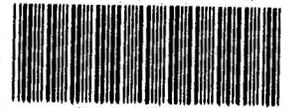


**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**103928Orig1s000**

**OTHER ACTION LETTERS**



000360646

Our STN: BL 103928/0 (replaces Ref. No. 99-1407)

SEP 25 2000

Charles Putnam  
 Palatin Technologies, Incorporated  
 175 May Street, Suite 500  
 Edison, NJ 08837

Dear Mr. Putnam:

This letter is in regard to your biologics license application for Technetium Tc-99m Anti-CD 15 Antibody (LeuTech™) for the diagnosis of appendicitis in patients with equivocal signs and symptoms submitted under section 351 of the Public Health Service Act. Reference is also made to our information requests and your responses received through September 21, 2000.

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

1. Please submit data from the successful manufacture of three consecutive lots of product. The data submitted must include the results from all in-process testing performed to monitor the manufacturing process and the Certificates of Analysis from the bulk drug substance, the partially reduced bulk drug substance, and the drug product.
2. Microbial contamination has occurred several times during the manufacture of RB5 IgM and partially reduced RB5 IgM at the DSM Biologics production facility. At one point in the manufacturing process, this was addressed by incorporating a (b) (4) (b) (4) To ensure the ability to detect and quantitate microbial contamination of in-process intermediates, please revise your Master Batch Record to require that all samples collected for bioburden testing are gathered prior to (b) (4) Please submit a tabulated summary of these changes to the Master Batch Record. In addition, please submit bioburden data from project P118P and all subsequent lots attempted.
3. Validation of the cell culture process entailed assessing the performance of pre-culture lots 9607-151, 9706-023 and 9710-012 and fermentation lots 9607-221, 9706-002 and 9710-01. During this time period, pre-culture lot 9705-126 and fermentation lot 9706-060 failed. Although your validation protocol requires three consecutive lots, neither of these two failures, nor the failures occurring in the cell culture process after the validation period, were taken into consideration during the evaluation of the validation results. Please evaluate the appropriateness of your validation parameters and process, in light of these failures, and revise your validation protocol to include the next three consecutive lots.

FILE  
 COPY

OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE	OFFICE	SURNAME	DATE
DARP	Bernice	9-28-00	DARP	Clim	9/25/00	DINA	Green	9-25-00
DARP	C. Grogan	9-22-00	DMPA	Rubas for	9/25/00	DARP	A. Williams	9-25-00
DMA	K. Williams	9-22-00		Elsherman				

4. Please set relevant specifications for IgM concentration in the (b) (4) (b) (4)
5. Coomassie blue stained SDS-PAGE , by itself, is not an appropriate analytical method for detection of host cell proteins. Please develop a more sensitive host cell protein assay, such as an ELISA or Western blot-based method. Retention samples from lots 9610-113, 9709-056, 9712-073 and 9912-024, as well as future lots, should be evaluated for host cell proteins using the new method and lot release specifications should be developed accordingly.
6. In-process and release specifications are not consistently reported throughout the BLA. For example, In section 4.2.4.1a, the raw harvest bioburden specification is (b) (4). This is in contrast to information found in other locations in the BLA, including section 4.2.3.5.f (“If at any point the culture is found to be contaminated with microbes, the fermentation is terminated and contaminated harvests are excluded from the bulk pool”) and batch records (specification is 0 CFU/ml or no growth). Please submit a comprehensive table of all in-process testing, lot-release testing, and associated specifications that you are proposing for future productions. Please clearly note any changes made to the testing procedures and/or specifications during production of P17R, P65P and P87P.
7. Validation protocol, PQ336: *stability study for RB5 IgM intermediates*, was submitted (section 4.7.15) but no results were included in the BLA . Therefore, the stability of in - process intermediates at different temperatures and hold times could not be assessed and are not considered validated for the production process. Please submit the results from validation protocol PQ336. In addition, please submit validation data supporting the (b) (4) Master batch records should be modified appropriately.
8. Please revise your Master Batch Records to include alert, action, and rejection limits for your in-process specifications.
9. Please submit an assessment of all chromatography media used during manufacturing for leachable material that may elute with the product, and demonstrate the removal of any such contaminants.
10. During validation of the potency assay for RB5 IgM drug substance, a deviation occurred while executing procedure 9.2 for linearity, range and accuracy, necessitating a repeat of the procedure. One of the possibilities you suggested for the deviation was an error in sample dilution. Please show that you have controls in place to assure that technical errors in execution of procedures would be detected for this and other assays used for lot release and stability testing.

11. The performance qualification of the RB5 IgM reduction process is incomplete because the 3<sup>rd</sup> consecutive qualification lot, reduction lot 0002-085, failed lot release specifications for the free thiol assay and partially reduced RB5 IgM concentration and the qualification protocol does not address reproducibility. Please revise your qualification protocol to include duplicates for each of the incubation temperature and time extremes. Please submit the revised qualification protocol and resulting data. In addition, as discussed in item #2, please modify the reduction process qualification protocol to include bioburden sampling prior to (b) (4)
12. Please submit process validation for the lyophilization method. The study should include data demonstrating that the following significant product attributes are consistently achieved whenever the process is carried out as specified: (1) potency; (2) (b) (4) (b) (4) (3) cake appearance for uniformity, shape and color; (4) reconstitution time and appearance; and (5) stability. Validation should include a minimum of three batches at target set points for pressure, temperature, and time. In addition, please submit complete lyophilization charts used to assess process-validation product attributes.
13. Please submit your protocol and data from assessing the suitability of the final product container/closure system for the following attributes: light protection, reactive gas permeation (b) (4) and compatibility of the elastomeric components.
14. Please set an upper limit on the immunoreactivity specifications for the purified RB5 IgM drug substance and for LeuTech™ finished drug product.
15. Please amend the master batch records to reflect current specifications.
16. Please submit data demonstrating that the Lymulus Ameobocyte Lysate endotoxin assay used for lot release testing of LeuTech has been validated to be equivalent to the rabbit pyrogen test as described in 21 CFR 610.13.
17. Please submit your procedures on how and when contract facilities will be periodically assessed for compliance with applicable product and establishment standards and cGMP.
18. Please submit written commitments from contract manufacturers stating that all proposed changes to manufacturing and facilities, introduction of additional marketed products, and clinical material processing operations will be communicated to you prior to implementation. In addition, please submit your procedure for reporting changes to the Agency, as specified in 21 CFR 601.12.
19. Please submit written commitments from contract manufacturers stating that you will be informed of all errors and deviations in manufacturing methods and test results, as well as adverse events, for the affected products.

20. Please provide relevant data, including specific lot numbers and quantities of samples used to generate the results described in your Stannous Iodimetric Validation Report “VPR 027.01” of October 27, 1999 in Volume 4 on page 4-4077. In addition, please describe in detail each error mentioned and your corrective measures employed to resolve each error.
21. Your label lists the stannous tartrate content as 54 µg per vial, corresponding to 23.9 µg of stannous ion per vial. Values reported for all lots released range between (b) (4) of stannous ion per vial (Volume 1.14 on pages 4-3518 to 4-3793). Your Stannous Iodimetric assay was validated to have a recovery of 100%. Please account for the low stannous values reported for all released lots.
22. Please provide relevant data, including specific lot numbers and quantities of samples, used to generate the results described in your (b) (4)
23. Please submit densitometric scanning results and good quality duplications of the SDS-PAGE and IEF gels for the reference standards and qualification lots.
24. Please provide relevant data, including representative copies of gels with their Laser Densitometry measurements, specific lot numbers and quantities of samples used to generate the results described in your Purity and Identification by SDS-PAGE Assay Validation Report “VPR 012.01” of October 5, 1999 in Volume 4 on page 4-4055.
25. Please provide relevant data, including representative chromatograms, specific lot numbers and quantities of samples used to generate the results described in your Purity Assay for LeuTech Protein Materials by High Performance Size Exclusion Chromatography (HP-SEC) Validation Report “VPR 023.01” of November 2, 1999 in Volume 4 on page 4-4109.
26. The specification for the HP-SEC assay does not discriminate between monomeric and aggregated IgM. Please revise the specification to read (b) (4) IgM monomer.
27. Please submit results from the stability testing study SS006.01 for partially reduced RB5 IgM.
28. Stability data from the immunoreactivity assay, the free Tc-99m assay, and the colloidal Tc-99m assay exceeded the two standard deviation limit for drug product lots 882-23-0001 and 882-23-26047 stored at the recommended temperature of 2-8<sup>0</sup> C. This suggests a lack of control for these assays. Please submit additional stability data on LeuTech<sup>TM</sup> Lots 882-23-0001, 882-23-26047, 882-23-47313, and 882-23-47314 to support the proposed expiration date of 24 months.

29. Please submit the shipping validation protocol and results for the shipment of drug substance from DSM Biologics, The Netherlands to the Ben Venue Laboratories, Inc, Ohio location, and for the shipment of LeuTech™ drug product from Ben Venue to the distributor.
30. Human Anti-Murine Antibody (HAMA) assay validation studies show the ability to capture and detect HAMA. However, since Rb5 IgM is used for both capture and detection, the potential exists for masking of HAMA which binds divalently to the capture IgM and would not be available for binding to the detecting molecule. As requested in our telephone calls of May 3 and May 18, 2000, please supply data to show that your HAMA assay is able to detect all HAMA present in patients' serum samples. Additionally, please submit results showing reproducibility and ruggedness of the assay with different iodination preparations of the antibody, assessment of potential prozone effects using HAMA positive samples, and the SOP for testing patient samples, including a description of the dilutions, number of replicates, standards, and controls used.
31. Please clarify the difference between cell culture media BM28SF and BM75SF, and at which stages of RB5 development and production culture each of these was used. According to section 4.2.3.5.d and figure 4.6, medium BM75SF is used for pre-culture (b) (4). However, in appendix 4.7.9, cell culture process validation, medium BM28SF was used for the validation process.
32. In addition to color and appearance, please describe the identity tests that DSM Biologics uses to qualify (b) (4).
33. Please describe the identity test that Ben Venue Laboratories uses to qualify the Ascorbic Acid Injection, USP (Cenolate) (500 mg/mL, 2 mL Ampoule) which is used to reconstitute your LeuTech™ kit.
34. Please submit a full, completed batch record for one of the new consistency lots manufactured after all changes to the master batch record are implemented and the process is validated.
35. Please submit documentation from the United States Adopted Name Council to verify the proper name for LeuTech™.
36. Outstanding pre-approval inspectional issues identified on the FDA Form 483s dated March 21, 2000, issued to your contract manufacturer, Ben Venue Laboratories at their Bedford, Ohio location; May 5, 2000, issued to your contract manufacturer, DSM Biologics at their Groningen, Netherlands location; and July 28, 2000, issued to your

Edison, New Jersey location, will need to be adequately resolved prior to approval of this product.

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/gdlms/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. Should you have any questions or need additional information, please call Michael Noska, in the Division of Application Review and Policy at (301) 827-5101.

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 response will not be considered for review nor will the review clock be reactivated until all deficiencies have been addressed.

Sincerely yours,

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

cc:	Mary Andrich, M.D.	HFM-650
	Leon Epps, Ph.D.	HFM-596
	Chana Fuchs, Ph.D.	HFM-558
	Bette Goldman	HFM-500
	M. David Green, Ph.D.	HFM-579
	Glen Jones, Ph.D.	HFM-585
	Peter Lachenbruch, Ph.D.	HFM-215
	Julia Lukas	HFM-675
	Robert Lindblad, M.D.	HFM-582
	Lydia Martynec, M.D.	HFM-573
	Satish Misra, Ph.D.	HFM-215
	Michael Noska, M.S.	HFM-588
	Sharon Risso	HFM-500
	William Schwieterman, M.D.	HFM-582
	Kathryn Stein, Ph. D.	HFM-555
	Jay Siegel, M.D.	HFM-500
	Deborah Trout	HFM-675
	Keith Webber, Ph.D.	HFM-556
	Karen Weiss, M.D.	HFM-570
	Julia Lukas	HFM-675
	RIMS	HFM-110

CBER:DARP:Noska:9-17-00,Crim:9-19-00:amw:9-21-00:kow:9/22/00:amw:9-22-00  
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COMPLETE RESPONSE (CR)