

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**103948/0**

**MICROBIOLOGY REVIEW**

APR 25 2001

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

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Date: April 27, 2000  
To: File, CAMPATH Ref. No. 99-0786  
From: Walter Lange *W Lange*  
Subject: BLA review for CAMPATH

*concur - JML 4/25/01*

The sponsor has submitted this application for CAMPATH-1H, CAMPATH-1H is the proprietary name applied to Drug Substance or antibody molecule while CAMPATH is applied to Drug Product.

The proposed indication for CAMPATH is for the treatment of patients with B-Cell Chronic Lymphocytic Leukemia (CLL) who have received an alkylating agent and have failed fludarabine therapy.

Early development work was conducted by Burroughs-Wellcome (now Glaxo-Wellcome, GW). GW established the ~~cell~~ cell line used for clinical studies and developed ~~the~~ suitable for commercial production. GW also conducted a number of clinical studies in both hematological and non-hematological indications before discontinuing development. The Sponsor, L&I Partners, LP, (L&I) has continued the development of CAMPATH. The formulation of CAMPATH was modified from that used by GW to include ~~the~~. The Sponsor has conducted the confirmatory clinical trial (CAM211) in CLL that is described in this application. Subsequently, the Sponsor has modified the scale of CAMPATH-1H manufacture from ~~the~~ as described in this application.

A summary of recent regulatory communications between the Sponsor and the FDA regarding Chemistry, Manufacturing, and Control of CAMPATH-1H is shown in Table 4.1-1 below:

**Table 4.1-1 Summary of Regulatory Communications on the Manufacture of CAMPATH-1H**

Topic	Date	FDA IND Serial #	Primary Outcome
Pre-BLA CMC Meeting	10/30/97	131	<ul style="list-style-type: none"> <li>• Change of site of manufacture from GW to — acceptable</li> <li>• 3 batches will be sufficient to show product consistency</li> <li>• Product comparability plan acceptable</li> <li>• Stability protocol adequate</li> <li>• Cell bank characterization adequate</li> <li>• Potency assay, _____ adequate</li> <li>• Host Cell Protein Assay adequate</li> </ul>
Update IND to reflect manufacture at _____	2/19/98	141	<ul style="list-style-type: none"> <li>• Change site of manufacture from GW to —</li> <li>• Acceptability of modifications and improvements to the manufacturing process</li> <li>• _____ scale material acceptable for confirmatory clinical trial</li> <li>• Viral clearance data sufficient</li> </ul>
Scale-up at _____	10/15/98	184	<ul style="list-style-type: none"> <li>• _____ scale approved</li> <li>• Change of expiration dating</li> </ul>

A pre-licensing inspection of \_\_\_\_\_ is planned for May, 2000.

This review is organized using the key issues (r

This review concentrates on section IV of that Guidance, Information for Manufacturing processes which should be included in drug applications. Other aspects of the submission are addressed by product reviewers.

The following outline will be used for this review.

- A. Buildings and Facilities  
Floor Plan and Location of Equipment
- B. Overall Manufacturing Operation  
Drug Product Filtration, Specification Concerning Holding Periods, Critical Operations
- C. Sterilization and Depyrogenation of Containers, Closure, Equipment, and Components  
Bulk Drug Solution Components that are sterilized Separately, Sterilization Information in the Batch Records
- D. Procedures and Specification for Media Fills  
Actions Concerning product when media Fills Fail
- E. Microbiological Monitoring of the Environment  
Microbiological Methods, Yeasts, Molds, and Anaerobic Microorganisms, Exceeded Limits
- F. Container-Closure and Package Integrity
- G. Sterility Testing Methods and Release Criteria
- H. Bacterial Endotoxins Test and Method
- I. Evidence for Formal Written Procedures
- J. Maintenance of Microbiological Control and Quality: Stability Consideration

**A. Buildings and Facilities**  
Floor Plan and Location of Equipment

Section 4.2.2.2 provides detailed description about the \_\_\_\_\_ facility. Each of the key areas has amplifying comments, and floor plans are provided in Appendix, Section 3.

Section 4.3.4.1 states that L&I Partners, LP has employed the use of a contract manufacturer, \_\_\_\_\_ to supply commercial CAMPATH v material. \_\_\_\_\_ performs all operations relating to the manufacture of CAMPATH v, including \_\_\_\_\_ as described in Section 4.2.2, and the filling operation as described in this section. The facility consists of \_\_\_\_\_ buildings including \_\_\_\_\_

\_\_\_\_\_ The \_\_\_\_\_ facility operates under cGMP conditions and has been licensed as a multi-product facility in the United States (License Number \_\_\_\_\_).

The following table from the submission identifies some of the key manufacturing areas.

**Table 4.3.4.2.1-1 Summary of Unit Operation for Manufacture of CAMPATH® Drug Product**

Operation	Building No.	Floor	Floor Plan No.
[Empty table body with a diagonal line drawn across it]			

Corresponding floor plans are included in Appendix Section 3. The floor plans appear to be appropriately scaled, with provisions for necessary physical separation of functions.

Section 4.3.4.2.2 states: "All product contact equipment used in the CAMPATH process is dedicated. The areas used for manufacture of the Drug Product are designed for ease of cleaning and sanitization. The floor plan is designed to facilitate efficient movement and control of components, personnel, product, and equipment to ensure product integrity. Adequate floor space has been provided within the facility to ensure segregation of materials and separation of unit operations to prevent cross contamination."

Section 4.3.5.1 states: "All functional areas involved in the manufacture of CAMPATH Drug Product in Building from other areas and supplied

**Review Comment:** The descriptions of facility and equipment appear to be adequate. To be confirmed during the Inspection.

**B. Overall Manufacturing Operation**

Drug Product Filtration, Specification Concerning Holding Periods, Critical Operations

The manufacturing process is described (in overview) in section 4.2.3. The descriptions inclu

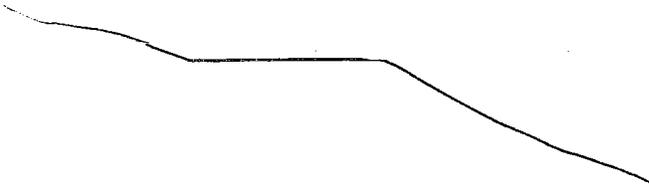
5 Page(s) Withheld

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

§ 552(b)(5) Deliberative Process

§ 552(b)(5) Draft Labeling

7



**I. Evidence for Formal Written Procedures**

The Submission has frequent reference to written procedures and standard procedures.

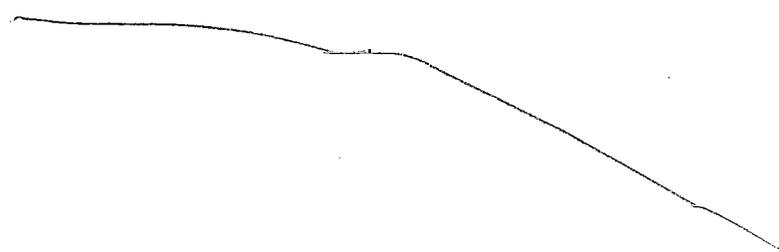
**Review Comment:** The descriptions and references to procedures appears to be adequate, and will be verified during inspection.

7

**J. Maintenance of Microbiological Control and Quality: Stability  
Consideration**

The following two sections (4.2.4.3.1 and 4.3.11.1.3) address some of the concerns about Microbiological Control and Quality.

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**Review Comment:** These descriptions appear to be adequate and will be verified during the inspection.

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**Concluding Review Comment:**

The BLA submission appears to be comprehensive and well documented. There are no egregious deficiencies in the submission. Issues that require particular attention during the inspection have been duly noted in the comments above.

Unless there are major deficiencies identified during the inspection, the manufacturing processes, equipment and facilities employed for CAMPATH appear to be adequate for the intended purposes.