CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125019/0

CHEMISTRY REVIEW(S)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Memorandum

Food and Drug Administration
Center for Biologics Evaluation and Research
Bethesda, MD 20892

Date: April 27, 2001

To: BLA ST125019/0 File

From: Marjorie A. Shapiro, Ph. D., Division of Monoclonal Antibodies, OTRR

Through: Kathryn E. Stein, Ph. D., Acting Chief LMDI, DMA, OTRR K.E. Stein 4/30/01
Keith Webber, Ph.D., Deputy Division Director, DMA, OTRR K Webber 4-30-01

Subject: Zevalin BLA

Sponsor: IDEC Pharmaceuticals
3030 Callan Road
San Diego, CA 92121

Contact(s): Alice Wei (858) 431-8920
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Clinical Indication: Treatment of patients with relapsed or refractory low grade, follicular or CD20+ transformed B cell Non-Hodgkin's lymphoma, and rituximab refractory follicular NHL.

List of documents reviewed:

Original submission ST125019/0: November 1, 2000
CMC Section, Items relating to Drug Substance: Item 4A, 4F, and 4G, sections of 4B, 4H, 4I and 4J (Dr. Leon Epps will review sections pertaining to drug product)
Non-clinical Pharm/Tox Section: Sections of Item 5B
Human Pharmacokinetics: Item 6C

Amendment STN125019/0.11: February 22, 2001
Amendment STN125019/0.12: March 6, 2001
Response to Telecon (February 13, 2001) Request log #44367 : March 5, 2001
Amendment STN125019/0.14: April 4, 2001 Response to IR letter of March 23, 2001
Amendment STN125019/0.15: April 9, 2001

Product Description

IDEC 2B8 (Ibritumomab) is a murine IgG1, κ monoclonal antibody expressed by Chinese Hamster Ovary (CHO) cells. It binds to the CD20 surface antigen found on normal pre-B and B cells and established B cell lines. CD20 is not expressed by progenitor B cells and is lost upon terminal differentiation to plasma cells. It is also not expressed by other hematopoietic cell types. A majority of B-lineage malignancies express CD20. The molecular weight of IDEC 2B8 is [redacted] Daltons, calculated from the primary amino acid sequence. The light chain consists of 213 amino acids and the heavy chain consists of 445 amino acids. The 2B8 construct used for expression in CHO cells contains a [redacted] This change does not impact the function of ^{90}Y-Zevalin™ (see attachment 7). IDEC-2B8 is manufactured by IDEC as a purified bulk substance. Purified drug substance is formulated at [redacted] It is shipped to [redacted] for further manufacturing into IDEC 2B8 MX-DTPA (ibritumomab tiuxetan, Zevalin™) in which the antibody is [redacted] MX-DTPA which chelates yttrium- [90] (^{90}Y-Zevalin™).

This review contains a summary of the CMC section and conclusions of the reviewer pertaining to the drug substance. Dr. Leon Epps reviewed the CMC sections pertaining to drug product. The attachments contain details largely downloaded from CMC section and reviewer comments in this section are prefaced by "reviewer's comments". These comments are reflected in the summary of the BLA contained on pages 1-8 of this review.

Table of Contents

Review of IDEC 2B8 Drug Substance

I. Manufacturing sections of the BLA
History/development of product (Attachment 1)

[redacted]

Cell line establishment and banking (Attachment 2)

[redacted]

Cell Culture Process (Attachment 3)

[redacted]

Downstream processing (Attachment 4)

[redacted]

Formulation and filling of bulk substance (Attachment 5)

[redacted]

Shipping (Attachment 6)

[redacted]

II. Preclinical sections

Rationale for use (Attachment 7)

IDEC-2B8 is specific for human CD20 which is a B cell specific surface antigen found on >95% of peripheral blood B cells and on 93% of B-cell lymphomas. CD20 is not found on progenitor B cells. CD20 is present on the B cell surface at 200,000 to 400,000 copies per cell. Upon anti-CD20 binding, this complex is not internalized. CD20 is not shed from the cell surface. These two properties of CD20 make it a good target for an immunotherapeutic agent.

Potency (Attachment 8)

Studies done at IDEC demonstrate: 1) IDEC-2B8 produced in CHO cells binds specifically to CD20-expressing cells and not CD20 negative cells; 2) that it binds CD20 as effectively as 2B8 produced by the murine hybridoma; [redacted]

III. Validation sections

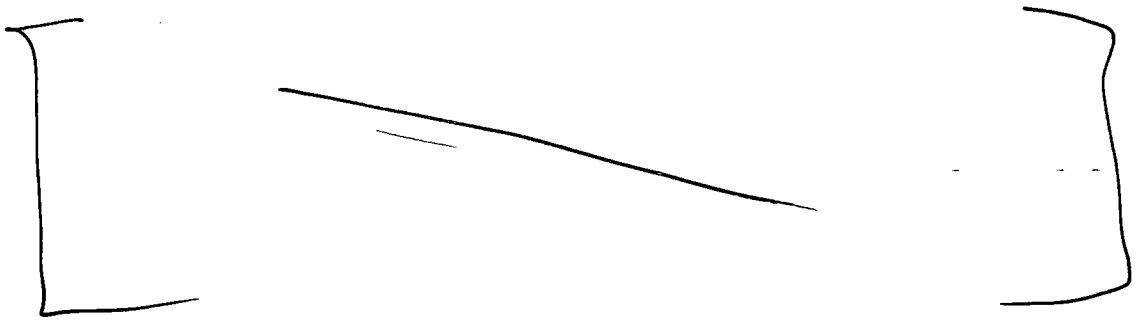
Process validation/Process Controls (Attachment 9)

The process controls used for the manufacture of IDEC-2B8 are a combination of detailed manufacturing instructions, action limits associated with routine analysis of in-process samples, and validation of process performance characteristics. In-process samples are collected at defined stages of the culture and purification processes. During development, these data were used to refine the in-process specifications. For the consistency lots, the data were used to show consistency and reliability of the process.

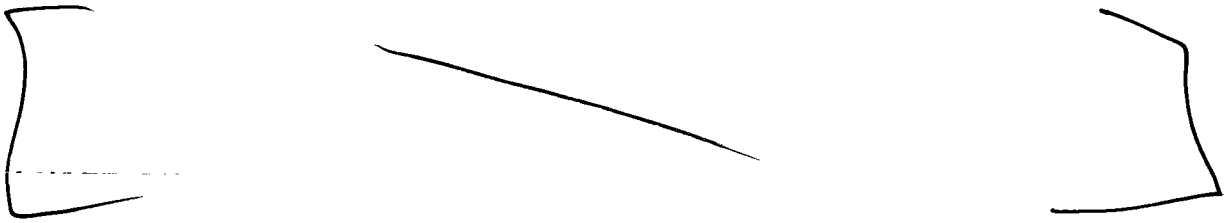
Assay validation (Attachment 10)

Assays used for in-process, release, and stability testing have been validated. The

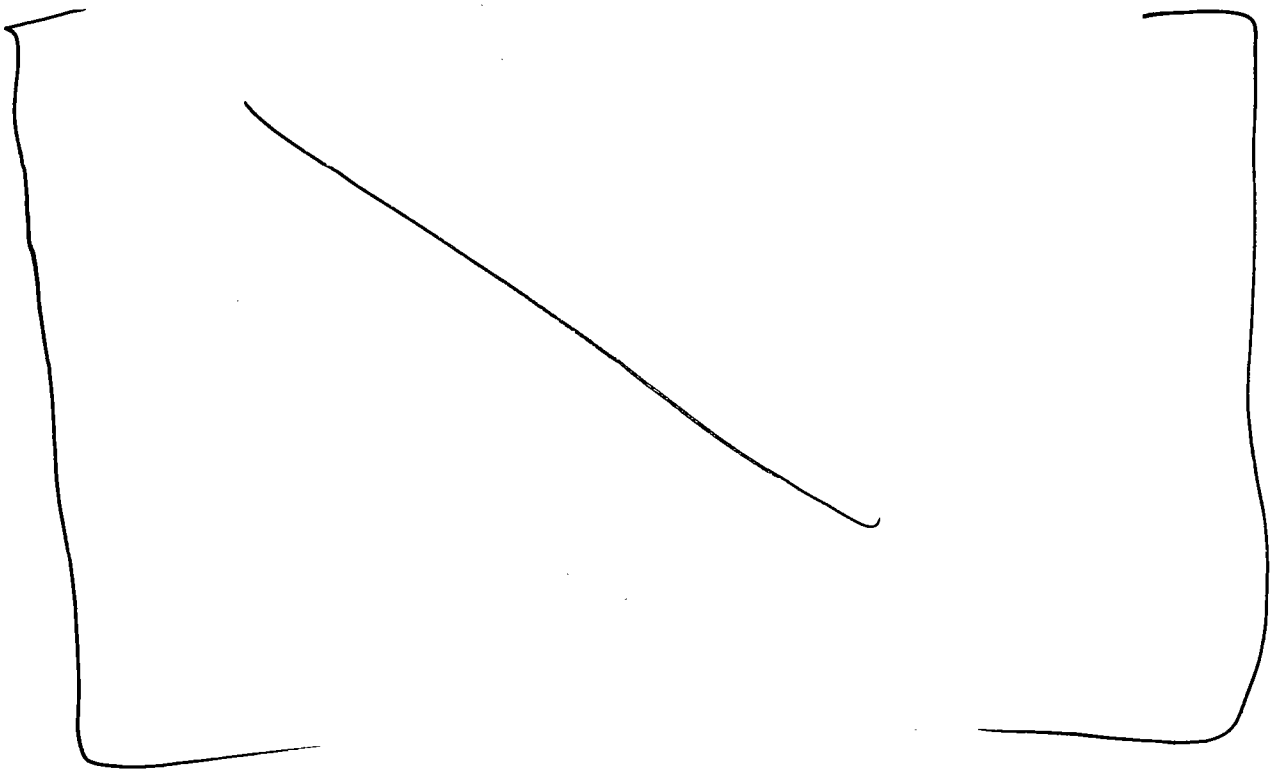
Column lifetime validation (Attachment 11)



Hold time validation (Attachment 12)



Viral clearance studies (Attachment 13)



Purification process validation studies (Attachment 14)

Validation studies have been performed and adequately demonstrate the removal of process contaminants.

Other validation studies (Attachment 15)

Cell Culture

Shipping

Shipping validations were performed. Shipping validation studies are incomplete and additional studies are required. This was discussed at the pre-license inspection (483 item 14) and has been addressed in the response to the 483.

IV. Reference Standard (Attachment 16)

A new reference standard manufactured by the process to be licensed has been qualified with validated methods. These methods include all those used for lot release as well as additional assays for biochemical comparability. This reference standard was shown to be comparable to the previous reference standard in potency, purity, strength, and composition profiles.

V. Comparability (Attachment 17)

Comparability was established between lots made by the commercial manufacturing process and lots manufactured for clinical trials. Comparability testing included a variety of assays that evaluated the

VI. Stability (Attachment 18)

Stability studies on drug substance will be carried out for up to

VII. Release tests and specifications

Bulk Substance (Attachment 19)

Release testing specifications for IDEC-2B8 bulk drug substance were established using lots manufactured during the 1999-2000 campaign. Specifications ensure IDEC-

2B8 quality and lot-to-lot consistency. The analytical methods used to characterize IDEC-2B8 demonstrate that the safety, identity, composition, quality, potency, and purity do not vary beyond the established specification limits. The specifications set for the IDEC-2B8 drug substance are appropriate based on limited manufacturing experience. The company states in section 4.A.6 of the BLA that it will re-evaluate the specifications upon completion of additional manufacturing lots.

Drug Product (Attachment 20)

The analytical methods used to characterize IDEC-2B8-MX-DTPA demonstrate that the attributes of safety, identity, strength, quality, purity, and potency do not vary beyond the established specification limits. The specifications are consistent with manufacturing history and are appropriate. Drug product has been more fully reviewed by Dr. Leon Epps.

VIII. Miscellaneous listings

Products of significance used in manufacture (Attachment 21)

No products of animal or human origin were used in the manufacture of IDEC-2B8 or it's derivative, IDEC-2B8-MX-DTPA.

Response to FDA Request for Information

On March 23, 2001, The Agency sent an information request to IDEC regarding the MDS Nordion and Amersham Master Files for yttrium-90 as well as the used of indium-111 with Zevalin. Letters of cross-reference for both Master Files have been submitted. A brief outline describing the responsibilities of IDEC and MDS Nordion for the manufacture, testing, release and distribution has been provided. Further details of this can be examined at the time of inspection of MDS Nordion. Responses to the remaining questions regarding the package insert and used of indium-111 will be submitted at a future date.

IX. Questions/comments for sponsor

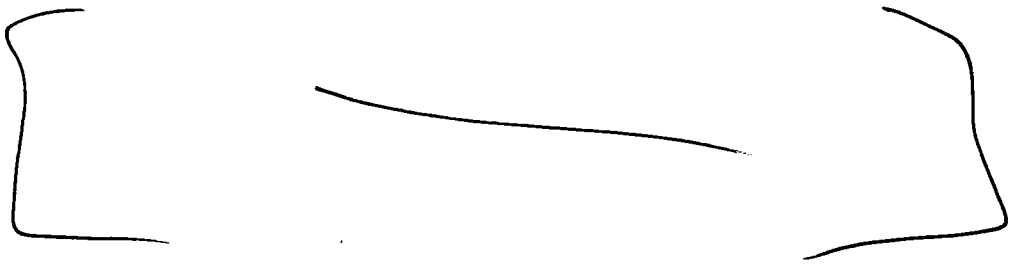
1) Please provide a description of the derivation of the 2B8

2) Regarding the qualification of the Master Cell Bank:

a

b

c)



3) Regarding testing of the , the Points to Consider in the Manufacture and Testing of Monoclonal Antibody Products for Human Use (1997) recommends that the be tested for sterility and retrovirus. No reports for such testing have been submitted to your BLA. Please comment.

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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X. Referenced master files (Attachment 22).
See attachment 23

XI. HAMA Assay (Attachment 23).

During the course of Zevalin™ treatment, patients receive two doses of Rituxan™ at days –7 and 0 followed on each day by Indium (day –7) or Yttrium (day 0) labeled Zevalin™. Patients were monitored for both HAMA (human anti-mouse antibodies generated against the Zevalin™ constant region and HACA (human anti-chimeric antibodies generated against the Zevalin™ and Rituxan™ variable regions). The clinical assays used to assess HAMA and HACA were the same as those that were validated and submitted to the Rituxan™ BLA. The HAMA assay is appropriate for measuring an immune response against Zevalin™ as the assay is able to detect antibodies directed against the murine constant region, which is not present in Rituxan™. A new study to validate the in-house HAMA assay against the commercially available _____ Test System showed that both assays are suitable to detect HAMA but that IDEC'S in-house assay is more sensitive.

XII. Summary

This review covers the IDEC-2B8 drug substance and includes some assays used for both the drug substance and drug product. It also covers some pre-clinical testing as well as the HAMA/HACA assays. Characterization, validation and manufacture of the IDEC-2B8 bulk substance are sufficient. Upon satisfactory response to questions in the complete review letter and to the 483 inspectional items, there will be no product issues concerning bulk substance to preclude licensure.

List of Attachments

Attachment 1 History/development of product: (Attachment 1)
Attachment 2 Cell banking.:(Attachment 2)
Attachment 3 Cell culture process:(Attachment 3)
Attachment 4 Downstream processing: (Attachment 4)
Attachment 5 Formulation and filling: (Attachment 5)
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Attachment 16 Comparability: (Attachment 16)
Attachment 17 Stability determining assays: (Attachment 17)

Attachment 18 Stability data supporting dating period: (Attachment 18)
Attachment 19 Release tests and specifications for the bulk: (Attachment 19)
Attachment 20 Release tests and specifications for the final product: (Attachment 20)
Attachment 21 Products used in manufacture of significance: (Attachment 21)
Attachment 22 Referenced master files: (Attachment 22)
Attachment 23: HAMA Assay: (Attachment 23)

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

Withheld Track Number: Chemistry- 2

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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