurances there would be that Option 2 would lead to a December 2002 ODAC meeting. Dr. Keegan responded that it is not possible to give 100 percent assurance but that the review team should be able to ascertain the completeness and validity of the data in time to make a decision about the December ODAC.

Corixa asked whether they could receive any feedback on the review performed by Dr. Mills to this point on 35 patients. Dr. Keegan replied that Dr. Mills could provide some feedback when he returns to the office on Monday, July 29; however, it was emphasized that all 75 patients had not been reviewed and that there was further review needed for the 35 patients referred to above. (Dr. Keegan later provided a few examples of some discrepancies in the data which had been noted by Dr. Mills.)

Drs. Litwin and Keegan commented that it is hoped that only supportive data, but no new information, will be submitted to the BLA so that holes in the current database can be filled and review issues can be resolved.

Representatives of Corixa stated that they will need to discuss this decision with the managements of Corixa and Glaxo SmithKline before committing to a path.

Dr. Keegan reiterated that CBER cannot commit to a December 2002 ODAC meeting but that the team should have all the information necessary to complete the review in time for that meeting.

Participants:

Agency	Sponsor
Patricia Keegan, CBER/OTRR/DCTDA	Monica Krieger, Corixa
Stephen Litwin, CBER/OTRR/DCTDA	Jill Henrich, Corixa
Michael Noska, CBER/OTRR/DARP	Cindy Jacobs, Corixa

Final

RECORD OF TELEPHONE CONVERSATION - CORIXA CORP - BEXXAR

DATE: July 11, 2002

PARTICIPANTS:

CBER: Terrye Zaremba, Leon Epps, Keith Webber

Corixa: Jill Henrich, Monica Krieger, Mike Buckley, Patrick Navarre, Jon Demarest, Beth Keij, Bill Pfeffer

Nordion: Bonnie Hamilton, Susan Dew

PURPOSE: To discuss Corixa's June 28th submission to their BLA for BEXXAR regarding the out of specification (OOS) result obtained in February 2002 for povidone (PVP) concentration in the final radiolabeled product.

SUMMARY: The OOS result appeared to be due to the use of a different lot of PVP b(4) for the standards. However, while investigating this result, Corixa determined that the RP-HPLC method they have been using to measure PVP was actually measuring [redacted], a normally occurring contaminant. Included in the June 28th submission was a draft validation for a new method using SEC-HPLC. However, they need to have a formal validation at MDS Nordion. They would like to treat some patients in July and August who are still undergoing therapy, prior to completion of the validation.

POINTS DISCUSSED:

1. The OOS result obtained in February gave the value of 15.9% (instead of 5-6%), however they said this was actually do to an anomalously low value for the standard, not a true high value in the sample. b(4)

2. The RP-HPLC method apparently only measures the [redacted] due to the use of a [redacted]

3. The PVP [redacted] of the stock concentrate solution of PVP.

4. [redacted]. The final concentration is [redacted] PVP. The stock solution may be stored up to 10 days at 2-8°C. The stock solution is prepared on a weight per volume basis and analyzed by OD.

b(4)

5. The Certificates of Analysis for PVP from their supplier, ISP, indicated that the level of [redacted] is [redacted] %. The SEC-HPLC chromatograms submitted for the PVP solution also showed the level of [redacted] to be [redacted] %, suggesting that this detection method is working.

6. The OOS lot was retested using the same lot of PVP for the standard curve and a value of [redacted] % was obtained for the PVP concentration. Therefore, it appeared that the lot used for the standard curve had less [redacted] than the lot used for formulation. The [redacted] has a much higher extinction coefficient than PVP, so a small increase in [redacted] in the formulation could lead to this OOS result. b(4)
However, they will need to examine the Certificates of Analysis for the different lots of PVP.

7. They do have some retain samples of the product lot tested in February and CBER encouraged them to analyze this by their new SEC-HPLC method. They agreed to do this, but the [redacted] it is not clear what the result will be. Corixa is looking into a comparison of the two different assay methods using a number of retain samples from MDS Nordion.

8. After Corixa qualifies the new assay, CBER suggested that they check to be sure the PVP concentration doesn't change over the period of time the dosimetric samples are stored.

9. Corixa should submit the details of their re-analysis of the OOS result ASAP. We will have a discussion with the clinical group to determine if patients can be treated as requested and if additional concerns need to be addressed. We will get back to Corixa after this discussion.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

JUN 2 6 2002

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

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

I have completed my review of your Formal Dispute Resolution Request submitted May 31, 2002. I grant your request to present your BLA at an Oncologic Drugs Advisory Committee (ODAC). The timing of the presentation at the ODAC meeting will be dependent upon the timing of the receipt of the information requested in items 1-3 and responses to items 4 and 5 of our letter to you dated May 13, 2002. You have indicated that you will submit a complete response to the May 13, 2002 letter no later than July 3, 2002. If you submit a complete response by this date, it is highly likely that there will be adequate time for review and preparation of materials needed for the September 24, 2002 ODAC meeting.

Should you need additional information or have any questions concerning administrative or procedural matters please do not hesitate to contact the Regulatory Project Manager, Mr. Michael Noska, at 301-827-5115 or the Dispute Resolution Project Manager, Dr. Sherry Lard, at (301) 827-0379.

Sincerely yours,

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

cc: Sherry Lard, Ph.D., Associate Director for Quality Assurance

CONCURRENCE PAGE

cc: HFM-1/K.Zoon
HFM-4/H.Balick
HFM-500/S.Risso
HFM-500/P.Bishop
HFM-585/G.Jones
HFM-585/E.Dye
HFM-588/M.Noska
HFM-570/K.Weiss
HFM-570/P.Keegan
HFM-573/G.Mills
HFM-573/S.Litwin
HFM-555/K.Webber
HFM-596/T.Zaremba
HFM-675/J.Eltermann
HFM-675/C.Kelley
HFM-650/E.Cole
HFM-650/M.Andrich

CBER:DARP:M.Noska:6-25-02:Townsend:6.26.2002
(S:\Noska\Letters\License\Disp_Res_Corixa.doc)

COMMUNICATION TYPE:
LETTER: Other – Dispute Resolution

SS Data Check:
- **Communication**

Division	Name/Signature	Date
HFM-500	[signature]	6/26/02
DARP	[signature]	6/27/02

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our Reference: BL 125011/0

MAY 24 2002

Corixa Corporation
Attention: Monica S. Krieger, Ph.D.
Vice President, Regulatory Affairs
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

Please refer to your **Biologics License Application (BLA)** for Tositumomab and to the meeting held on April 24, 2002, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact Mr. Michael Noska at (301) 827-5101.

Sincerely yours,

Sharon Sickafuse

Sharon Sickafuse, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Meeting Summary

OTRR:DARP:Sickafuse:5-20-02:BARNES:5/20/02
(S:\Sickafuse\letters\ms\Corixa.doc)

MEETING SUMMARY ENCLOSED (MS)

Division	Name/Signature	Date
DARP	Sickafuse	5-24-02
DARP	JMDixon	5-24-02

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

Memorandum

Date: May 24, 2002 SKS

From: Sharon Sickafuse, Regulatory Project Manger, DARP/OTRR

Subject: April 24, 2002, meeting regarding Tositumomab (Bexxar) for the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD20 positive B-cell non-Hodgkin's lymphma

To: STN 125011/0
Attendees

The purpose of this meeting was to discuss clinical issues related to the March 12, 2002, complete response letter.

Sponsor's List of Questions/Issues

1. Corixa stated that they believe that Bexxar merits accelerated approval based on identification of several subjects with durable long-term responses (up to 8+ years). Corixa reviewed information on subjects with durable responses and on the progression-free survival (PFS) of subjects enrolled in clinical studies of Bexxar.

   CBER stated that they were not convinced that the current Bexxar data submitted tothe BLA meets the criteria for accelerated approval. Dr. Keegan noted that there are no data within the BLA to support statements that Bexxar is superior to Zevalin regarding more durable responses. Corixa agreed that the application lacks data to support statements of superiority. In this regard, it was agreed that it is not known at this time how durable the responses will be for Zevalin because there are only 2 year data available on Zevalin. Corixa also confirmed that there was no discrete, separate dataset of long-term responders in the BLA.

   In support of their request for accelerated approval based on long-term responses, Corixa presented PFS curves during the meeting. These data were included in the pre-meeting package in the section highlighting analyses of durable responses. CBER noted that the population from which the PFS curves was generated was not clearly documented in the pre-meeting package. During the meeting, Corixa clarified that these curves represented all patients in the studies and not just responding subjects. Because improved PFS (or the presence of a "tail" on the PFS curves) was not identified prior to the meeting or in the questions presented as a potential measure of benefit, CBER stated that they were not prepared to provide comment on the acceptability of any effects on PFS based on these data. CBER committed to providing advice after further consideration of the matter.

   After Corixa's presentation of the PFS curves, Dr. Siegel asked Corixa if they have data that demonstrated that patients with stable disease for 8-10 years were outside the expected range based on the natural history of the disease. Corixa replied that only single center trials have been conducted and reported in the medical literature and no randomized trials have been done to collect these data. Dr. Siegel inquired if it is

unusual for 15-20% of the patient population to be progression free after 5 years. [redacted] (Corixa consultant) replied that it is unusual because these patients typically would have undergone 4 or 5 previous therapies in the same time period.

Dr. Keegan raised the concern that in a single arm study, as opposed to controlled clinical trials, one cannot isolate the contribution of Bexxar to PFS because there is no control for unique biologic characteristics that would lead to an unusually favorable clinical course i.e., different from what would normally be expected. CBER noted that without a controlled study arm, it would be very difficult to distinguish between patients with an atypical or indolent course and the true effect of Bexxar.

b(4)

[redacted] Corixa consultant) noted that the responding patients had been closely followed. Corixa clarified that in studies 000 and 001, patients who had not progressed were followed every 6 months by CT scans. CBER noted in our review of the BLA, that Corixa had submitted case report forms in which the physician investigator appeared to be confirming response in many cases through telephone contact with the patients only, rather than through regular patient clinic visits and radiographic studies reviewed by the study investigators. Furthermore, Dr. Mills noted that the CT scan assessments of response in some subjects were conducted at significantly longer intervals than 6 months. Corixa confirmed that CT assessments in some subjects were not completed at the stated 6 month intervals. Instead, if a subject was reported as a long term responder, the subject was re-assessed at one or two additional timepoints.

2. In response to Corixa's request to have their Bexxar BLA presented to FDA's Oncologic Drugs Advisory Committee (ODAC), Dr. Siegel said that Corixa may request an opportunity to present their data before ODAC as part of an appeal under FDA's dispute resolution. CBER would also present their assessment of the BLA to ODAC including the fact that additional studies are needed. Dr. Siegel stated that CBER would get back to the sponsor within a month regarding the path they would need to take in order to present to ODAC.

   A proposed randomized controlled study design in 280 patients comparing Bexxar to Zevalin and intended to demonstrate that the over-all response rate (ORR) to Bexxar is non-inferior to the ORR to Zevalin while resulting in a 20% lower incidence of hematologic toxicity as compared to Zevalin, was discussed. CBER stated that demonstrating an improved safety profile with comparable efficacy would be sufficient to show a meaningful therapeutic advance, noting that the proposed trial would also need to assess the impact on PFS, time-to-progression, and over-all survival. To be eligible for this trial, Corixa proposed that patients would have to have had at least one prior therapy, but not more than two prior therapies and that one of the prior therapies could be Rituxan.

3. The Integrated Summary of Safety (ISS) submitted on March 4, 2002, has reduced some of CBER's uncertainty about the safety data. CBER noted there was some additional data for the common toxicities of hypothyroidism, development of HAMA, and cytopenia. Nonetheless, there is still a large amount of missing safety data. Because of missing data, CBER will have to rely on imputations for missing safety datapoints in generating incidence and time-to-event information for the package insert.

4. Corixa had previously provided information on the clinical comparability of Tositumomab produced by three different manufacturers (study RIT-II-003). Are these data adequate to demonstrate clinical comparability?

   CBER noted that the three different antibody products produced by Coulter, Lonza and BI Pharma are biochemically nonidentical; however, pharmacokinetics (PK), and biodistribution are comparable. In addition, the clinical activity, safety data, and incidence of HAMA are similar. Therefore, CBER concluded that the products are not biochemically comparable, but based on comparability in PK and biodistribution, as well as the lack of clinically important differences in the outcomes of the clinical studies, CBER will accept data from clinical studies using the Coulter and Lonza manufactured material in support of the licensure of the BI Pharm manufactured material.

   CBER also advised Corixa to improve the potency assay.

5. Regarding protocol CCBXO01-048 "A Multi-Center, Randomized, Bioequivalence Study of Tellurium-Derived vs. Fission-Derived Iodine I 131 Tositumomab for Patients with Relapsed, Refractory Low-Grade Non-Hodgkin's Lymphoma", the sponsor stated that some of the clinical sites are having difficulties with scanning the patient at the protocol specified rate of 10 cm/min. (This rate is the same rate that was used in the Zevalin trials). Dr. Mills asked Corixa to submit an outline of their issues and concerns on this matter. He would then be happy to have a telephone conference to discuss them.

Attendees

Center for Biologics Evaluation and Research

Office of Therapeutics Research and Review
Jay Siegel, M.D.

Division of Application Review and Policy
Wendy Aaronson, M.S.
Earl Dye, Ph.D.
Sharon Sickafuse, M.S.

Division of Clinical Trial Design and Analysis
Philippe Bishop, M.D.
Susan Jerian, M.D.
Patricia Keegan, M.D.
Stephen Litwin, M.D.
George Mills, M.D.
Karen Weiss, M.D.

Division of Monoclonal Antibodies
Keith Webber, Ph.D.
Terrye Zaremba, Ph.D.

Office of Biostatistics and Epidemiology

Division of Biostatistics
Peter Lachenbruch, Ph.D.
Ghanshyam Gupta, Ph.D.
Satish Misra, Ph.D.

Office of Special Health Issues
Patty Delaney

Corixa Corporation
Jill Henrich, Director, Regulatory Affairs
Steve Gilllis, CEO
Cindy Jacobs, Senior Vice President, Clinical Research

Steward Kroll, Director, Biostatistics
Monica Kreiger, Vice President, Regulatory Affairs
Stanford Stewart, Senior Medical Director, Clinical Research

GlaxoSmithKline
J. Michael Hamilton, Group Director, Biologics
Meg Martin, Director, Regulatory Affairs - Oncology
Jean Viallet, Head Oncology, Biologics

Consultants b(4)

5-9-02; finalized 5-24-02

MEETING ATTENDANCE LIST

Meeting between Corixa and the

Center for Biologics Evaluation and Research.

DATE: 4-24-02 Time: _____ Room: _____

NAME Please Print	AFFILIATION
x Sharon Sickafuse	OTRR/DARP
x Patricia Keegan	CBER/OTRR/DCTDA
x Jill Henrich	Corixa
x Terry G. Zaremba	CBER/DMA
x Ghanshyam Gupta	CBER/OBE/DB
x Monica Krieger	Corixa
x Keith Webber	DMA/OTRR/CBER
x Peter A Lachenbruch	CBER/OBE/DB
x Stephen Kitwin	CBER/DCTDA
x STANFORD STEWART	CORIXA
x Stewart M. Knoll	CORIXA
x Cindy Jacobs	Corixa
x Steve Gillis	CORIXA
x	
x	
x [redacted]	CBER/OTRR/DCTDA
x Wendy Aaronson	OTRR/DARP
x EARL Dye	OTRR/DARP
x Susan Jenion	OTRR/DCTDA
x Philippe Bishop	CBER/OTRR
x J. MICHAEL HAMILTON	GLAXO SMITH KLINE
x Satish C. Misra	OBE/DB
x Karen Weiss	OTRR/DCTDA
x MEG MARTIN	GSK REG. AFF. ONCO
x JEAN VIALLET	GSK CLINICAL DEVELOPMENT

b(4)

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

MAY 13 2002

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application (BLA) for Tositumomab and Iodine-131-Tositumomab (Bexxar™) submitted under Section 351 of the Public Health Service Act. Reference is made to the meeting with representatives of Corixa and Glaxo-Smith-Kline (GSK) on April 24, 2002, and to our official summary of that meeting which will be provided at a later date under separate cover. We have the following additional comments on the information presented at the meeting and in your briefing materials.

During the April 24, 2002 meeting, you requested that the Agency schedule your BLA for presentation at the Oncologic Drugs Advisory Committee (ODAC). This request was based upon your belief that your application meets the criteria for accelerated approval. Specifically, you stated in the pre-meeting materials that "Bexxar therapy produces a significant and unprecedented number of long-term complete responses extending up to 8 years in patients with multiply relapsed or refractory low-grade non-Hodgkin's lymphoma (NHL) with or without transformation. Corixa/GSK believe that accelerated approval is appropriate based on these data...Neither rituximab nor Yttrium-90 ibritumomab tiuxetan have demonstrated the ability to produce these long-term durable responses."

Having considered data in your BLA and the discussions of April 24, 2002, we do not believe that you have convincingly demonstrated that Bexxar provides meaningful therapeutic benefit over existing treatments for patients with relapsed or refractory low-grade NHL with or without transformation. A demonstration of meaningful therapeutic benefit would require comparing Bexxar in adequate and well-controlled trials to existing treatments. As previously stated in our Complete Response letters, you are advised to begin such randomized, controlled trials.

In the absence of controlled trials against existing therapy, you would need to rely on retrospectively identified external control groups. This approach is not recommended since it is always difficult, and in many cases impossible, to establish comparability of the treatment and control groups. Such controls are generally acceptable only when the effect of the treatment is dramatic, the usual course of disease is highly predictable, the endpoints are objective and the impact of baseline and treatment variables on the endpoint are well-characterized. We do not believe that the clinical setting of relapsed or refractory low-grade NHL is sufficiently predictable nor that the baseline variables are sufficiently well-

characterized to provide convincing evidence in the absence of a concurrently controlled clinical trial.

While it is FDA's position that additional adequate and controlled clinical trials are necessary to support the safety and efficacy of Bexxar, the agency offers mechanisms for addressing scientific disputes. During the April 24, 2002 meeting, the dispute resolution process was briefly discussed. Under this process, you may submit a written request to appeal our position and to request a presentation of your data to FDA's scientific advisers, the Oncologic Drugs Advisory Committee. Among other things, the request should summarize the basis for your appeal and your proposal to address the issues outlined above. Because all Agency decisions on the matter must be based on information in your BLA, no new information should be submitted as part of a request for reconsideration or appeal. If you have new information that may affect the original decision, any appeal should be deferred and the new information should be submitted and reviewed as an amendment to the BLA. Please refer to the February 2000 FDA Guidance for Industry "Formal Dispute Resolution: Appeals Above the Division Level," available at http://www.fda.gov/cber/gdlns/dispute.pdf, for information regarding the content and submission of an appeal. If your appeal is granted, the timing of an advisory committee hearing would be dependent upon the nature and timing of receipt of additional information in the BLA, as discussed below. That additional information must be submitted with sufficient time for FDA review and preparation of a briefing document for disclosure prior to an advisory committee.

Please note that the information requested below should not be provided as part of an appeal, but should be promptly submitted to the BLA if your appeal is granted.

1. At the meeting of April 24, 2002, you presented data on durable response, complete response and progression-free survival (PFS). It is necessary to clarify the meaningful therapeutic benefit(s) that you believe is/are attributable to Bexxar. If you believe that durable responses in retrospectively selected case reports from selected studies can meet the regulatory standards for meaningful therapeutic benefit, you must provide additional information about the patient subset and the population from which these data are drawn. Specifically needed are the criteria used to define this patient subset, a listing of all subjects (by unique patient identifier), descriptive statistics for baseline characteristics including all relevant prognostic factors, and a copy of all case report forms (CRFs) not previously submitted. Please provide an integrated summary of efficacy in a suitable format, based upon uniform criteria for response and for duration of response and include a clearly marked set of response assessments by investigators for all subjects and, as a separate component, the response assessments performed by the independent committee for selected studies.

2. If you believe that meaningful therapeutic benefit is limited to patients with durable complete responses, please provide your rationale for excluding subjects with durable

partial responses, since there is no evidence that complete responses to treatment prolong survival or result in cures. You may also provide data on the subset of patients with durable complete responses as an additional patient subset.

3. It is necessary for you to provide information on external control populations to support your statements that durable responses would not be anticipated in this population and could not be achieved with existing treatments. For each of the external control populations, provide data on the subset who responded to therapy. Provide a detailed summary and descriptive statistics for the demographic characteristics, diagnostic criteria, stage and severity of disease, concomitant treatments, and observational conditions (e.g., definition of response, required methods of assessment for onset and durability of response, intervals of assessment) for the subset of patients with objective responses. For each external control population, please provide a copy(ies) of the protocol(s) if one existed and relevant publication(s) of study results. Identify those external control groups for which you are able to obtain primary (raw) data, if requested.

We also have the following additional comments:

4. At the meeting of April 24, 2002, you presented graphs of progression-free survival (PFS), which you identified as pertaining to all study subjects (not just responders). Improved PFS was not identified by you in your pre-meeting materials or in questions directed to the Agency as a meaningful therapeutic benefit conferred by Bexxar, although consideration of this endpoint was discussed during the meeting. On further consideration, we find it highly doubtful that you will be able to provide convincing evidence of an effect on PFS and strongly recommend against expending any additional efforts to assess the effect of Bexxar on this outcome except in an appropriately designed and controlled study.

   Our concern with this approach is that you would not be able to provide evidence that you have minimized bias through identification of an external control population that has been appropriately matched for demographic characteristics, diagnostic criteria, stage and severity of disease, concomitant treatments, and observational conditions (e.g., definition of response, required methods of assessment for onset and durability of response, intervals of assessment) in order to establish the acceptability of the control group. In addition, a consequence of the inability to control bias is that the potential persuasiveness of findings from externally controlled trials depends on obtaining much more extreme levels of statistical significance and much larger estimated differences between treatment than would be considered necessary in concurrently controlled trials.

5. With regard to your assessment of the safety data contained within your application, upon further consideration of the issues discussed during the April 24, 2002 meeting, we still believe that due to missing data, a precise characterization of the toxicity profile

for common and significant adverse events cannot be made. Using the "worst-case" scenario for hematologic toxicities and using 95% confidence intervals around point estimates for the time-to-event incidences for hypothyroidism, immunogenic responses, and myelodysplasia/secondary leukemias, we are able to sufficiently characterize toxicity to permit an assessment of the net clinical benefit. However, additional studies are needed to more carefully assess the true incidence of adverse events and to assess for factors that may correlate with an increased risk of adverse events.

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,

Patricia Keegan for Dr. Weiss

Karen D. Weiss, M.D.
Director
Division of Clinical Trial
Design and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

CONCURRENCE PAGE

cc: HFM-555/K.Webber
HFM-570/P.Keegan
HFM-594/T.Zaremba
HFM-573/G.Mills
HFM-573/S.Litwin
HFM-585/Glen Jones
HFM-585/E.Dye
HFM-500/P.Bishop
HFM-500/S.Risso
HFM-500/Jay Siegel
DARP BLA file

CBER:DARP:M.Noska:5-13-02:DIXON:5.13.02
(S:\Noska\Letters\License\Bexxar_Advice.doc)

COMMUNICATION TYPE:

LETTER: ~~**Information Request (IR)**~~ Advice (AD)

SS Data Check:
- **Communication**

Division	Name/Signature	Date
DARP	Michael G. Noska	5/13/02
DARP	Lt Aeraa	5/13/02
DCTDA	P. Keegan	5-13-02
DARP	JJ Dixon	5-13-02

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

Our STN: BL 125011/0

MAR 1 2 2002

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street, Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application for Tositumomab (Anti B1) and Iodine-131-Tositumomab (Bexxar™) submitted under section 351 of the Public Health Service Act. Reference is also made to our Complete Response letter dated March 16, 2001, and your responses dated June 7, June 15, August 6, August 27 and September 7, 2001.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Clinical Section:

As stated in our March 16, 2001 letter, you have failed to provide sufficient evidence of safety and effectiveness. Supplementation of the earlier dataset by inclusion of data from additional subjects has not fully addressed the issues in our previous letter. The amount of missing data is substantial and precludes an accurate characterization of acute hematologic toxicity and of delayed hematologic and non-hematologic toxicity. Thus, there is insufficient information to describe the safety profile for labeling purposes and insufficient information to permit an assessment of net clinical benefit of your product. In addition, there is insufficient evidence that your product provides a significant advance for the treatment of a serious and life-threatening disease as compared to available therapy or that it meets an unmet medical need. These deficiencies will need to be addressed through the conduct of additional clinical trials that are adequate and well-controlled. With regard to the clinical information provided, we have the following specific comments:

1. The application contains insufficient information to adequately characterize the incidence and time-course of acute hematologic toxicity. The integrated safety summary (ISS) database contains information on 620 of the 813 subjects enrolled in clinical studies. This subset of 620 patients consists of all subjects enrolled more than 13 weeks prior to the data-cutoff date and thus represented an adequate opportunity to collect information for acute hematologic toxicity and recovery. However, there is insufficient information to adequately characterize acute hematologic toxicity for 42% of these subjects. The

subjects for whom safety data are not provided do not appear to be missing at random, but include those who withdrew from the study for toxicity and/or lack of efficacy. Therefore, analyses of the incidence and severity of adverse events conducted only in patients with complete information would be biased and are not sufficient to identify infrequent and rare serious adverse events.

2. There is substantial loss to follow-up beyond study day 90, resulting in insufficient information to fully assess and characterize delayed hematologic toxicity. This is compounded by the significant amounts of missing data for those subjects who were not lost to follow-up. Among the 620 subjects in the ISS, there were 70 subjects who died and 86 subjects who were lost to follow-up prior to day 152. Hematologic data for study month 4 (encompassing data collected between study days 107-152) are not provided for 111 (24%) of the 464 subjects who were alive and had not been "lost-to-follow-up" through study day 152. Similarly, although there were 234 subjects who were followed through month 13, the application contains hematologic data for only 145 subjects. We also note that of those assessed at month 4, 49 (16% of the 353 for whom there were hematologic data) had grade 3 or grade 4 hematologic toxicity. In our review, these subjects did not have evidence of concurrent chemotherapy. Thus, we cannot rule out that patients do not have significant risks of delayed hematologic toxicity.

3. The amount of missing data and loss-to-follow up impairs the ability to characterize the incidence, time of onset, and persistence of an immune response (human anti-murine antibody [HAMA]) to your product. Of the 620 subjects in the ISS, 244 (39%) have been excluded as "inevaluable" due to a positive HAMA at baseline or failure to collect HAMA at baseline and/or follow-up. Based on our review of the data provided, the time to development of HAMA appears to be delayed, with seroconversion to positive HAMA first occurring 3 to 12 months after exposure. This time-course is atypical of immune responses to other murine antibodies. We cannot determine whether this is due to suppression of humoral immunity by the disease process, prior immunosuppressive therapy, or immunosuppression resulting from administration of your product. Given this delayed pattern of seroconversion, your analyses of the incidence of immunogenic response, based on a subset of subjects with substantial loss-to-follow-up and lack of serial evaluation over the critical time period, is not adequate to characterize the incidence or time-course to development of an immunogenic response. In order to adequately assess the incidence and level of HAMA responses in your population, additional studies are needed in which a sufficient number of patients has been evaluated for HAMA both at baseline and at regular intervals following treatment.

4. There is insufficient information to accurately assess the rate and time-to-development of hypothyroidism. Based upon data from treatment with sodium iodide-131 and with external beam irradiation, the development of hypothyroidism months to years after administration of your product is an expected adverse event. Since these data were not collected systematically during the conduct of the clinical studies, you attempted to

collect additional information to permit an assessment of the rate of development of thyroid dysfunction through a survey of patients alive and remaining in follow-up. The survey attempted to identify the number of subjects:

a. who initiated thyroid medication after enrollment in study; or

b. who had initial evidence of elevated TSH after enrollment in study.

These data supplemented the previously submitted adverse event reports of "hypothyroidism" as a specific AE term. We note that the reports of hypothyroidism (AE reports) do not include all subjects receiving thyroid replacement therapy and/or with an elevated TSH. The lack of correlation suggests a lack of rigor in identification of expected adverse events that are likely to be associated with your product.

We also note that despite your efforts to recover data by survey of patients continuing in follow-up, there were only 315 subjects evaluated for thyroid dysfunction post-Bexxar treatment using a sensitive method (i.e., TSH assay). Similarly, 109 subjects remained in follow-up at 2 years, but only 43 subjects were assessed by a sensitive assay for thyroid dysfunction. Of these, 4 had evidence of new-onset thyroid dysfunction. Analyses of thyroid dysfunction based upon TSH values is more appropriate because of the greater sensitivity, however the number of subjects not assessed is substantial. Analyses of a subset of patients with available data may be biased and not representative of the population as a whole. While we agree that it appears that the cumulative incidence of hypothyroidism increases over time, the loss of substantial numbers of patients seriously diminishes your ability to accurately characterize the incidence and time-to-development of thyroid dysfunction.

5. On November 25, 1998, you received Fast Track designation for patients with low-grade NHL that had undergone histologic transformation. In April 9, 2001 you requested accelerated approval based on an analysis of this subset of the study population; this request was supplemented by information in your July 23, 2001 submission to the BLA. We have identified a total of 41 subjects with low-grade NHL for whom histologic transformation to a more aggressive histology was independently confirmed by histopathologic review and who received Bexxar at the dose and schedule for which you are seeking licensure. Since your request was received, another product was approved for this patient population and therefore an unmet medical need no longer exists. Based on the design of the clinical studies and the information submitted, we cannot conclude that Bexxar provides a significant advance over Zevalin therapy.

6. The level of activity (overall response rate and duration of response) in patients with CD20+ low grade NHL that is refractory to chemotherapy, including those whose tumor has undergone transformation to a more aggressive histology, does not support a claim that your product offers a significant advance over alternative therapy and meets an

unmet medical need. The overall response rate observed in RIT-II-004, was 47% [95% confidence interval (34%, 60%)] with a median duration of response of 12.5 months. This level of activity is similar to that observed with Rituxan, however, your product is associated with a higher level of toxicity. This level of activity is lower than that observed with Zevalin, among subjects who are not Rituxan-refractory. It is not possible to determine whether, and to what extent, these differences may be due to differences in the studies. Based on the design of the clinical studies and the information submitted, we cannot conclude that Bexxar provides a significant advance over Rituxan or Zevalin. There are several potential approaches to address this concern and we would work with you to help identify approaches that are acceptable. Any additional trial(s) also should be adequate in design to characterize both acute and delayed toxicity associated with your product, as well as benefit.

7. We are concerned with the continuing high rate of loss-to-follow-up and the inability to collect safety information for subjects enrolled in more recent studies, particularly with regard to the large number of subjects enrolled in Study 98-020, the expanded access protocol. Please describe the procedures that have been implemented to increase compliance with the conduct of clinical studies and to verify the accuracy of the data collected. In your response, specifically address the corrective actions taken to address the issues noted below. Both bioresearch monitoring inspections by FDA and reports submitted to the IND and BLA indicate that there have been multiple instances of dosing errors and failure to ensure that iodide blockade of the thyroid was conducted in all patients.

   a. There were delays in reporting of two early and unexplained deaths at a study site outside the U.S. in early clinical trials. Despite discussion with you regarding reporting requirements, adverse event reports of death on study or shortly after receipt of the study drug are not being submitted as expedited reports.

   b. The collection of acute hematologic data is deficient in Protocol 98-020, despite the protocol requirements for mandatory collection of blood samples during weeks 3 thru 13.

8. We cannot reconcile dates of duration of response and dates of follow-up within the SAS datasets against the case report forms. Because the SAS datasets have been updated while the case report forms have not, we do not have CRF documentation of dates in the SAS datasets for the period between 1999 and 2001. In addition, there are irregularities in the SAS dataset that were present in earlier datasets and persist in the current update. We provide the following examples from the SAS datasets for studies RIT-II-002 and RIT-II-004:

   a. The duration of response exceeds the duration of follow-up for the following subjects: 004-013-008, 004-013-009, 004-013-015, 004-014-001, 004-021-002,

002-011-001, 002-011-016, 002-011-022, 002-025-003, 002-031-001, 002-032-001, 002-034-003, 002-034-005, 002-034-017, and 002-030-013.

b. The duration of response is censored and is far shorter than the duration of follow-up for the following subjects: 004-016-008 (duration of response 366 days and ongoing, duration of follow-up 974 days and ceases with patient's death). Additional examples include subjects 004-020-005, 004-020-007, 004-029-003, 002-011-009, 002-030-020, and 002-030-906.

Similar issues exist with the datasets for the subset of patients with confirmed, transformed NHL:

c. The duration of response is longer than the duration of follow-up for subjects 001-007-002 and 001-007-004, as well as 004-013-015 (noted above). The duration of response is censored and is far shorter than the duration of follow-up for subject 001-003-004, as well as for 002-030-906 and 004-016-008 (noted above).

Chemistry, Manufacturing, and Controls Section:

Biochemical differences are noted in the Anti-B1 antibody products manufactured at the three different sites as a result of changes occurring during storage, the differences in ——— b(4)
———————————————— and changes made to various lot release assays. We also note that the clinical pharmacology data obtained in study RIT II-003 suggest that there are no important differences in the pharmacokinetics and biodistribution of the products. However, due to the differences in design of the clinical studies, we cannot assess comparability (or lack of) with regard to anti-tumor activity or toxicity profile. Because the product to be marketed (manufactured at BI Pharma KG) has the poorest quality safety and efficacy data, additional studies adequate in design to assess activity and safety profile are needed.

The following refers to items listed in our March 16, 2001 complete response letter. Items 9-15 relate to manufacturing operations at BI Pharma KG. Items 16-18 relate to manufacturing at MDS Nordion.

9. The validity of the immunoreactive fraction (IRF) assay for determining the potency of your product cannot be verified for the following reasons:

a.

b(4)

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 24

You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf)

Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

We acknowledge receipt of your amendment dated March 4, 2002. You may cross reference applicable sections of the amendment in your complete response to this letter and those sections will be reviewed as a part of your complete response.

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,

Patricia Keegan for Dr. Weiss

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design
and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Kathryn E. Stein

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

cc: HFM-594/T.Zaremba
HFM-594/L.Epps
HFM-675/W.Lange
HFM-675/D.Trout
HFM-579/M.David Green
HFM-573/S.Litwin
HFM-573/G.Mills
HFM-215/S.Misra
HFM-664/M.Andrich
HFM-588/M.Noska
HFM-555/K.Webber
HFM-570/P.Keegan
HFM-215/G.Gupta
HFM-215/P.Lachenbruch
HFM-675/C.Kelley
HFM-675/J.Eltermann
HFM-585/G.Jones
HFM-500/P.Bishop
HFM-500/S.Risso
HFM-500/Jay Siegel
HFM-4/QAS
DARP BLA file

CBER:DARP:M.Noska:3-8-02:aw:3-8-02:mn:3-11-02:mn:3-12-02
(S:\Noska\Letters\License\BL125011.0.CR2.doc)

COMMUNICATION TYPE:

LETTER: Complete Response (CR)

SS & RIS Data Check:

- **Communication**
- **Milestone: Confirm First Action Due Closed Date. Ltr. Date And CR Milestone Date Should Match**
- **Submission Screen: STN Status – Complete Response Ltr.**

Division	Name/Signature	Date
DARP	Michael A Marchi	3/12/02
DMA	Stein	3/12/02
DETDA	Kuyan	3-12-2002
DMA	Jerry C. Ebersole	3/12/02
DARP	Deje La Enes	3-12-02
DARP	A. Williams	3-12-02

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

OCT 30 2001

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

We acknowledge receipt on September 10, 2001 of your September 7, 2001 resubmission to your license application for Tositumomab and Iodine-131-Tositumomab.

This resubmission contains additional chemistry, manufacturing and controls and clinical information submitted in response to our March 16, 2001 complete response letter.

We consider this a complete, class 2 response to our action letter. CBER intends to review this submission and take action on it by March 12, 2002.

If you have any questions, please contact the Regulatory Project Manager, Mr. Michael Noska, at (301) 827-5115.

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

CONCURRENCE PAGE

cc: HFM-594/T.Zaremba
HFM-588/M.Noska

CBER:DARP:M.Noska:10-3-01:mn:10-24-01:mn:10-25-01:amw:10-26-01
(S:\Noska\Letters\License\125011_ACK_Class2.doc)

COMMUNICATION TYPE:
LETTER: Acknowledgement Letter (ACK)
Summary Text: Class 2 Resubmission (6 mos)

SS & RIS Data Check:
- Communication
- Milestone: Receipt Date In Ltr. & Milestone (Response To CR) Should Match

RIS Data Check:
- Confirm New Action Due Date

Division	Name/Signature	Date
DARP	Michael G. Noska	10/29/01
DARP	Teresa	10/29/01
DARP	for Dr. Jones	10/30/01
DARP	A. Williams	10/30/01

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

JUN 15 2001

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

Please refer to your **Biologics License Application (BLA)** for Tositumomab and Iodine-131-Tositumomab and to the meeting held on May 31, 2001, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Michael A. Noska, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Meeting Summary

CONCURRENCE PAGE

OTRR:DARP:Noska:6-13-01:ms:6/14/01
(S:\Noska\Letters\License\MS_Corixa_5-31-01.doc)

MEETING SUMMARY ENCLOSED (MS)

Concurrence box

Division	Name/Signature	Date
DARP	Michael C. Noska	6/15/01

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

MEMORANDUM

Date: June 15, 2001

To: STN BL 125011/0 File

From: Leon Epps, Ph.D., Product Reviewer
Division of Monoclonal Antibodies
Office of Therapeutics Research and Review

Subject: Meeting with Corixa Corporation to discuss the product issues in the Agency's February 1, 2001 complete review letter for Tositumomab

May 31, 2001, 15:00-16:15

Location: WOC I/Room 200 South

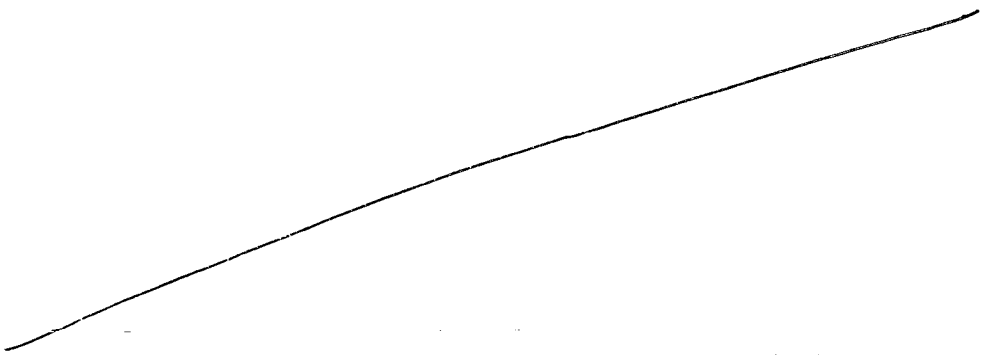
MEETING OBJECTIVES

Corixa requested this meeting to seek clarification and resolve the manufacturing issues conveyed in the Agency's complete review letter for the BLA for Tositumomab.

DISCUSSION

A brief overview of each issue is summarized below. The applicant's summaries of the issues appear in boldface by each item number.

1.



b(4)

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 25

Participants:

Agency	Sponsor
Terrye Zaremba, CBER/OTRR/DMA	Monica Krieger, Corixa
Leon Epps, CBER/OTRR/DMA	Jill Henrich, Corixa
Kathryn Stein, CBER/OTRR/DMA	David King, Corixa
Martin D. Green, CBER/OTRR/DCTDA	Stewart Kroll, Corixa
George Mills, CBER/OTRR/DCTDA	Kent Iverson, Corixa
Patricia Keegan, CBER/OTRR/DCTDA	Marcia Federici, Glaxo SmithKline
Mary Andrich, CBER/OCBQ/DIS	
Keith Webber, CBER/OTRR/DMA	
Walter Lange, CBER/OCBQ/DMPQ	
Kevin O'Brien, CBER/OCBQ/DMPQ	Michael Buckley, Corixa b(4)
Carolyn Renshaw, CBER/OCBQ/DMPQ	Uwe Bucheler, BI Pharma KG
	Roger Guest, Glaxo SmithKline
	Meg Martin, Glaxo SmithKline
	Ronald McGregar, MDS Nordion, Inc.

CBER:DMA:L. Epps:6/11/01:mn:6/12/01:mn:6/13/01:mn:6/15/01
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RECORD OF TELEPHONE CONVERSATION – BLA 125011 – Corixa, Bexxar

DATE: 7/10/01

PARTICIPANTS: T. Zaremba & L. Epps, CBER
J. Henrich & M. Krieger, Corixa & Buckley, Nordion

PURPOSE: To discuss Corixa Corporation's recent lot release data for the I-131 Anti- B1 antibody product described in amendment 577 to IND 3323 which showed that several lots reached the upper the pH limit of 7.2. We also discussed the information Corixa submitted in the attached FAXes dated 7/01/01 & 7/10/01.

CBER: Please clarify why the 2 diagrams in each of the two FAXes appear to be different for the various lots vs. pH values.

Corixa: The diagram submitted on 7/10 shows our complete manufacturing history from June of 1997 to the present while the diagram submitted on 7/1 only shows our manufacturing experience over the last 1.5 years.

CBER: Were all 238 lots made in the interim facility rather than the primary facility?

Corixa: Yes. We only produced 15 lots in the primary facility. These pH values shown in a separate table include a variation in pH $\pm$ 3 SD and are plotted in a separate diagram in the FAX of 7/10.

CBER: What was the date of the 1st lot that produced a pH value of — in the 7/1 FAX? b(4)

Corixa: The first lot was released on 11/12/00 and the 2nd lot was released on 11/19/00.

CBER: What is the identity of diagnostic & therapeutic lots released?

Corixa: This really makes no difference at the interim facility since both are produced from the same radiolabeled material. We dispense smaller volumes to produce the diagnostic dose form.

CBER: We thought you had instituted a second column step for the therapy dose.

Corixa: Our primary facility performs larger scale production. We don't experience a problem with ——————— facility because the total volume of radiolabeled material is on a much smaller scale. b(4)

CBER: In the FAX of 7/1, it appears that more variation in the pH values occurred after 11/12/00 compared with 1/4/00 to 11/12/00. Was anything in the process changed prior to 11/12/00?

Corixa: We are not aware of any changes. The [redacted] is the same and it is used throughout our processes. b(4)

CBER: Given the significant number of pH values at your upper limit of [redacted] you may want to consider revising your current pH specification range prior to licensure. In your FAX of 7/10, it appears that most lots varied between pH values of 7.0 to [redacted].

Corixa: We submitted information to IND 3323 on August 18, 2000 indicating that we would modify the pH specification in the primary facility (commercial scale) from a range of [redacted]-7.2 to [redacted]. A CBER letter dated 9/15/00 requested a rationale for this change. We responded in amendment 1 to our BLA (10/5/00).

CBER: We have requested a copy of this amendment from the document center. Did this submission contain validation data that show your range of [redacted] to [redacted] has no adverse affect on your product? b(4)

Corixa: No, we only provided a rationale that at the commercial scale the pH values trended toward the lower end of the specification and, at the interim facility, 3/6 validation runs performed in 1999 resulted in a pH of [redacted]

CBER: The 7/10 FAX shows the mean pH for the product at the interim facility to be 7.1±0.1, while the mean pH for the primary facility for both the diagnostic and therapeutic doses was 6.9±0.1. It is not clear if this is due to the small sample size in the primary facility compared with the interim facility (15 vs. 238) or if there really is a difference due to the scale of production. This needs to be resolved prior to licensure. In general, specifications ranges are usually narrowed and not widened as you gain more experience with the process. You need to validate that your product is not adversely affected at the pH extremes.

Corixa: We agree. How and when should we submit these data?

CBER: Submit the data to the IND first since you still have an ongoing protocol. Submit the data to the BLA second. This pH specification issue needs to be resolved prior to any facility inspections.

Corixa: We understand.

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

MAY 0 9 2001

Our STN: BL 125011/0

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

Please refer to your **Biologics License Application (BLA)** for Tositumomab and Iodine-131-Tositumomab and to the meeting held on April 9, 2001, between representatives of your firm and this agency. A copy of our memorandum of that meeting is attached for your information.

If you have any questions, please contact me at (301) 827-5101.

Sincerely yours,

Michael A. Noska, M.S.
Regulatory Project Manager
Division of Application Review and Policy
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Enclosure: Meeting Summary

CONCURRENCE PAGE

OTRR:DARP:Noska:5-8-01:ms:5/8/01
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MEETING SUMMARY ENCLOSED (MS)

Concurrence box

Division	Name/Signature	Date
DARP	Mindy Co. Nas	5/8/01

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

MEMORANDUM

Date: May 9, 2001

To: STN BL 125011/0 File

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

Subject: Meeting with Corixa Corporation to discuss the clinical aspects of the Agency's February 1, 2001 complete review letter for Tositumomab

April 9, 2001, 15:30-17:00

Location: WOC I/Room 200 South

MEETING OBJECTIVES

Corixa requested this meeting to seek clarification on the clinical issues conveyed in the Agency's complete review letter for the BLA for Tositumomab and to discuss their plans for revising the application for future re-submission.

DISCUSSION

Corixa and their experts began the discussion by making a presentation from the attached slides. The critical element from this presentation was Corixa's contention that, based on a new understanding of the molecular biology of non-Hodgkin's lymphoma (NHL) relative to the time of initiation of the Phase 3 study, low grade NHL now is seen to be a continuum of clinical manifestations. Specifically, the development of histologic transformation is a subtle one, which does not clearly delineate a new prognostic subgroup, and is merely one of a series of factors which collectively affect prognosis. Therefore, the company believes that all the data in the –004 trial should be pooled.

Dr. Keegan pointed out that treating this study population as a single disease group would impact the Fast Track indication. Corixa replied that the –004 population represents an unmet medical need based on the late stage and refractory nature of their disease. Dr. Keegan noted that the Agency's analysis revealed a bimodal profile in safety and efficacy in this group and asked how that could be explained in the context of a homogeneous population. The company responded that the most important prognostic factor for this group appears to be the number of previous therapies and not

histology. The –004 group had bulkier disease overall and more negative prognostic factors. Dr. Keegan stated that the Agency would need to consider this new position further and would need to review and confirm the post-hoc analyses that were presented at the meeting (as this analysis was not in the original BLA). Therefore, it would not be possible to reach any agreements at this meeting. This issue will be followed up at a later time.

Corixa raised a question regarding the statistical significance of the Agency's post-hoc analysis of the efficacy data cited in the complete review letter. The Agency stated that the there was a transcription error in the letter. While noting that statistically significant results were observed in the –004 study, Dr. Keegan pointed out that the Agency remains concerned about the very small sample size (total of 60 patients) and the unexpectedly high rate of severe toxicity. Dr. Keegan also commented on the many modifications to the statistical plan, including Corixa's reference to an analysis based upon a modification which occurred after full accrual in the study. Dr. Keegan reiterated the Agency's consistent position that the Agency will only accept the analysis in which documented, confirmed durable responses are used to define the primary endpoint for the study.

Regarding the total safety database, Corixa noted that they have considerable follow up data from multiple studies on durability of response and safety. Dr. Keegan asked Corixa to clarify the number of patients with complete follow up (as specified in the protocol) for at least three months, and whether this constitutes 300-600 patients as advised in the ICH guidance. The company replied that more than 280 patients would have greater than six months of follow up at the time of the next safety update. Corixa stated that they feel that they meet the ICH guidelines for six and twelve month follow up for rare diseases. However, Dr. Keegan pointed out that NHL is not a rare disease for the purposes of establishing an adequate safety database.

Among the safety issues, Dr. Keegan noted that the Agency concurred that treatment-induced hypothyroidism is an easily treatable complication, however the Agency's concern is the inadequacy of the data to describe the incidence or time-course for development of this event. While Corixa and their experts assured the Agency that the oncology community is well aware of this complication, Dr. Mills noted that, despite their awareness, TSH values were not monitored as required by the protocol. Corixa replied that they were measured, but not at the necessary frequency.

Dr. Litwin commented on the apparent inability to follow the clinical protocol for safety monitoring particularly with regard to missing hematologic data. Dr. Keegan also raised a concern about missing HAMA values particularly in light of what appears to be the development of late HAMA reactions, which is an unusual time-course and appears, from observations by the Agency, to be related to the prolonged and profound effects on normal B cells. Dr. Keegan also asked about the appearance of myelodysplasia in patients. Corixa replied that the incidence was not different from other cytotoxic agents and that, in the context of risk/benefit, this is not a concern. Corixa asked if cumulative incidence curves for delayed toxicity with variable follow-up, such as the incidence of MDS and secondary leukemia, would be acceptable. Dr. Keegan replied that this analytic approach to characterize the risk would be acceptable.

In concluding this discussion, Dr. Keegan again stated that it does not appear that the Agency has enough data to adequately inform patients about the risks of treatment in the package insert. Corixa stated that the next update will contain more data and asked how much would be enough. Dr. Keegan replied that safety database must be sufficient to identify serious adverse events which occur at an incidence of one percent in the population (ordinarily a minimum of 300 patients would be required to accomplish this).

Corixa asked whether their proposed design of the final analysis of the –002 trial (analysis at one year) was acceptable and noted that they wish to declare that long term partial responses are not complete responses. Dr. Keegan stated that the Agency needs to review the entire analytic plan and then follow up with a telephone conference for further discussion. Dr. Mills noted that the Agency would like to assess whether the –002 trial has a parallel design with the –004 trial. The Agency requested updated safety information on ongoing or recently completed trials, including the –002, -003, and –012 trials, which should be submitted in a revised, updated, and all-inclusive Integrated Summary of Safety (ISS). The efficacy data from the -012 and the –003 trial should be submitted, however, since the trials were not appropriately designed to establish the relative effectiveness of Bexxar in either setting, their usefulness is limited. The final study report from the –002 trial is essential in proceeding with the application (as it is the only data which establishes the contribution of the radiolabeled antibody). Further discussions will be required to resolve the outstanding issues.

Corixa inquired whether they could request an accelerated approval based on the results of the –004 trial. Corixa identified the randomized, controlled study from SWOG (comparing CHOP vs. CHOP + Bexxar vs. CHOP + Rituxan as first line treatment of follicular lymphoma) as a confirmatory trial. Dr. Keegan noted that, given the interim approval of Rituxan for chemotherapy-resistant/refractory NHL, it is not clear that the clinical setting studied in –004 represents an unmet medical need. Further, the sample size is quite small and the safety profile is worse than expected in terms of the severity and duration of hematologic toxicities; thus determination of net risk/benefit is difficult at best. Both sides agreed that accelerated approval could be further investigated, however, FDA advised Corixa that the Oncologic Drugs Advisory Committee is also likely to be very concerned about the lack of post-treatment and long-term follow-up in considering this application. Therefore Corixa was advised that it may not be possible to collect sufficient information at this point and the best course of action, which is strongly recommended by FDA, would be to conduct an additional study in which all the necessary safety information is carefully collected prospectively.

Dr. Zaremba also pointed out that the Agency still needs to assess the impact of the change in product from Coulter to Lonza to BI Pharma.

ACTION ITEMS

- Corixa should submit, and the Agency needs to review, the data set and analytic program used to generate the post-hoc, exploratory analysis from which Corixa determined the relative importance of histologic transformation as a risk factor. After reviewing these data, the Agency will respond to the proposal to pool the results from Protocol –004.

- The Agency needs to re-assess Protocol –002, including all revisions, in order to comment on the adequacy of the proposed "final" analysis. Corixa could facilitate this process by providing a copy of the original protocol, and all revisions with the date of implementation. Corixa should also clarify the extent of their knowledge of the interim results of this trial as it relates to all protocol revisions.

- Corixa must submit the final study report from Protocol –002, as soon as possible after the determination of the acceptability of the final analytic plan has been discussed.

- In considering pooling of safety information or in accepting additional efficacy data, all trial data sets should identify the source (Coulter, Lonza, BI Pharma) of the product used, for each dose if necessary.

Participants:

Agency	Sponsor
Terry Zaremba, CBER/OTRR/DMA	Monica Krieger, Corixa
Leon Epps, CBER/OTRR/DMA	Steven Gillis, Corixa
Richard Steffen, CBER/OTRR/DCTDA	Cindy Jacobs, Corixa
Stephen Litwin, CBER/OTRR/DCTDA	Stewart Kroll, Corixa
George Mills, CBER/OTRR/DCTDA	Stella Jones, Glaxo SmithKline
Patricia Keegan, CBER/OTRR/DCTDA	Mel Sorenson, Glaxo SmithKline
Michael Noska, CBER/OTRR/DARP	[redacted] b(4)
Kathryn Stein, CBER/OTRR/DMA	
Mary Andrich, CBER/OCBQ/DIS	
Peter A. Lachenbruch, CBER/OBE/DB	
Ghanshyam Gupta, CBER/OBE/DB	
Satish Misra, CBER/OBE/DB	

DEPARTMENT OF HEALTH & HUMAN SERVICES

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

Our STN: BL 125011/0

March 16, 2001

Monica Krieger, Ph.D.
Corixa Corporation
1124 Columbia Street
Suite 200
Seattle, WA 98104

Dear Dr. Krieger:

This letter is in regard to your biologics license application for tositumomab (Anti-B1) and Iodine-131-tositumomab (Bexxar™) submitted under section 351 of the Public Health Service Act. Reference is also made to our clinical Discipline Review letter dated February 1, 2001.

The Center for Biologics Evaluation and Research (CBER) has completed the review of all submissions made relating to this application. Our review finds that the information and data submitted are inadequate for final approval action at this time based on the deficiencies outlined below.

Chemistry, Manufacturing, and Controls Section:

Items 1 through 5 refer to Section 4CP of the BLA regarding the comparability of Tositumomab manufactured at Coulter Pharmaceuticals, Lonza/CYTOGEN and BI Pharma:

1.

b(4)

12 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 26

that affect the receipt, testing, storage and distribution of Bexxar™ or identify where this information has been provided in the application.

38. Please provide a comprehensive description of plans and procedures that will enable Corixa to maintain effective managerial oversight and quality assurance for all stages of manufacture at the contract manufacturers (Boehringer Ingelheim, Nordion, and McKesson BioServices).

39. Regarding sterility testing, Section 4.1.3.4 ND (page 120) states that: "There is no sterility testing performed on the sterile [radiolabeled] bulk because sterility testing on the [radiolabeled] DP is not used for release." Although it may be necessary for you to release lots of the radiolabeled drug product before the results of sterility testing become available, it will be necessary for you to submit a justification including a comprehensive plan with appropriate validation data demonstrating that all equipment, components and materials used in manufacture of the radiolabeled drug product are sterile. In addition, sterility testing of both the sterile radiolabeled bulk drug substance and the drug product should be performed at the time of release. As part of your plan for assuring sterility of the radiolabeled drug product, please describe the procedures that will be followed, including notification of health care providers, in the event that sterility test results are positive.

Clinical Section:

40. In a meeting held on July 20, 1995 and a telephone conference held on June 18, 1997 between representatives of your organization and this agency to discuss the design of the major efficacy trial, FDA raised concerns regarding the appropriateness of pooling data from patients with low-grade non-Hodgkin's lymphoma (NHL) with those obtained from patients with low-grade NHL that had undergone transformation. We stated that the two groups were biologically different (different histology and different clinical course) and therefore, data from the two groups should not be combined. Your response was that, based on previous studies, the clinical activity of Bexxar™ (response rate and duration) was the same in the two groups. You were informed that if the results of the trial did not confirm this assumption, FDA would not pool the results from the two subpopulations. You were also informed that if the data from the two groups could not be pooled, the RIT-II-004 trial would be unlikely to provide sufficient information to convincingly establish the clinical effectiveness in either setting.

Our review confirms that patients with low-grade non-Hodgkin's lymphoma (NHL) that has not undergone transformation (37 patients) and those with low-grade NHL that has undergone transformation (23 patients- see next two comments) represent subpopulations in which the activity of Bexxar™ is significantly different. You will need to conduct additional studies to develop an adequate experience in each of the

subpopulations to establish the clinical effectiveness of Bexxar™. Additional trials conducted in patients with low-grade NHL which has not transformed should be conducted using a randomized, active control study design to permit an assessment of net clinical benefit.

41. We note that the primary efficacy endpoint of the study for Protocol RIT-II-004 was the comparison, as assessed by the Masked Independent Randomized Radiology and Oncology Review (MIRROR) panel, of the number of patients having a longer duration of response (i.e., more than 30 days) on their last qualifying chemotherapy regimen to the number of patients having a longer duration of response on Bexxar™. Notwithstanding the fact that we do not agree with pooling the two subpopulations, we also note that our analysis of the study results for the primary efficacy endpoint does not confirm your findings. Specifically, we find that the number of subjects for whom Bexxar™ resulted in a clinically longer duration of response was 27, not 32, and the number of patients for whom the duration of response to Bexxar™ was less than the duration of prior chemotherapy was 5, not 11. Please clarify how you identified subjects in this analysis and provide a detailed description of how you performed the primary efficacy analysis. Consistent with the statistical plan (BLA submission; Final Report, Protocol RIT-II-004, Section 11.3, Efficacy Results, Subsection 11.3.1, Primary Endpoint Analysis), this analysis must be based on the prospectively stated differences between the duration of response to the I-131 antibody therapy and the prior chemotherapy using the MIRROR panel determination for duration of response.

    We have also conducted an exploratory analysis, using information on durability of response in all 60 patients including the 28 for whom there was no clinically important difference in the duration of response to Bexxar™ or chemotherapy. In this analysis, a comparison of the most durable responses also favors Bexxar™, but the level of significance is $p > 0.01$ (sign-rank test).

42. The number of subjects studied with transformed NHL is insufficient to establish clinical effectiveness in this patient population and you must conduct additional studies. You have identified 60 patients enrolled in three separate studies with a histologic diagnosis of low-grade NHL with transformation, however this diagnosis was appropriately confirmed by central review for only 22 of the 37 subjects for whom central pathologic review was performed (see next comment). In subsequent studies, all subjects must have independent confirmation of the original diagnosis of low-grade NHL and the histologic diagnosis of transformation. You must establish the credentials of the central reviewing pathologist(s), provide a detailed description of the procedure for central pathologic review, and provide a detailed description of the pathologic findings from both the original pathologist and the central pathologic reviewer(s). In the current application, there is insufficient pathologic description to document the

findings that formed the basis of the diagnosis. This is particularly important when the diagnosis of transformation might be influenced by knowledge of the timing of the biopsies and/or subject to interpretation.

43. There is insufficient documentation to confirm the diagnosis of low-grade NHL with transformation. The application contains the Maskpath, transformed dataset with central pathologist's histologic diagnosis for only 37 patients enrolled in the RIT-II-001 and RIT-II-004 trials. The data for central pathologic review is not provided for 23 additional patients. With regard to the 37 patients included in the Maskpath, transformed dataset, we note the following areas of concern regarding the quality of the data:

a. Six patients' records (001-003-004; 001-003-007; 001-004-007; 004-013-003; 004-013-004; and 004-016-006) contain the same date for the diagnoses of both low-grade NHL and low-grade NHL with transformation. We also note that for patient 001-003-007, the date of diagnosis of low-grade NHL differs between the Dxhist, transformed dataset (2/9/93) and the Maskpath, transformed dataset (9/9/94).

b. Seven patients' records (001-005-002; 001-005-003; 001-005-006; 001-006-002; 001-007-002; 001-007-004; and 001-008-005) do not have a date for the diagnosis of low-grade NHL with transformation.

c. Two patients' records (001-005-003; and 001-007-004) do not contain the date for the diagnosis of low-grade NHL.

In order to support the clinical activity of Bexxar™ in patients with low-grade NHL with transformation, you must submit documentation confirming the histologic diagnosis, objective tumor response, and response duration, and provide sufficient data to adequately characterize the safety profile of Bexxar for all 60 subjects. In addition, you must address the reasons for the very disparate clinical activity in low-grade NHL with transformation for patients in RIT-II-004 as compared to the other two trials. In order to provide adequate confirmation of the histologic diagnosis, you must provide revised electronic datasets for Dxhist, transformed and Maskpath, transformed. You must also provide copies of the original and central pathology reports which contain detailed descriptions of the pathologic findings and establish the original diagnosis of low-grade NHL and the diagnosis of NHL with transformation for each of the 60 patients. In addition, please provide the prospective criteria applied by the central pathology reviewer to establish the diagnosis of low-grade NHL with transformation. In particular, provide the criteria utilized to establish a diagnosis of low-grade NHL and low-grade NHL with transformation on the same date (presumably in the same biopsy material).

44. The safety experience for Bexxar™ is incomplete and therefore insufficient to adequately characterize the toxicity profile of Bexxar. You must provide sufficient data to characterize both immediate and delayed toxicities in an adequate number of subjects (300-600 patients).

45. If it is your intent to utilize the results of Protocol RIT-000-004 to characterize the toxicity profile of Bexxar, you must provide the following information:

a. There is insufficient information regarding patients who died within 90 study days of therapy administration. Specifically, provide data on the 11 patients (004-013-012; 004-013-005; 004-018-001; 004-016-011; 004-014-007; 004-014-002; 001-009-006; 001-008-002; 000-002-021; 002-030-002; and 002-030-009) who died before study day 90. The causes of these deaths and the clinical events prior to these deaths are not adequately documented in the application.

For each patient, you must provide a narrative summary, and the complete medical record covering the period from registration on study until death. The medical record should contain all physician's and nurse's notes, the results of all laboratory tests, and copies of radiographic study reports, and cytology/histopathology reports. Autopsy and death certificate records should be provided in the submission; you must indicate if no autopsy was performed in your response.

We further note that for two of these patients (001-008-00; and 004-018-001) who were enrolled at the same institution, death from undetermined causes occurred within several days of their dosimetric infusion. In addition to the information requested above, you must provide a complete summary of the preparation, handling and administration of the dosimetric dose for these individuals. Please include the hospital radiopharmacy records, including the lot numbers and all other identifiers for the components of the radiolabeled antibody administered to these patients, and any test results performed for "release" of the final product prior to administration.

b. There is insufficient information regarding patients who suffered non-fatal serious adverse events (SAE) within 90 study days following administration of the radiolabeled antibody. Please provide a narrative summary for all patients who suffered serious but non-fatal adverse events during this timeframe.

In addition to the narrative summary, please provide additional information for the patients who experienced serious adverse events identified as hematologic, infectious, pulmonary, or gastrointestinal. A listing of these patients is provided

below, by ID number. Provide the primary (source) documents from the time of study registration through resolution of the adverse event. The source documents should include physicians', nurses' and consultants' notes; results of all laboratory tests performed; reports for all radiographic studies; and any other information relevant to the serious adverse event.

1) Infections: 001-005-003; 001-006-003; 002-026-004; 002-030-019; 002-030-24; 001-008-002; 001-008-004; 001-008-006; 004-013-001; 004-013-010; 004-015-005; 001-005-005.

2) Hematology: 001-004-006; 001-005-001; 004-016-001; 002-025-901.

3) Pulmonary: 002-030-002; 004-013-017; 004-013-002; 004-013-005; 004-016-011.

4) Gastrointestinal: 001-004-002; 001-008-003; 002-011-016; 002-011-018; 002-034-008.

c. There is insufficient information regarding patients with persistent hematologic toxicity at 120 days or longer after receiving the therapeutic dose. Please provide a narrative summary for two patients (002-011-917 and 002-030-019) who continued to have hematologic toxicity beyond study day 120. If you are aware of any additional patients with persistent hematologic toxicity (beyond day 120), please provide narrative summaries for these patients as well.

d. There is insufficient information regarding patients who withdrew or dropped out of the trial during the first 90 days of study. Please provide narrative summaries for the following patients:

1) Three patients (000-002-021; 004-015-005; and 004-018-001) who are reported to have dropped out as a consequence of infusion-related toxicity.

2) Eleven patients (000-002-021; 000-002-031; 001-003-004; 001-008-002; 002-025-901; 002-030-019; 002-030-906; 004-013-008; 004-014-002; 004-015-006; and 004-018-001) who are stated to have withdrawn from the study for reasons other than progressive disease.

e. The first organ toxicity from the administration of I-131-B1 therapy is myelosuppression. The protocol-specified monitoring schema required complete blood count (CBC) evaluations weekly during the first 12 weeks. In addition, CBCs were to be obtained more frequently in patients with grade III or IV

hematologic toxicity and such monitoring was to continue until resolution of the grade III or IV toxicity (i.e., weekly or more frequent monitoring beyond 12 weeks in the presence of persistent toxicity). The complete results of this monitoring are required for the following: assessment of the incidence, severity and duration of hematologic toxicities and for the determination of the recovery (or lack of) from these toxicities. Our review of the BLA notes the following:

1) There are patients with grade III or IV hematologic toxicities where follow up CBC evaluations are not reported (i.e., time to resolution and documentation of resolution are not provided).

2) The results of protocol-required CBC evaluations during the first 12 weeks are not reported for all patients.

In order to provide sufficient information regarding the hematologic toxicity profile of Bexxar™, you must provide an electronic dataset containing the results of all CBCs obtained in accordance with the clinical protocol for all patients enrolled. The electronic dataset should integrate previously reported data with the data that was omitted.

f. There is essentially no information on the effects of Bexxar™ on thyroid function beyond the first 90 days post- Bexxar™ therapy. These data must be provided for all patients exposed to Bexxar™ until their death, since there is clear evidence of localization of Bexxar™ to the thyroid in multiple subjects.

As discussed in the telephone conversation of January 11, 2001, you have committed to contact all subjects who are living and obtain TSH results for each subject, to inform these subjects of the potential risks of late onset hypothyroidism and of the need for life-long monitoring. You have agreed to amend ongoing studies to require continued close monitoring of TSH for the first two years after therapy and annually thereafter until death.

g. There is inadequate information regarding delayed immunogenic response to Bexxar™. The data provided on the two subjects in RIT-004 suggest that delayed immunogenic responses (positive human anti-murine antibody responses) do occur and may be common, as it was observed in all three of the subjects monitored beyond six months. As discussed during the teleconference of January 11, 2001, you will attempt to contact and obtain sera to conduct HAMA assays for all subjects who are alive. You have also committed to amend ongoing protocols to ensure that HAMA results are collected in a complete and systematic fashion for an adequate number of patients followed for up to 2 years.

h. The follow-up on all subjects is relatively short, yet among the 286 subjects in the original application, there have been seven cases of myelodysplastic syndrome (MDS) and four cases of acute leukemia. Given the relatively short duration of follow-up available on patients who have "withdrawn" from the trial, please provide the annualized rate for MDS and leukemia based upon patients known to be alive and in continuing follow-up.

46. The tumor and organ dosimetry data and assessments are inadequate and incomplete. As stated in the BLA, residence times of Iodine-131 anti-B1 antibody were calculated for the kidney, liver, lung, spleen, bone marrow, blood, and total body. For the organ dosimetry calculations, all other organs were assumed to have localized the radiolabeled antibody at the whole body background level. However, this assumption is inconsistent with our review of the whole body biodistribution images which demonstrates prominent uptake of I-131 in the thyroid gland, as well as prominent localization in the stomach, small bowel, and large bowel, in multiple patients. Please reassess and report the organ dosimetry studies with additional regions of interest for the thyroid gland, stomach, small bowel, and large bowel to establish residence time data for these organs.

47. The goal of Iodine-131 anti-B1 antibody therapy is localization of the radiolabeled antibody in tumor sites to deliver therapeutic radiation. Our review of the tumor radiation dosimetry notes that summary results for selected tumor sites from 45 patients enrolled in the RIT-I-000 study, 7 patients enrolled in the RIT-II-001 study and 53 patients enrolled in the RIT-II-003 study are provided. However, we are unable to complete our independent review of the tumor dosimetry because you have not submitted the primary (source or raw) radiation dosimetry data and the time-activity data for these tumor sites. Please submit the dosimetry source data with the time-activity data results, for all tumor sites evaluated for tumor dosimetry.

48. The application refers to a population of 14 patients who received more than one therapeutic dose of Bexxar™ (re-treatment). Data on the re-treatment group are presented in tabular form but there are no list files which would permit evaluation of the individual patients. Please identify the patients in the re-treatment group according to unique patient identifiers and provide separate electronic datasets containing all data collected for these patients.

49. You were informed that you would need to establish the contribution of the Iodine-131 radiolabeled antibody by a comparison of the clinical activity of cold anti-B1 and Bexxar™ in a randomized study (RIT-II-002). Please provide a final report for this study in your response. In the final study report, include a narrative description for all patients who withdrew prematurely, suffered serious adverse events (including death),

or experienced prolonged, unresolved toxicity and delayed toxicities. The updated safety database for this study should be included in the integrated safety dataset. The final study report should also include complete information on all patients registered in the study. These data include, but are not limited to data on baseline entry characteristics, and all clinical and laboratory data which were to be collected according to the study protocol. Please include the documentation of the central/independent assessment of the onset of response and the confirmation of the response at day 28, and documentation of the original and independent review of the histological diagnosis.

50. Please provide the final study report for the RIT-II-003 study. In the final study report, include a narrative description for all patients who withdrew prematurely, suffered serious adverse events (including death), or experienced prolonged, unresolved toxicity and delayed toxicities. The final report safety database for this study should be included in the integrated safety dataset.

We reserve comment on the proposed labeling until the application is otherwise acceptable.

You may request a meeting or teleconference with CBER to discuss the steps necessary for approval. Should you wish to have such a meeting, please submit your meeting request as described in the FDA Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products – February, 2000 (http://www.fda.gov/cber/gdlns/mtpdufa.pdf) Within 10 days after the date of this letter, you are requested to take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; (3) withdraw the application; or (4) request an opportunity for a hearing on the question of whether there are grounds for denying approval of the application. In the absence of any of the above responses, CBER may initiate action to deny the application.

Please note that our review clock has been suspended with the issuance of this letter. Note also that any amendment should respond to all deficiencies listed, and that a partial reply will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

We acknowledge receipt of your amendment dated February 16, 2001. You may cross reference applicable sections of the amendment in your complete response to this letter and those sections will be reviewed as a part of your complete response.

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,

Karen D Weiss

Karen D. Weiss, M.D.
Director
Division of Clinical Trial Design
and Analysis
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

Kathryn E. Stein

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

CONCURRENCE PAGE

cc: HFM-594/T.Zaremba
HFM-594/L.Epps
HFM-675/W.Lange
HFM-579/M.David Green
HFM-573/S.Litwin
HFM-573/G.Mills
HFM-215/S.Misra
HFM-664/M.Andrich
HFM-588/M.Noska
HFM-555/K.Webber
HFM-570/P.Keegan
HFM-573/R.Steffen
HFM-675/J.Lukas
HFM-215/G.Gupta
HFM-215/P.Lachenbruch
HFM-585/G.Jones
HFM-500/B.Goldman
HFM-500/S.Risso
HFM-500/Jay Siegel
HFM-110/RIMS

CBER:DARP:M.Noska:3-2-01:lt:3-6-01:mn:3-13-01:dixon:3.14.01
(S:\Noska\Letters\License\Coulter_125011_CR.doc)

MILESTONE - COMMUNICATION TYPE:
LETTER: Complete Response (CR)

Division	Name/Signature	Date
DARP		3-16-01
DMA		3/16/01
OCTDA		3-16-01
DMPQ	J M Lukas for J Eltermann	3/16/01
DMA	Terrye C. Zaremba	3/16/01
DARP		3-16-01
DARP	A. Williams	3-16-01

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

Date: March 5, 2001

To: M. Noska; L. Tull
BLA committee STN 125011/0.0

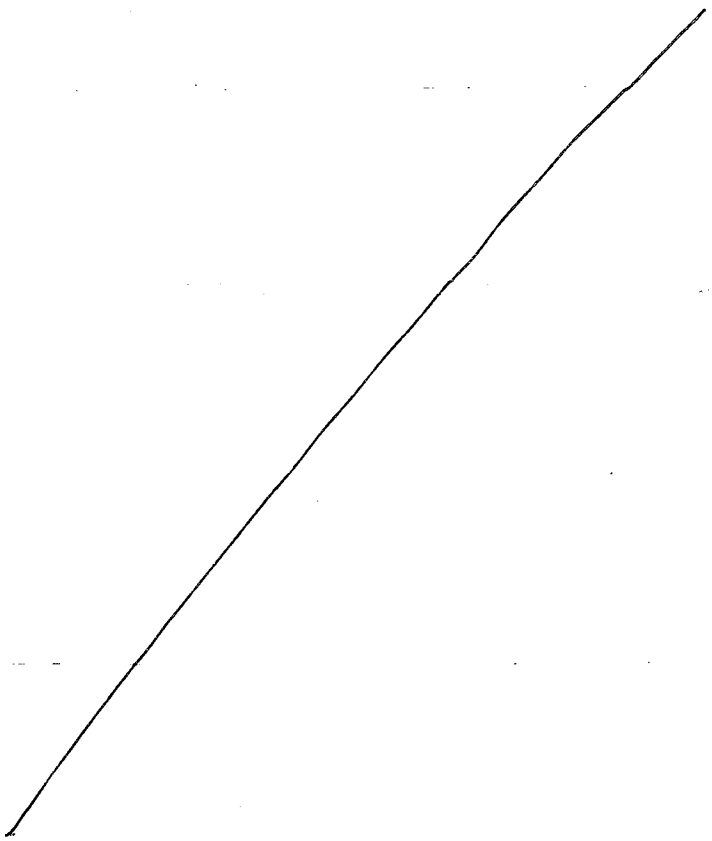
From: Walter Lange

Subject: Questions to be forwarded to Corixa regarding the review of the BLA for Tositumomab (Bexxar). STN 125011

With respect to the review of the subject BLA submission for Tositumomab (Bexxar). The following questions are forwarded for inclusion in a review letter to Corixa

Regarding operations at MDS Nordion:

1. In BLA section 4.1.3.2 ND p. 10 the following table is presented, with a summary description.



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4 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 28

Our STN: BL125011/0

FEB 01 2001

Ms. Patricia Oto, R.Ph.
Corixa Corporation
600 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Oto:

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 reviewed the clinical section of your biologics license application for tositumomab and Iodine-131-tositumomab (Bexxar™). Preliminary comments, deficiencies, and information requests identified during this review are summarized as follows:

1. In a meeting held on July 20, 1995 and a telephone conference held on June 18, 1997 between representatives of your organization and this agency to discuss the design of the major efficacy trial, FDA raised concerns regarding the appropriateness of pooling data from patients with low-grade non-Hodgkin's lymphoma (NHL) with those obtained from patients with low-grade NHL that had undergone transformation. We stated that the two groups were biologically different (different histology and different clinical course) and therefore, data from the two groups should not be combined. Your response was that, based on previous studies, the clinical activity of Bexxar (response rate and duration) was the same in the two groups. You were informed that if the results of the trial did not confirm this assumption, FDA would not pool the results from the two subpopulations. You were also informed that if the data from the two groups could not be pooled, the RIT-II-004 trial would be unlikely to provide sufficient information to convincingly establish the clinical effectiveness in either setting.

   Our review confirms that patients with low-grade non-Hodgkin's lymphoma (NHL) that has not undergone transformation (37 patients) and those with low-grade NHL that has undergone transformation (23 patients- see next two comments) represent subpopulations in which the activity of Bexxar is significantly different. You will need to conduct additional studies to develop an adequate experience in each of the subpopulations to establish the clinical effectiveness of Bexxar. Additional trials conducted in patients with low-grade NHL which has not transformed should be conducted using a randomized, active control study design to permit an assessment of net clinical benefit.

2. The number of subjects studied with transformed NHL is insufficient to establish clinical effectiveness in this patient population and you must conduct additional studies. You have identified 60 patients enrolled in three separate studies with a histologic diagnosis of low-grade NHL with transformation, however this diagnosis was appropriately confirmed by central review for only 22 subjects. In subsequent studies, all subjects must have independent confirmation of the original diagnosis of low-grade NHL and the histologic diagnosis of transformation. You must establish the credentials of the central reviewing pathologist(s), provide a detailed description of the procedure for central pathologic review, and provide a detailed description of the pathologic findings from both the original pathologist and the central pathologic reviewer(s). In the current application, there is insufficient pathologic description to document the findings that formed the basis of the diagnosis. This is particularly important when the diagnosis of transformation might be influenced by knowledge of the timing of the biopsies and/or subject to interpretation.

3. There is insufficient documentation to confirm the diagnosis of low-grade NHL with transformation. The application contains the Maskpath, transformed dataset with central pathologist's histologic diagnosis for only 37 patients enrolled in the RIT-II-001 and RIT-II-004 trials. The data for central pathologic review is not provided for 23 additional patients. With regard to the 37 patients included in the Maskpath, transformed dataset, we note the following areas of concern regarding the quality of the data:

   a. Six patients' records (001-003-004; 001-003-007; 001-004-007; 004-013-003; 004-013-004; and 004-016-006) contain the same date for the diagnoses of both low-grade NHL and low-grade NHL with transformation. We also note that for patient 001-003-007, the date of diagnosis of low-grade NHL differs between the Dxhist, transformed dataset (2/9/93) and the Maskpath, transformed dataset (9/9/94).

   b. Seven patients' records (001-005-002; 001-005-003; 001-005-006; 001-006-002; 001-007-002; 001-007-004; and 001-008-005) do not have a date for the diagnosis of low-grade NHL with transformation.

   c. Two patients' records (001-005-003; and 001-007-004) do not contain the date for the diagnosis of low-grade NHL.

   In order to support the clinical activity of Bexxar in patients with low-grade NHL with transformation, you must submit documentation confirming the histologic diagnosis, objective tumor response, and response duration, and provide sufficient data to adequately characterize the safety profile of Bexxar for all 60 subjects. In addition, you must address the reasons for the very disparate clinical activity in low-grade NHL with

transformation for patients in RIT-II-004 as compared to the other two trials. In order to provide adequate confirmation of the histologic diagnosis, you must provide revised electronic datasets for Dxhist, transformed and Maskpath, transformed. You must also provide copies of the original and central pathology reports which contain detailed descriptions of the pathologic findings and establish the original diagnosis of low-grade NHL and the diagnosis of NHL with transformation for each of the 60 patients. In addition, please provide the prospective criteria applied by the central pathology reviewer to establish the diagnosis of low-grade NHL with transformation. In particular, provide the criteria utilized to establish a diagnosis of low-grade NHL and low-grade NHL with transformation on the same date (presumably in the same biopsy material).

4. The safety experience for Bexxar is incomplete and therefore insufficient to adequately characterize the toxicity profile of Bexxar. You must provide sufficient data to characterize both immediate and delayed toxicities in an adequate number of subjects (300-600 patients).

5. If it is your intent to utilize the results of Protocol RIT-000-004 to characterize the toxicity profile of Bexxar, you must provide the following information:

   a. There is insufficient information regarding patients who died within 90 study days of therapy administration. Specifically, provide data on the 11 patients (004-013-012; 004-013-005; 004-018-001; 004-016-011; 004-014-007; 004-014-002; 001-009-006; 001-008-002; 000-002-021; 002-030-002; and 002-030-009) who died before study day 90. The causes of these deaths and the clinical events prior to these deaths are not adequately documented in the application.

      For each patient, you must provide a narrative summary, and the complete medical record covering the period from registration on study until death. The medical record should contain all physician's and nurse's notes, the results of all laboratory tests, and copies of radiographic study reports, and cytology/histopathology reports. Autopsy and death certificate records should be provided in the submission; you must indicate if no autopsy was performed in your response.

      We further note that for two of these patients (001-008-00; and 004-018-001) who were enrolled at the same institution, death from undetermined causes occurred within several days of their dosimetric infusion. In addition to the information requested above, you must provide a complete summary of the preparation, handling and administration of the dosimetric dose for these individuals. Please include the hospital radiopharmacy records, including the lot numbers and all other identifiers for the components of the radiolabeled

antibody administered to these patients, and any test results performed for "release" of the final product prior to administration.

b. There is insufficient information regarding patients who suffered non-fatal serious adverse events (SAE) within 90 study days following administration of the radiolabeled antibody. Please provide a narrative summary for all patients who suffered serious but non-fatal adverse events during this timeframe.

In addition to the narrative summary, please provide additional information for the patients who experienced serious adverse events identified as hematologic, infectious, pulmonary, or gastrointestinal. A listing of these patients is provided below, by ID number. Provide the primary (source) documents from the time of study registration through resolution of the adverse event. The source documents should include physicians', nurses' and consultants' notes; results of all laboratory tests performed; reports for all radiographic studies; and any other information relevant to the serious adverse event.

1) Infections: 001-005-003; 001-006-003; 002-026-004; 002-030-019; 002-030-24; 001-008-002; 001-008-004; 001-008-006; 004-013-001; 004-013-010; 004-015-005; 001-005-005.

2) Hematology: 001-004-006; 001-005-001; 004-016-001; 002-025-901.

3) Pulmonary: 002-030-002; 004-013-017; 004-013-002; 004-013-005; 004-016-011.

4) Gastrointestinal: 001-004-002; 001-008-003; 002-011-016; 002-011-018; 002-034-008.

c. There is insufficient information regarding patients with persistent hematologic toxicity at 120 days or longer after receiving the therapeutic dose. Please provide a narrative summary for two patients (002-011-917 and 002-030-019) who continued to have hematologic toxicity beyond study day 120. If you are aware of any additional patients with persistent hematologic toxicity (beyond day 120), please provide narrative summaries for these patients as well.

d. There is insufficient information regarding patients who withdrew or dropped out of the trial during the first 90 days of study. Please provide narrative summaries for the following patients:

1) Three patients (000-002-021; 004-015-005; and 004-018-001) who are reported to have dropped out as a consequence of infusion-related toxicity.

2) Eleven patients (000-002-021; 000-002-031; 001-003-004; 001-008-002; 002-025-901; 002-030-019; 002-030-906; 004-013-008; 004-014-002; 004-015-006; and 004-018-001) who are stated to have withdrawn from the study for reasons other than progressive disease.

e. The first organ toxicity from the administration of I-131-B1 therapy is myelosuppression. The protocol-specified monitoring schema required complete blood count (CBC) evaluations weekly during the first 12 weeks. In addition, CBCs were to be obtained more frequently in patients with grade III or IV hematologic toxicity and such monitoring was to continue until resolution of the grade III or IV toxicity (i.e., weekly or more frequent monitoring beyond 12 weeks in the presence of persistent toxicity). The complete results of this monitoring are required for the following: assessment of the incidence, severity and duration of hematologic toxicities and for the determination of the recovery (or lack of) from these toxicities. Our review of the BLA notes the following:

1) There are patients with grade III or IV hematologic toxicities where follow up CBC evaluations are not reported (i.e., time to resolution and documentation of resolution are not provided).

2) The results of protocol-required CBC evaluations during the first 12 weeks are not reported for all patients.

In order to provide sufficient information regarding the hematologic toxicity profile of Bexxar, you must provide an electronic dataset containing the results of all CBCs obtained in accordance with the clinical protocol for all patients enrolled. The electronic dataset should integrate previously reported data with the data that was omitted.

f. There is essentially no information on the effects of Bexxar on thyroid function beyond the first 90 days post-Bexxar therapy. These data must be provided for all patients exposed to Bexxar until their death, since there is clear evidence of localization of Bexxar to the thyroid in multiple subjects.

As discussed in the telephone conversation of January 11, 2001, you have committed to contact all subjects who are living and obtain TSH results for each subject, to inform these subjects of the potential risks of late onset hypothyroidism and of the need for life-long monitoring. You have agreed to

amend ongoing studies to require continued close monitoring of TSH for the first two years after therapy and annually thereafter until death.

g. There is inadequate information regarding delayed immunogenic response to Bexxar. The data provided on the two subjects in RIT-004 suggest that delayed immunogenic responses (positive human anti-murine antibody responses) do occur and may be common, as it was observed in all three of the subjects monitored beyond six months. As discussed during the teleconference of January 11, 2001, you will attempt to contact and obtain sera to conduct HAMA assays for all subjects who are alive. You have also committed to amend ongoing protocols to ensure that HAMA results are collected in a complete and systematic fashion for an adequate number of patients followed for up to 2 years.

h. The follow-up on all subjects is relatively short, yet among the 286 subjects in the original application, there have been seven cases of myelodysplastic syndrome (MDS) and four cases of acute leukemia. Given the relatively short duration of follow-up available on patients who have "withdrawn" from the trial, please provide the annualized rate for MDS and leukemia based upon patients known to be alive and in continuing follow-up.

6. The tumor and organ dosimetry data and assessments are inadequate and incomplete. As stated in the BLA, residence times of Iodine-131 anti-B1 antibody were calculated for the kidney, liver, lung, spleen, bone marrow, blood, and total body. For the organ dosimetry calculations, all other organs were assumed to have localized the radiolabeled antibody at the whole body background level. However, this assumption is inconsistent with our review of the whole body biodistribution images which demonstrates prominent uptake of I-131 in the thyroid gland, as well as prominent localization in the stomach, small bowel, and large bowel, in multiple patients. Please reassess and report the organ dosimetry studies with additional regions of interest for the thyroid gland, stomach, small bowel, and large bowel to establish residence time data for these organs.

7. The goal of Iodine-131 anti-B1 antibody therapy is localization of the radiolabeled antibody in tumor sites to deliver therapeutic radiation. Our review of the tumor radiation dosimetry notes that summary results for selected tumor sites from 45 patients enrolled in the RIT-I-000 study, 7 patients enrolled in the RIT-II-001 study and 53 patients enrolled in the RIT-II-003 study are provided. However, we are unable to complete our independent review of the tumor dosimetry because you have not submitted the primary (source or raw) radiation dosimetry data and the time-activity data for these tumor sites. Please submit the dosimetry source data with the time-activity data results, for all tumor sites evaluated for tumor dosimetry.

8. The application refers to a population of 14 patients who received more than one therapeutic dose of Bexxar (re-treatment). Data on the re-treatment group are presented in tabular form but there are no list files which would permit evaluation of the individual patients. Please identify the patients in the re-treatment group according to unique patient identifiers and provide separate electronic datasets containing all data collected for these patients.

9. You were informed that you would need to establish the contribution of the Iodine-131 radiolabeled antibody by a comparison of the clinical activity of cold anti-B1 and Bexxar in a randomized study (RIT-II-002). Please provide a final report for this study in your response. In the final study report, include a narrative description for all patients who withdrew prematurely, suffered serious adverse events (including death), or experienced prolonged, unresolved toxicity and delayed toxicities. The updated safety database for this study should be included in the integrated safety dataset.

10. Please provide the final study report for the RIT-II-003 study. In the final study report, include a narrative description for all patients who withdrew prematurely, suffered serious adverse events (including death), or experienced prolonged, unresolved toxicity and delayed toxicities. The final report safety database for this study should be included in the integrated safety dataset.

These comments are being provided to you prior to the completion of our review of your entire application to give you preliminary, advance notice of clinical issues that have been identified. Please note that these comments are subject to change as the complete review of your application is finalized. Final comments, if any, will be communicated to you at a later date after the review of the application is complete. You may, but are not required to, respond to these preliminary comments. If you respond, we may or may not consider your response prior to taking a complete action on your application. If your response is determined to constitute a major amendment, you will be notified of this decision in writing. Review of the remaining sections of your application is continuing.

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,

Terrye Zaremba, Ph.D.
Committee Chair
Division of Monoclonal Antibodies
Office of Therapeutics
Research and Review
Center for Biologics
Evaluation and Research

cc:

HFM-573/S. Litwin	(comments received 01/23/01)
HFM-573/G. Mills	(comments received 01/23/01)
HFM-579/Martin D. Green	
HFM-594/L. Epps	
HFM-215/S. Misra	
HFM-664/M. Andrich	
HFM-675/W. Lange	
HFM-675/P. Hughes	
HFM-588/M. Noska	
HFM-573/R. Steffen	
HFM-570/P. Keegan	(comments received 01/23/01)
HFM-570/K. Weiss	
HFM-555/K. Stein	
HFM-555/K. Webber	
HFM-585/G. Jones	
HFM-585/L. Burbank	

CBER:DARP:M.Noska:1/24/01:Mildred:1.25.01:1.26.01:mn:1/31/01:Mildred:1.31.01
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COMMUNICATION TYPE:

LETTER: Other (OT)

Summary Text: Discipline Review Letter - Clinical

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. Noska	1/31/01	OTRR/DIR	Lapeyre	2/1/01			
OTRR/CCR		1/31/01	DARP	Orfor	2/2/01			
OTRR/BOTOX	Lehrman	2/1/01						

BEST COPY AVAILABLE

MEMORANDUM OF TELECON

Date: January 11. 2001

To: BLA File (STN 125011/0)

From: Michael A. Noska, M.S., Regulatory Coordinator, DARP

Subject: Minutes from telecon with Corixa (formerly Coulter) regarding safety monitoring

CBER Participants: George Mills
Stephen Litwin
Patricia Keegan
Michael Noska
Richard Steffen
Terrye Zaremba

Corixa Participants: Patti Oto
Stu Kroll
Robert Stagg
Jill Henrich
Monica Krieger
Tim Pinkerton
Stella Jones
Nancy Valenti
Cory Nadeau

This call was initiated by the Agency to discuss safety monitoring based on the clinical review of the BLA for I-131-Tositumomab.

Dr. Keegan informed the company that thyroid uptake of I-131 has been seen in the nuclear medicine scans by the clinical reviewers. She also noted that there is a lack of information on TSH levels and that there is a concern for the safety of patients. She asked the company whether they are monitoring for thyroid function. The company replied that patients are being monitored for thyroid function and medications. TSH levels are captured for all patients on study per the protocol and then every six months after going off-study. These data are contained in the long term follow-up (LTFU) section of the BLA. Dr. Litwin asked whether there are data missing from the THYROUT dataset. Dr. Keegan noted that TSH data are not being captured in the case report forms as called for in the protocol. The company stated that 100 percent of patients are being followed on the LTFU form.

Dr. Mills reiterated that additional follow-up on TSH levels is needed for all patients and that the Agency is concerned that some patients could be hypothyroid based on the nuclear medicine images. Every patient who received a therapeutic administration of I-131-B1 should have follow-up beyond two years. For those patients still on-study, the protocol schedule should be followed. The Agency would like all patients to have a TSH measurement now and then follow-up at least annually (beyond two years) or according to protocol if inside of two years. Patients who were removed from the protocol due to progression should not be excluded from this follow-up; all patients on-protocol, including the open access trial, should be monitored.

Dr. Litwin requested that the consent form be amended to inform the patients that they need to have their thyroid function monitored at least yearly or according to the protocol-defined timepoints.

Dr. Mills also asked that the company acquire HAMA measurements along with the TSH levels, noting that the Agency has seen the late development of HAMA in patients who were negative at early timepoints.

The company asked about the potential scheduling of an Advisory Committee meeting. The Agency informed the company that this will not be possible until adequate follow-up has been obtained on all patients.

The call was concluded.

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: January 4, 2001

From: Leon Epps LAE

Subject: Teleconference on Coulter's Proposed Addition of a [redacted] Exchange Column to Produce the Lowest Achievable Levels of Free I-131 in Therapeutic Doses of I-131 Tositumomab Received on December 26, 2000 (BLA 125011/0)

CBER: Leon Epps, Ph. D. and Terrye Zaremba, Ph. D.

Coulter Pharmaceutical, Incorporated (CPI): Patricia A. Oto, R.Ph.

To: File

SUMMARY:

[redacted] b(4)

After discussing CPI's faxed proposal of December 26, 2000 (see Attachment) with Drs. Keith Webber and Terrye Zaremba, we agreed to allow CPI to proceed. Today at 5:30 P.M., Dr. Zaremba and I spoke with Patricia Oto regarding CPI's current proposal for reducing and controlling levels of free I-131. We agreed that the validation studies could proceed on the I-131 therapeutic dosage form as outlined in the submission of December 26, 2000 and that the data from these studies would be submitted to the BLA and IND 3323.

MEMORANDUM

Date: December 22, 2000

To: BLA File (STN 125011/0))

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

Subject: Minutes of Mid-cycle Meeting for Coulter BLA Submission for I-131-Tositumomab (Anti-B1 Murine Monoclonal Antibody for non-Hodgkin's Lymphoma)

Participants:

Walter Lange
Patricia Hughes
George Mills
Stephen Litwin
M. David Green
Terrye Zaremba (Chair)
Mary Andrich
Satish Misra
Leon Epps
Patricia Keegan
Keith Webber
Richard Steffen
Katy Stein
Jay Siegel
Bette Goldman
Ghanshyam Gupta
Glen Jones
Michael Noska

Mr. Noska opened the meeting by reviewing the milestones of the BLA review.

Dr. Zaremba provided a review of the Tositumomab drug substance.

Dr. Epps provided an update on the review of the final drug product and commented that data are needed on the lapse in time from the shipment of radiolabeled B1 by Nordion to the receipt of the product in the clinic.

Mr. Lange provided and update on the CMC and facilities review noting that a waiver has been requested for the inspection of BI Pharma. He also noted that some process validation data are needed. Dr. Siegel commented that this data should be requested soon and that no inspections should be conducted until these data are received.

Dr. Andrich gave an update of the clinical site inspections noting that the sites were all inspected during the first submission of the BLA in 1999. The data were found to be valid, however, a 483 was given to the University of Michigan for failure to properly block the thyroid for I-131 uptake prior to treatment.

Dr. Green commented that PK comparability of the three sources of antibody (Coulter, Lonza and BI Pharma) had been assessed and all were found to be comparable.

Dr. Mills presented the efficacy data from the BLA. He noted that the company has not yet submitted a final study report for the –002 trial which has been open since March 1999. Dr. Siegel stated that this report should be obtained. Dr. Mills also commented on the lack of documentation regarding biopsies and the assessment of histological transformation. Some data were missing and for other patients, the same date was given for the initial diagnosis and the date of transformation.

Dr. Litwin reviewed the safety database commenting on the potential risk of administering G-CSF along with I-131-labeled antibody. Additional safety data are needed. Further analysis needs to be conducted to study the differences between patients receiving different products.

Dr. Keegan noted that the efficacy database is considered to be too small because the company pooled data for two different subpopulations against the advice of the Center.

Dr. Siegel summarized the meeting by stating that the product seems to have adequate efficacy and although the toxicity is somewhat unknown due to missing data, it will probably be acceptable given the response.

The meeting was concluded.

Coulter
PHARMACEUTICAL

FACSIMILE COVER SHEET

DATE:	December 22, 2000	**TIME:**	3:30 PM PST
TO:	Dr. Terry Zaremba, DMA, Mr. Mike Noska, DARP **CBER, FDA**	**PHONE:** **FAX:**	301-827-5136 301-827-5397
FROM:	Patricia Oto	**PHONE:**	650-553-1917
SUBJECT:	CMC Proposal	**FAX:**	650-553-1910

If there is a problem with this transmission, or if any of the 8 page(s) are missing, please call Patricia Oto at 650-553-1917.

Dear Dr. Zaremba and Mr. Noska:

Please find attached a manufacturing proposal to address the FDA's concern regarding the controlling of the [redacted] I in the product, Bexxar™. This proposal was discussed with Mr. Noska in a teleconference last week. As described in the attachment, CPI is proposing to making a manufacturing change in the production process for the therapeutic dosage form (TX). This change incorporates the addition of a [redacted] exchange column upstream of the final [redacted] of the bulk product. b(4)

[redacted] b(4)

CPI needs to initiate these process validation runs as soon as possible to have this information available for the upcoming Pre-Approval Inspection at MDS Nordion, therefore CPI requests a teleconference the first week of January to discuss this proposal. I will be contacting Mr. Noska in the immediate future to schedule this teleconference. If you have any questions please contact me at 650-553-1917. I will also be submitting this fax as a formal BLA amendment.

Sincerely,

Patricia A. Oto, R.Ph.
Senior Director
Regulatory Affairs

6 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Administrative- 27

Memorandum
DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public health service
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: December 18, 2000

From: Terrye Zaremba, Ph.D., BLA committee Chair
Walter Lange, PE HFM 675

Through
Julia Lukas	HFM-675	JML 1/25/01
John Eltermann	HFM-670	
Jacqueline Little	HFM-604	
Kathryn Stein	HFM-555	
Glen Jones	HFM-555	

To: BLA File – STN 125011

Subject: Recommendation for waiver of the pre-approval inspection of Boehringer Ingelheim Pharma, for BLA STN 125011, for - treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20-positive, B-cell non-Hodgkin's lymphoma, produced at Boehringer Ingelheim Pharma, Biberach, Germany.

Sponsor: Coulter Pharmaceuticals Inc U. S. license No. 1604

Product: **BEXXAR.** Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody. The common (scientific) name for the monoclonal antibodies contained in BEXXAR™ combination therapy are Anti-B1 Antibody for the unradiolabeled component and Iodine-131 Anti-B1 Antibody for the radiolabeled component.

Tositumomab, for treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20-positive, B-cell non-Hodgkin's lymphoma

Concurrence with recommendation for Waiver of Inspection:

Kathryn E. Stein, Ph.D. Director, CBER/OTRR/ DMA HFM-555	CONCUR ✓	DO NOT CONCUR	DATE 1/22/2001
Glen Jones, Ph.D. CBER/OTRR/DARP HFM-555	CONCUR ✓	DO NOT CONCUR	DATE 1/29/01
John A. Eltermann, Jr. R. Ph, M.S. Director, CBER/OCBQ/DMPQ HFM 670	CONCUR ✓	DO NOT CONCUR	DATE 1/26/01
Jacqueline Little, Ph.D,. CBER/OCBQ/DIS HFM 604	CONCUR ✓	DO NOT CONCUR	DATE 1/26/01

Summary: This memorandum recommends that inspection be waived for the evaluation contract manufacturing procedures performed by Boehringer Ingelheim Pharma, KG.

Product Description from CMC section of BLA supplement STN 125011
Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody (all configurations) will be produced commercially for CPI by BI Pharma KG, McKesson, and MDS Nordion under contract manufacturing agreements with CPI. This section provides a brief description of the manufacturing history of Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody (from clinical manufacture through commercial product manufacture). Anti-B1 Antibody and Iodine-131 Anti-B1 Antibody are administered in combination for the treatment of patients with relapsed or refractory low-grade or transformed low-grade, CD20-positive, B-cell non-Hodgkin's lymphoma (NHL). Anti-B1 Antibody is an IgG2a murine monoclonal antibody that binds to the CD20 antigen present on the surface of normal and malignant human B cells.

Brief History of Inspections of Boehringer Ingelheim Pharma, KG

A The BI facility is located in Biberach, Germany. BI is an affiliate company of Boehringer
Ingelheim, an international pharmaceutical company. The facility consists of several buildings including pharmaceutical and biotechnical manufacturing facilities, quality control laboratories, storage areas, research and development facilities, and administration buildings. The BI facility operates under cGMP conditions and has been licensed as a multi-product facility in the United States (License Number 1251).

The firm has been inspected several times during the past two years. Each inspection found some objectionable conditions but all inspections were classified as VAI (Voluntary Action Indicated).

The previous inspections and findings are summarized below.

- Inspection of 10/12-21/98: CGMP for Verluma only, classified VAI
- Inspection of 10/5-8/98: Pre-license for Enbrel only, Classified VAI
- Inspection of 4/27-5/11/98: CGMP Verluma and pre-license for Enbril and Synagis,
- Classified VAI
- Inspection 3/22-25/99: Pre-approval for CDER capsules and tablets, classified VAI
- Inspection 5/2-5/9/00: Pre-license for Campath & biennial for Enbrel, Synagis, and Verluma. Classified VAI (see last page for 483 observations).

Review of SOPP 8410" Determining when pre-license/Pre-Approval Inspections are Necessary" for the determination of planning an inspection of Boehringer Ingelheim Pharma for the manufacture of Coulter's (CPI) BLA for I-131-B1 (Tositumomab/Bexxar) for the treatment of non-Hodgkin's lymphoma.

The following criteria are required for the pre-license/pre-approval inspection according to CBER's policy: SOP 8410	*Justification for waiving the pre-approval inspection:*
• The facility does not hold an active U.S. license	• BI Pharma KG holds active U.S. license (# 1251).
• The facility has not been inspected in the last 2 year by the FDA.	• BI Pharma has been inspected several times during the past two years. Each inspection found some objectionable conditions but all inspections were classified as VAI (Voluntary Action Indicated). • Inspection of 5/2-5/9/00 Pre-license for Campath (L&I Partners); CGMP for Enbrel (Immunenx), Synagis (Medimune), and Verluma (Boehringer Ingelheim) classified VAI • Inspection of 10/12-21/98: CGMP for Verluma only, classified VAI • Inspection of 10/5-8/98: Pre-license for Enbrel only, Classified VAI • Inspection of 4/27-5/11/98: CGMP Verluma and pre-license for Enbril and Synagis, Classified VAI
• The establishment is performing significant manufacturing step(s) in new (unlicensed) areas using different equipment (representing a process change). This would include areas that are currently dedicated areas that have not been approved as multi-product facilities/buildings/areas.	The manufacturing process uses conventional processes that are similar to processes recently approved (see above). The processes do not use new (unlicensed) areas using different equipment. The follow text is quoted from the BLA supplement, Section 4.1.2.2.3.BI The following list of equipment is product-specific and dedicated to Anti-B1 Antibody: • [redacted] b(4)

	With the exception of the equipment discussed above, all equipment used for the manufacture of Anti-B1 Antibody BDS may be used for other products. Equipment that is used for multiple products undergoes product changeover prior to use in a subsequent campaign ... Additionally, equipment may have a validated cleaning protocol that has demonstrated adequate removal of the previous product. Section 4.1.2.2.4 BI
• The previous inspection revealed significant GMP deficiencies in areas related to the processes in the application/supplement (similar processes) or systemic problems, such as QC/QA oversight.	• No official action indicated from previous inspections. The four inspections cited above were VAI. See Page 5 of this memo for list of inspectional observations identified during the May 2000 inspection.
• The manufacturing process is sufficiently different (new production methods, specialized equipment or facilities) from that of other approved products produced by the establishment.	• The manufacturing process for Tositumomab is similar to that of other approved products produced by the establishment.

b(4)

Based on the information provided above, the BLA STN 125011 review committee recommends waiving the requirement for the pre-approval inspection of Boehringer Ingelheim Pharma KG facilities at this time. Should a long delay occur prior to approval, an inspection of the facility might be reconsidered.

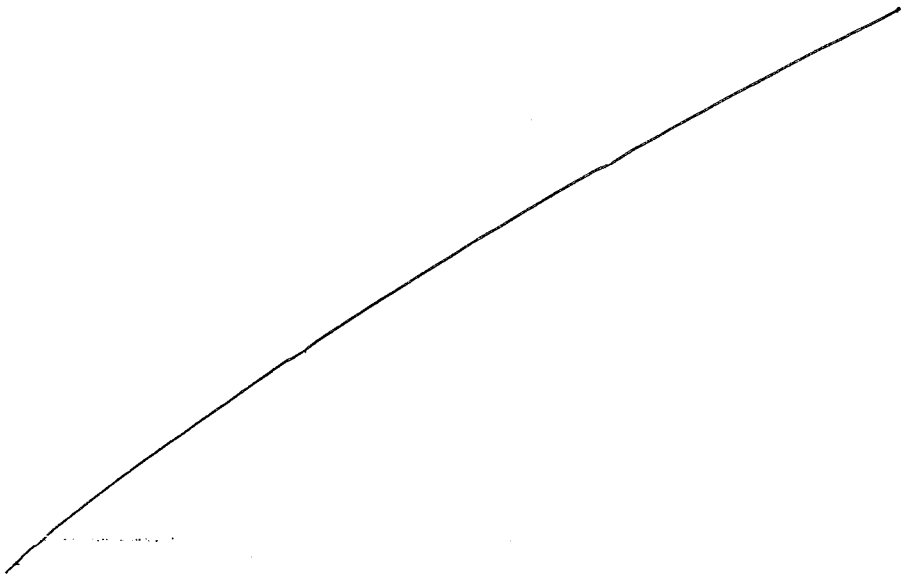
Committee members

Andrich, Mary
Epps, Leon
Green, Martin
Hughes, Patricia
Lange, Walter
Litwin, Stephen
Mills, George
Misra, Satish
Noska, Michael
Zaremba, Terrye

The following text supports the rationale for waiver of inspection based on the SOPP criterion which states: "The previous inspection revealed significant GMP deficiencies in areas related to the processes in the application/supplement (similar processes) or systemic problems, such as QC/QA oversight."

During the inspection of May 2000, the inspection team found that the facilities, equipment and processes were generally in conformance with regulations and with good manufacturing practices. Personnel appeared to be competent and well trained in their areas of responsibility.

Three observations were cited on form FDA 483 as a result of this inspection.



b(4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Our STN: BL 125011/0

NOV 14 2000

Patricia Oto, R.Ph.
Coulter Pharmaceutical, Inc.
600 Gateway Boulevard
South San Francisco, CA 94080

Dear Ms. Oto:

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 September 15, 2000 for tositumomab/Iodine-I-131-tositumomab, for the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20 positive, B-cell non-Hodgkin's lymphoma, 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

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTRR/DARP	M. Noska	11/13/00						
DARP	G. Jones	11-13-00						
DARP	A. Williams	11-14-00						

cc: HFM-585/DARP File
HFM-588/M.Noska
HFM-594/T.Zaremba
HFM-594/L.Epps
HFM-579/Martin D. Green
HFM-573/S.Litwin
HFM-573/G.Mills
HFM-200/S.Misra
HFM-675/W.Lange
HFM-675/P.Hughes
HFM-650/M.Andrich
HFM-555/K.Webber
HFM-570/P.Keegan
HFM-570/K.Weiss
HFM-515/P.Harris
HFM-585/G.Jones
HFM-110/RIMS

CBER:DARP:M.Noska:11-6-00:11-7-00:amw:11-7-00:11-13-00
(S:\Noska\License\BL125011FA.doc)

MILESTONE: FILING LETTER - (FA)

MEMORANDUM

Date: November 9, 2000

To: BLA File (STN BL125011/0)

From: Michael A. Noska, M.S. MAN
Regulatory Coordinator
OTRR/DARP/AAB

Subject: Minutes of Filing Meeting for BLA from Coulter for Iodine-131 Tositumomab (I-131-B1 anti-CD20 Murine Monoclonal Antibody) for the treatment of non-Hodgkin's lymphoma, held November 3, 2000 from 11:00-12:00, WOC I/200 South

Attendees: Keith Webber, George Mills, Ghanshyam Gupta, Walter Lange, Patricia Hughes, Patricia Keegan, Satish Misra, Steven Litwin, Leon Epps, Terrye Zaremba, Michael Noska, Mary Andrich

Dr. Terrye Zaremba briefly commented on the status of her review and stated that the application can be filed.

Dr. Leon Epps stated that the BLA can be filed.

Dr. George Mills gave an update on the clinical review and stated that the BLA can be filed.

Dr. Steven Litwin stated that the BLA can be filed.

Dr. Satish Misra noted that all statistical files were present and could be opened and manipulated and, therefore, the application can be filed.

Dr. Walter Lange noted that it might be necessary to request information from the sponsor, however, from the facilities perspective, the BLA can be filed.

Dr. Mary Andrich indicate that clinical site inspections were well under way.

The meeting was concluded.

MEMORANDUM OF TELECON

Date: October 20, 2000, 13:30

To: BLA File (STN 125011/0)

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

Subject: Minutes from telecon with Coulter regarding free I-131 iodide specs

CBER Participants:		**Coulter Participants:**	
	George Mills		Patti Oto
	Leon Epps		Stu Kroll
	Keith Webber		Robert Stagg
	Michael Noska		Kent Iverson
	Martin D. Green		
	Terrye Zaremba		

This telecon was initiated by Coulter to discuss the change in specification for free I-131-iodide in the final drug product, the qualification of a new source of I-131 and the BLA safety update.

Coulter indicated that, in response to the Agency's letter of September 15, 2000 to IND 3323, they would be reverting to the original specification for free-I-131-iodide in the final drug product. This will require an additional [redacted] step which will need to be validated. Dr. Epps indicated that it would be preferable to have data from three consecutive runs for both the diagnostic and therapeutic doses. Coulter estimated that the data would be submitted in December. Dr. Webber reminded the company that no changes in specification should be made until the data are submitted and reviewed. b(4)

Regarding the new source of [redacted] I-131, Coulter stated that they have secured a long-term source of [redacted] I-131 to supply the market while the new material is being qualified. Dr. Mills stated that the new [redacted] material should not be introduced into any other clinical trials, except the qualification trial. The other trials would need to be suspended until the company can return to production of the [redacted] -based I-131. Coulter stated that they would have an interim facility available to continue production of the [redacted] based product while the [redacted] qualification is proceeding. Dr. Green stated that the proposed design for the comparability protocol is not optimal but the Agency understands the reasons for the design. However, it will be necessary to review the final study design to determine its acceptability. b(4)

Dr. Litwin informed the company that their proposal for the BLA safety update as outlined in amendment 541 of IND 3323 is acceptable.

Coulter asked whether changes in labeling could be submitted along with the safety update or should be held for final labeling discussions. They were informed that it would be acceptable to submit them earlier.

Coulter indicated that new investigators would be involved in the expanded access and qualification trials and asked whether additional financial disclosure information would be needed. They were informed that disclosure information should be submitted as soon as possible.

Dr. Webber asked for a clarification of "radiochemical purity" versus " radionuclidic purity" and inquired as to what impurities might be present. Coulter stated that they would consult with MDS Nordion.

Dr. Zaremba inquired about the detection of [redacted] The company responded that there is some overlap but they have determined that [redacted] They do not measure non-radioactive [redacted] routinely as part of lot release. Dr. Zaremba asked whether they could assess [redacted] at least at the end of the shelf life of the product. Coulter stated that they would do this. b(4)

Dr. Zaremba asked whether any patients had been treated with the commercial product. Coulter replied that the BI Pharma product, which is intended for commercialization, has been used since September 1998 in 359 patients to date. As a point of clarification, the company stated that product from the commercial scale facility at Nordion has been used since September 2000.

The call was concluded.

MEMORANDUM

Date: October 17, 2000

To: BLA File (STN 125011/0))

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

Subject: Minutes of First Committee Meeting for Coulter BLA Submission for I-131-Tositumomab (Anti-B1 Murine Monoclonal Antibody for non-Hodgkin's Lymphoma)

Participants: Walter Lange
George Mills
Stephen Litwin
Patricia Hughes
M. David Green
Terrye Zaremba (Chair)
Mary Andrich
Satish Misra
Leon Epps
Michael Noska

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 November 14, 2000 and a filing meeting has been scheduled for November 3, 2000. The mid-cycle meeting with Dr. Siegel is scheduled for December 22, 2000. The final action due date is March 17, 2001. Oncology Drug Advisory Committee meetings are currently scheduled for March 14-15 and June 6-7, 2001.

The committee briefly discussed several issues relevant to the BLA review including:

1. The potential need for a clinical study to qualify a new source of NaI-131 (——— derived) b(4)

2. The recent change in specification for free iodide in the final drug product

3. Apparent gaps in monitoring of patients for TSH and HAMA levels

4. The shipment scheme for hot and cold antibody.

The meeting was adjourned at 10:10 am.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Patricia A. Oto, R.Ph.
Coulter Pharmaceutical, Inc.
600 Gateway Boulevard
South San Francisco, CA 94080-7014

OCT 02 2000

Dear Ms. Oto:

SUBMISSION TRACKING NUMBER (STN) BL 125011/0 has been assigned to your recent submission of your biologics license application, received on September 15, 2000, for tositumomab, iodine I 131 tositumomab, for the treatment of patients with relapsed or refractory low-grade or transformed low-grade CD-20 positive, B-cell 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

FILE COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
OTER/DARP	M. Hoshe	9/28/00	DARP	A. Williams	10-2-00			
DARP	Barnes	9/28/00						
DARP	M. Jones	9/29/00						

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

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

OTRR/DARP: A.Williams:9/26/00:9/28/00
S:\STN 2000\125011/0.org.doc
STN ASSIGNMENT - APPLICATION
CORR: ACKNOWLEDGMENT LETTER

REVIEW COMMITTEE ASSIGNED MEMORANDUM

Date: 9/15/00

STN: 125011.0.

Regulatory coordinator: Mike Noska

Job Type: administrative/regulatory

Applicant: Coulter

Product: Tositumomab

Type of submission: BLA

Purpose of submission: Treatment of non-Hodgkin's lymphoma

Review time frame: 6mth. Priority

The review committee for this BLA/Supplement is as follows:

Chairperson: Terrye Zaremeba

Job Type: Product

Reviewers:	Name
Administrative/Reg.	Mike Noska
BIMO	Mary Andrich
Biostatistics	Satish Misra
Clinical	Steve Litwin/George Mills
CMC	Leon Epps
Facility	Walter Lange/Patricia Hughes
Inspector	
Labeling	
Other	
Pharm/Tox	Martin (Dave) Green
Product	
SOP	

Consultative reviewers:

Reviewer Name:

Job Type:

Comunications Memo Entered Q.H. Date 10/4 QC LKB Date 10/4/00

RPMS: You need to indicate who is the committee chair. If a reviewer is a consult, you must indicate this, as well the area they are consulting. At this time there is no Epidemiology category. Hopefully, that will be added in the future. In the meantime, if you have an epidemiology reviewer, capture them as other. For job type of the chairperson, enter either clinical or product as appropriate.

Department of Health and Human Services

MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research

DATE: September 18, 2000

FROM: Karen D. Weiss, M.D. KDW 9-18-00
Director
Division of Clinical Trial Design and Analysis
Office of Therapeutics Research and Review

SUBJECT: Designation of BLA application review status
Sponsor: **Coulter Pharmaceutical**
Product: **Tositumomab (I-131-B1)**
Indication: **Treatment of non-Hodgkin's lymphoma**

TO: BLA file

The review status of this file submitted as a BLA application is designated to be:

☐ Standard ☑ Priority