CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125011

CHEMISTRY REVIEW(S)

REVIEW OF CMC FOR BEXXAR (ANTI-B1 ANTIBODY, TOSITUMOMAB)
CORIXA CORP. (FORMERLY COULTER) – BLA STN 125011

DOS: 9/15/00

REVIEWER: Terrye G. Zaremba, Ph.D. 6-27-03

DATE: 4/20/01 (revised [redacted])

SUMMARY: This BLA was submitted almost entirely in electronic format. Two summary volumes were submitted in hard copy. This review is divided into three parts: 1) review of the production processes at three different sites, 2) review of the comparability of the products produced at the three sites, and 3) review of the current manufacturing for licensure at Boehringer Ingleheim Pharma KG (BI Pharma).

PRODUCTION – The product was originally manufactured at Coulter Corp. for diagnostic and *ex vivo* studies under INDs [redacted] & [redacted] IND 3323 was submitted on 10/13/89 for *in vivo* treatment of Non-Hodgkin's Lymphoma (NHL). Coulter manufactured, tested, and released the product through April 1995. The product produced at Coulter (or [redacted]) was used in clinical trials until June 1997. CPI (South San Francisco, CA) was established in 1995. At that time Coulter transferred IND 3323 to CPI. In 1995, CPI initiated cooperative manufacturing relationships with Lonza for the production and testing of Anti-B1 Antibody bulk drug substance (BDS) and packaged bulk drug substance (PBDS), and with CYTOGEN for the final filling, release testing, packaging, and distribution. [Note that standardized radiolabeling kits using IODO-GEN- based labeling were developed by CPI & Coulter. These were distributed from Coulter to the clinical sites from December 1995 to July 1997. The radiolabeling with I-131 is reviewed by Dr. Leon Epps]. The Coulter product using radiolabeling on site was used to treat 159 patients. b(4) b(4)

CPI coordinated the transfer of frozen ampoules of Coulter's WCB to Lonza. Lonza adapted the cell line to serum-free growth by re-cloning and renamed the clone B1R1. Clinical site radiolabeling with Lonza production & CYTOGEN filling was used for four patients in July 1997. Lonza/CYTOGEN-production with central radiolabeling at MDS Nordion was used clinically from July 1997 to September 1998. A total of 89 patients were treated with product made under this scenario. b(4)

In 1997, CPI established a cooperative manufacturing agreement with [redacted]. The MCB produced by [redacted] was transferred to [redacted], from which they produced a WCB. The product manufactured by [redacted] with radiolabeling at MDS Nordion was used to treat 34 patients beginning in September 1998. b(4)

A. Coulter Corp.

1. Anti-B1 was originally produced from a murine hybridoma cell line created by the Dana Farber Cancer Research Institute at the Harvard School of Medicine prior to 1980. The creation of the cell line was [redacted] b(4)

95 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 1

FINAL CMC REVIEW FOR BEXXAR (Anti-B1, Tositumomab) CORIXA CORPORATION BLA STN 125011

Reviewed by: Terrye G. Zaremba/DMA

DATE: June 27, 2003

Following review of all submissions to this file including those of April 30, 2003, May 12, 2003, June 11, 2003, June 25, 2003 and June 28, 2003, all concerns have been addressed except for those delineated as post-approval commitments in the approval letter. I, therefore, recommend approval of this product.

CONCERNS REGARDING ITEMS 1 & 2 IN CORIXA'S 4/3/03 RESPONSE TO CMC DR LETTER STN 125011/054

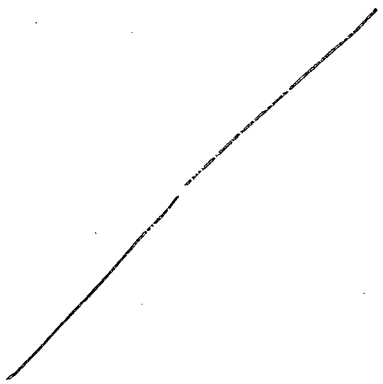
Reviewed by: T. Zaremba/DMA

DATE: 4/21/03

SUMMARY: Stability studies performed on the ——— reagent assessing the number of binding sites by the Lindmo & saturation binding methods have led to large differences in the number of sites depending on which method is used. The saturation binding method indicates many fewer binding sites (e.g., Lindmo > ———; saturation > ———. Furthermore, the number of sites decreased with time in storage when assessed by saturation binding, but increased with time when assessed by Lindmo. The moisture content was also rather high — to —% & increased with time of storage, suggesting that the lyophilization was not performed properly (See Tables 2.1-2.3). What values were obtained at time zero for lot 2310301? Has ——— validated their lyophilization cycle and has Corixa inspected this facility? b(4)

In addition, with both saturation binding & Lindmo, the lines drawn through the plotted points using various software packages, do not always appear to go through the points, suggesting that the software packages may not be operating properly (See figs. below).

b(4)



Would like to see the data points obtained for the accelerated stability studies shown in Tables 1.1 & 1.2 for the —assay and those obtained for the saturation binding curves shown in Figs 2 & 3 (we note that the lines drawn as the best fit for the saturation binding curves do not necessarily look like the best fit). Please submit the actual data points used to validate the 3 curve-fitting software packages used to obtain the ——results shown in Tables 4 & 5 (Item 1, pages 39 & 40).

Unclear if the differences between the saturation binding & the Lindmo are related to certain assumptions made for the Lindmo analysis. Also it is not clear why the formula used for the ——calculation leads to sites/cell/nM, which is not the manner in which Lindmo data are generally calculated. It may be illuminating to plot the data in a linear form. Depending if the plot is linear or curves up or curves down, some conclusion

regarding the assay parameters can be obtained (e.g., not enough cells, not enough antibody, too large % bound, etc). Would like to see the curve-fitting algorithm that corrects non-specific binding values for ligand depletion (Item 1, p. 42, Coulter B1-CM-030P, or paper by Swillens, 1995).

Misc. items:

Item 1, p.58, 6.2.3, Reproducibility: Only one set of data, where are the data for the 2nd analyst?

Item1, p.61, Working Range of Cell Reagent: What were the different cell binding capacities used in this assay? b(4)

Item 1, p.78, Table 3: Final Cell Conc. Should be [redacted]; shown as [redacted]

Item1, p.87, Appendix A: Cannot read this.

Item 1, p.98, Lindmo plots: Submit data points. Comment on what [redacted] values were obtained.

Item 1, p. 7 & 8, accelerated stability: Note that %IRF never went below [redacted] %. Suggest revising specification to ≥ [redacted] (rather than ≥ [redacted] %).

See telecon April 22, 2003 & Corixa's response dated May 12, 2003.

APPEARS THIS WAY
ON ORIGINAL

Table 2.1: Tabulated Stability Data

Product Attribute	Test Method	Specification	Time Zero	3 Month	6 Month	9 Month	12 Month
Lindmo Titration	SOP QC-681						
Saturation Binding	SOP QC-680						
Residual Moisture	SOP QC-353						

*Note: Saturation Binding data for 6 months test point has not completed QC review.

Table 2.2: Tabulated Stability Data

Product Attribute	Test Method	Specification	Time Zero	3 Month	6 Month	9 Month	12 Month
Lindmo Titration	SOP QC-681						
Saturation Binding	SOP QC-680						
Residual Moisture	SOP QC-353						

*Note: Saturation Binding data for 3 months test point has not completed QC review.

b(4)

Table 2.3: Tabulated Stability Data.

Product Attribute	Test Method	Specification	Time Zero	3 Month	6 Month	9 Month	12 Month
Lindmo Titration	SOP QC-681						
Saturation Binding	SOP QC-680						
Residual Moisture	SOP QC-353						

*Note: Testing ongoing for remaining time zero assays.

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

Date: March 7, 2002

To: Terrye Zaremba, Ph.D., Chair, BLA committee, STN 125011/0/0

From: Walter Lange, OCBQ/DMPQ/MRB1

Through: Cynthia Kelley, Branch Chief, OCBQ/DMPQ/MRB1

Subject: Summary of DMPQ review of the BLA and responses to a complete review letter.

The CMC review of this supplement has been performed by reviewers Patricia Hughes, Ph.D. and Walter Lange.

Their review comments have been recorded in memos during the review cycle.

Questions about CMC issues were forwarded to the committee chair in a memo dated March 5, 2001. These were incorporated in the "complete review letter" dated March 16, 2001, in questions 20-39.

Corixa provided a detailed response to the complete review letter. A review memo dated Dec. 3, 2001 evaluated the responses to the DMPQ issues.

The responses were satisfactory with the following exceptions.

Response to Question 23 was incomplete. However, the matter may be satisfied during the pre-approval inspection of the Nordion facility.

Responses for Questions 34 and 36 in the August 26, 2001 submission are not adequate. Details are provided below. ***These questions should be included in a follow-up Complete Review letter.***

Inspection Item for Nordion.

Question 23.

b(4)

In BLA section 4.1.3.3 ND, page 79, it is stated that: "To satisfy specifications,

General industry practice is to maintain 0.05 inches w.g. Please provide clarification with appropriate monitoring data to

3 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 2

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: February 28, 2002

From: Leon Epps LAEpps
Regulatory Review Officer, DMA/OTRR

Subject: Corixa, Inc. (Coulter Pharmaceutical, Inc.) Response to Complete Review Lettter of March 16, 2001 for BLA (STN# 125011\0\0): BEXXAR™ (Tositumomab, Iodine I 131 Tositumomab) Dated August 26, 2001

To: File

Through: Keith Webber
Deputy Director of DMA

CC: Kathryn Stein
Terrye Zaremba
George Mills
Stephen Litwin
M.David Green
Satish Misra
Walter Lange
Michael Noska

CR Response To Agency's Questions Cited Below in Bold Italics:

b(4)

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 3

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

Date: December 3, 2001

To: File STN 125011/0/0

Through: Cynthia Kelley, Acting Branch Chief. CK

From: Walter Lange WL

Subject: Corixa (STN 125011/0/0) Review memo for responses to the Complete Review letter dated March 16, 2001.

This memo serves as the review of responses to DMPQ generated questions that were in the March 16, 2001 Complete Review Letter. The response was dated August 26,2001.

The responses to questions 20-39 were generally acceptable. However, questions 23, 34, and 36 require follow-up. This follow-up will be in the form of attention during the pre-approval inspection, or in subsequent submission of clarifying information as noted in the review comments for each of these questions (23, 34 and 36.)

The original submission is available on EDR/ CBER, 2000 BLAs, 125011/0/0.

The responses to the CR letter are included in amendment 125011\0\23.

Summary: Responses to questions 20-39 are found to be acceptable with several requiring consideration by Branch Chief: 23, 34, 36.

QUESTION 20
In BLA section 4.1.3.2 ND, page 10, the summary description of the anti-B1 Identity Test (SOP# 960822.STM) states that: "This test was implemented after the original process validation runs and will be used for commercial manufacturing." Please submit the validation report for this assay.

The response notes, "The reports for the validation and successful technical transfer to MDS Nordion are enclosed as attachments and are as follows:

- B1-CM-088R, Validation of the Method for Identification of Anti-B1 Antibody by Test Tube ELISA,
- B1-CM-094R, Transfer of the Method for Determination of Identity of Anti-B1 Antibody by Test Tube ELISA from Coulter Pharmaceutical Incorporated to MDS Nordion"

These appear to be acceptable.

9 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 4

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

Date: December 4, 2001

To: Terrye Zaremba, Ph.D. HFM-594

Through Cynthia Kelley, Acting Branch Chief.

From: Walter Lange

Subject: Corixa (STN 125011/0/0) Review memo for responses to the Complete Review letter dated March 16, 2001.

This memo serves to forward the DMPQ review of Corixa's August 26, 2001 responses to the March 16, 2001 Complete Review Letter.

DMPQ has completed its review of those questions that had been generated by DMPQ for the Complete Review letter, and we have found that most responses are adequate.

There are a few remaining issues (see questions 23, 34 and 36) that may be resolved either during a Pre-Approval Inspection or through a follow-up telephone contact or letter with the firm.

In a conversation with me today, you indicated that there may be substantive issues that require decisions at the mid-cycle review. Therefore, I think it may be appropriate not to contact the firm with these few issues, until a determination is made about the scope of the other remaining issues. b(6)

I will leave it to your discretion as to how best to convey the issues identified in this memo, and described in the review memo dated December 3, 2001. You may wish to consolidate all questions into a telephone conversation or a letter.

Attachment:
Review memo dated December 3, 2001.

CMC REVIEW OF CORIXA'S RESPONSE TO CBER'S CR LETTER BLA 125011/023

DOS: AUG 27/SEPT 07, 2001

REVIEWER: T. ZAREMBA, DMA T.Z. 6-27-03

DATE: 11/29/01

SUMMARY: CBER sent Corixa a CR letter dated March 16, 2001. This letter contained questions/comments from all disciplines. This review covers items 1-10 of their response. Corixa also answered additional CMC questions regarding comparability addressed to them in the meeting on May 31, 2001. These responses were contained in a "preamble" and are also reviewed.

Preamble: Corixa contends that the products produced from the three different manufacturing schemes are comparable, but admits that there are some structural differences. These include the :

b(4)

35 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-_____

MEMORANDUM
Food and Drug Administration
Center for Biologics Evaluation and Research

Date: March 6, 2001

From: Leon Epps
Regulatory Review Officer, DMA/OTRR

Subject: Review of Coulter Pharmaceutical, Inc. (Corixa, Inc.) BLA (STN# 125011\0\0): BEXXAR™ (Tositumomab, Iodine I 131 Tositumomab)

To: File

Through: Keith Webber
Deputy Director of DMA

CC: Kathryn Stein
Terrye Zaremba
George Mills
Stephen Litwin
M.David Green
Satish Misra
Walter Lange
Michael Noska

SUMMARY: b(4)

BI Pharma KG manufactures the intended sources of product for commercial purposes, including Anti-B1 Antibody bulk drug substance (BDS), packaged bulk drug substance (PBDS) and [redacted]). MDS Nordion is responsible for inventory of Anti-B1 Antibody PBDS and production of Iodine-131 Anti-B1 Antibody. CMC information has been placed in a folder entitled **cmc.** This CMC folder contains folders for three manufacturers, BI Pharma KG (BI), MDS Nordion (ND), and Coulter Pharmaceutical, Inc. (CP).

CPI's CMC section also contains information regarding the manufacture of Anti-

B1 Antibody at Coulter Corporation (Coulter Corp.), [redacted] because these manufacturers produced product used in the clinical studies supporting this BLA. CMC information on Anti-B1 Antibody BDS and PBDS manufactured by [redacted] is provided for supportive information only. CPI has no intention to obtain licensure for [redacted] McKesson BioServices (McKesson) is responsible for inventory and distribution of Anti-B1 Antibody PBDS and drug product (DP) and for labeling and packaging of Anti-B1 Antibody DP. b(4)

The nonproprietary name adopted by the United States Adopted Name Council (USAN) is tositumomab for the unlabeled Anti-B1 Antibody and iodine I 131 tositumomab for the labeled Anti-B1 Antibody. Tositumomab was approved by the WHO Nomenclature Committee and has attained the status of a proposed International Nonproprietary Name (INN).

I. Composition of the Drug Product

The various components of Bexxar™ therapy have the following suffixes:

- **Bexxar™ QS:** Single-use 3 mL vial containing 35 mg of Anti-B1 Antibody.
- **Bexxar™ N:** Single-use 20 mL vial containing 225 mg of Anti-B1 Antibody.
- **Bexxar™ D:** Single-use 30 mL vial containing not less than 20 mL of iodine 131 Anti-B1 Antibody and a nominal activity concentration of 0.61 mCi/mL (at calibration).
- **Bexxar™ T:** Single-use 30 mL vial containing not less than 20 mL of iodine 131 Anti-B1 Antibody and a nominal activity concentration of 5.6 mCi/mL (at calibration).

Composition

Iodine-131 Anti-B1 Antibody DP is manufactured in two different dosage forms:

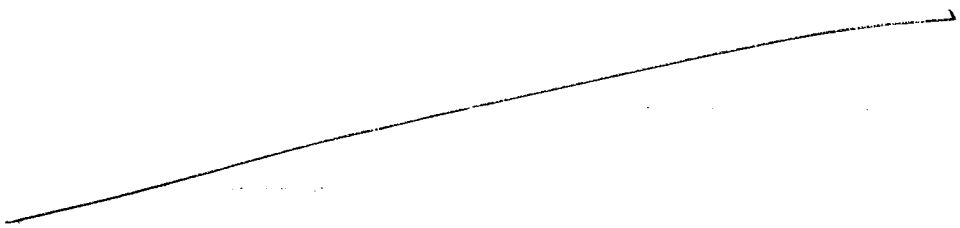
- Dosimetric: [redacted] mCi Iodine-131 with [redacted] mg Anti-B1 Antibody. A 5 mCi dose is prepared from the dosimetric dosage form DP. The dosimetric dose is used to assess the rate of body clearance to calculate the quantity of radioactivity necessary to deliver the therapeutic dose. b(4)

- Therapeutic: [redacted] mCi Iodine-131 with [redacted] mg of Anti-B1 Antibody. The therapeutic dose is prepared from the therapeutic dosage form DP. The activity (mCi) administered varies from patient to patient based on the whole body clearance rate calculated from the dosimetric dose. b(4)

Each dosage form contains a volume range of 20.0-[redacted] mL of DP dispensed into a 30-mL vial. The two product dosage forms contain the same concentrations of excipients, but different concentrations of Iodine-131 Anti-B1 Antibody DP.

The dosimetric and therapeutic dosage forms DP are manufactured in separate manufacturing runs using two distinct but similar manufacturing processes. The batch size for each dosage form DP is variable over a validated range and will be matched to demand to minimize the generation of radioactive waste.

[redacted] b(4)



31 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry- 6

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

Date: February 20, 2001

To: File STN BL 125011

From: Walter Lange

Subject: Review memo, CMC section Corixa,
BLA supplement for BEXXAR, Tositumomab

This review addresses the Chemistry, Manufacturing and Controls section of the Corixa (formerly Coulter Pharmaceuticals, Inc. (CPI))) submission for BEXXAR, (Tositumomab). This review is limited to consideration of GMPs, process validation, and of the facilities and equipment used in the manufacture of this product.

The submission is complex and overlapping. Therefore, this review is organized using the key issues cited in the *Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products* issued in 1994. This review concentrates on section IV of that Guidance, Information for Aseptic Fill Manufacturing processes which should be included in drug applications. Microbiological considerations were addressed in a review memo completed by P. Hughes, Ph.D, formerly of the Division of Manufacturing and Product Quality. Other aspects of the submission are addressed by product reviewers.

Questions are identified in the text of this review. All questions are consolidated at the end of this review memo in a form that may be considered by the review committee chairperson for formal communication to the sponsor.

Unique issues that are appropriate for consideration during an inspection are addressed in another separate section at the end of this review memo.

As stated in section 3.2.3 (page 88 of 302), the supplement "describes CPI's supervisory role over three commercial manufacturers in this Biologics License Application (BLA): Boehringer Ingelheim Pharma KG, Biberach, Germany (BI Pharma KG); MDS Nordion, Inc., Kanata, Ontario, Canada (MDS Nordion); and McKesson BioServices, Rockville, MD (McKesson). It also describes the contract labeling, packaging, and distribution performed by McKesson. All historical manufacturing information relevant to clinical supply and comparability, including CMC information for Coulter Corporation, Hialeah, FL (Coulter Corp.); [redacted] b(4
[redacted] are also included in this section because these manufacturers produced product used in the clinical studies supporting this BLA." The review does not include consideration of work by [redacted] or of [redacted], as these firms are no longer affiliated with the manufacture of Tositumomab (BEXXAR).

The responsibilities of the three commercial firms in this application are:

- **BI Pharma KG** manufactures ——— Bulk Anti B1 Antibody Drug Substance (PBDS); Anti B 1 Antibody Drug Product in labeled and unlabeled finished
- **MDS Nordion** manufactures Radiolabeled Anti B1 Antibody manufactured by BI. (also performs some distribution to radio-pharmacies.
- **McKesson** does labeling (except for those vials labeled by BI Pharma KG), packaging and storing and final distribution.

The application also cites a number of contracted firms that provide testing services or materials and components. The review found that these references were adequate, the contracted firms appear to have appropriate qualifications. The qualifications of these firms will be considered as part of the inspection.

General Issue: The complex manufacturing steps and the contractual relationships will require a well developed management and quality oversight of all phases of manufacturing, packaging and distribution. This oversight is described in BLA section 3.2. (p. 95 of 302) :

"CPI SOP CPC001 ———————————————

b(4)

A. Buildings and Facilities

Floor Plan and Location of Equipment

Boehringer Ingelheim Pharma, KG

Boehringer Ingelheim, Pharmaceuticals, (BI): buildings and facilities are described in section 4 of this submission. The text appears to be generally adequate. BI was also inspected by this reviewer for another PAI during May, 2000. The firm's facilities are well maintained, and adequate for manufacture of this product.

24 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

Withheld Track Number: Chemistry-7

Best Copy Available
11/9/01

Office of Compliance and Biologic Quality
Division of Manufacturing and Product Quality
HFM-675
Review of BLA

STN: 125011/0/0 **Original BLA**

Product: Tositumomab

Company: Coulter Pharmaceuticals Inc. **U.S. Agent:**

License No.: 1604 **CBER/DCC Number: 30414**

Date received in CBER/DCC: **Document Date: 14-Sept-2000**
15-Sept-2000
Dosage: Dosimetric and therapeutic dosage forms

Administration: Injectable

Method of Sterilization: ——————— b(4)

Remarks: This BLA contains CMC information and data for the following manufacturing processes:

- **———Bulk Anti B1 Antibody Drug Substance (PBDS) manufactured by BI Pharma KG**
- **Anti B 1 Antibody Drug Product in labeled and unlabeled finished vials manufactured by BI Pharma KG**
- **Radiolabeled Anti B1 Antibody manufactured by MDS Nordion**
- **Labeling (except for those vials labeled by BI Pharma KG), packaging and storing and final distribution is carried out by McKesson**

Conclusions: BLA 125011/0.0 which provides for tositumonab is not recommended for approval from the standpoint of product quality microbiology. Deficiencies are identified in section 4.1.3.7 ND and 4.1.3.7 CP of the BLA. Please see section A "Review Notes" and section B "List of deficiencies".

2001.

Reviewer: Patricia F. Hughes, Ph.D. **Date of completed review: January 19, 2000**

Review concurrence by: **Date of concurrence:**

Cc: Walter Lange

29 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

*Withheld Track Number: Chemistry-*8