

parameters of linearity, range, accuracy, robustness and precision as outlined in ICH Q2(R1) “Validation of Analytical Procedures: Test and Methodology.” Data from an additional validation protocol conducted in accordance with ICH Q2(R1) are required.

4. Please provide the data obtained from proposed study EX-PRT-124 “*Qualification and Comparability of -----(b)(4)-----*.”
5. During the Pre-License Inspection on September 1, 2009, it was noted that morphologic assessment is performed by -----(b)(4)-----

6. During the preparation of Bulk Drug Substance-Cryovial, the SOPs require -----(b)(4)----- . However, during the August 31 through September 4, 2009 pre-license inspection, it was noted from the master batch records that the -----(b)(4)----- is not specified. -----(b)(4)----- is not recommended and may result in poor outcomes with respect to product quality. Please revise the relevant SOPs to avoid this possibility.
7. We note that during the pivotal studies, lots exhibiting deviations in the time limits for culture at various steps in the process were allowed to proceed on a case-by-case basis. Clear criteria for time limits that would result in lot termination at each critical manufacturing step need to be established prior to commercialization. Similarly, clear criteria need to be established regarding the use of -----(b)(4)----- .
8. Under CTD section 3.2.S.2.2 it was noted that a time limit has not yet been established for the -----(b)(4)----- . A study (EX-PRT-129) has been proposed to address this issue. We recommend that a similar study is also conducted to establish a time limit for the (b)(4) ----- . Please submit to the BLA the results of the studies and the hold times that you establish for these steps.
9. Regarding the Container Closure Integrity Testing (CCIT) method:
 - a. The sensitivity of the method has not been validated. Please provide such data.
 - b. Please submit CCIT data generated after freezing and thawing of the container closure to simulate freezing of the Bulk Drug Substance-Cryovial.
10. The container closure failed -----(b)(4)----- in the initial and confirmatory testing. The cryovials tested -----(b)(4)----- specified

------(b)(4)-----.. Please describe the corrective actions that have been implemented to address this issue along with data for the final container that is within the limits described by the applicable (b)(4) test methods.

11. Please modify the post-approval stability protocol for the Drug Substance outlined in section 3.2.S.7.2 to include the -----(b)(4)--- assay. Although the ---(b)(4)---assay was not performed on the Drug Substance for manufacture of clinical lots, data obtained on -----(b)(4) production from lots on stability would provide valuable information for the assessment of stability.
12. The current identity/purity assay for fibroblasts and keratinocytes is based on independent analyses for the -----(b)(4)-----.. This assay method does not provide information on cells not detected by ----(b)(4)-----.. Please address this concern, either by providing data to adequately demonstrate the quantity and type of -----(b)(4)----- or by adding a quality control test.
13. -----(b)(4)-----

-----..

CLINICAL

14. Your application does not include sufficient data to determine whether azficel-T is safe for use under the conditions suggested in the proposed labeling draft (21 CFR §314.125(b)(4)). We note that there is essentially no information regarding the bioactivities of azficel-T and tissue responses to azficel-T, aside from that derived from visual inspection of the skin. The lack of such information limits our assessment of the safety of azficel-T. We are particularly concerned about the potential for scarring and inflammatory reactions following azficel-T injection. Additional data are needed to address these concerns. Such data should come from a histopathological study on biopsied tissue samples from patients following injection of azficel-T. We recommend that you discuss the study design with FDA prior to initiating the study.
15. Shipping errors during clinical development resulted in re-biopsy of several study subjects. Such errors may adversely impact the safety and/or efficacy of your product. To decrease the risk of errors and ensure product quality, your Clinical Support Center Policies and Procedures must specify your policies, procedures, and activities with regard to the commercial handling of biopsies and re-biopsies, and how shipping and post-release sterility testing failures will be addressed. These policies, procedures, and activities must comply with 21 CFR 1271.290 and ensure that each patient receives a product that is derived from his/her own cells. Please revise your Clinical Support Center Policies and Procedures accordingly and submit the revised document for our review.

LABELING

16. Your proposed manual for training health care providers in the administration of azficel-T does not include sufficient detail. This lack of detail may result in variations in administration that could lead to unacceptable variations in the efficacy and/or safety of your product. The training manual should include the following:
 - a. At a minimum, the level of detail that was provided in your manual for training clinical investigators in Studies IT-R-005 and IT-R-006.
 - b. The specific roles of the Centers of Excellence and Clinical Support Centers in training health care providers on biopsy collection, labeling and shipment, azficel-T injection technique, product accountability for patient specificity, and the reporting and management of adverse events or any product-related issues.
 - c. The details of common and less common adverse events reported in previous clinical trials and the management plans for those adverse events. This information will help health care providers to recognize, treat, and report treatment-related adverse events.

17. Your proposed prescribing information (PI) is in the general format set forth by the Physician’s Labeling Rule. However, there are many inaccuracies in your proposal. We recommend that you consult 21 CFR §201.57 and revise your PI as described to be in compliance with that regulation. For additional assistance, you may consult the following guidances available on the FDA website (<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065010.htm>):

Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format

Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format

Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products—Content and Format

Content and Format of the Dosage and Administration Section of Labeling for Human Prescription Drug and Biological Products

Labeling for Human Prescription Drug and Biological Products — Implementing the New Content and Format Requirements

18. In addition, we recommend that you amend your carton and container labels to be in compliance with 21 CFR §610.60, §610.61, and §610.62.

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

PROPRIETARY NAME REVIEW

20. We have reviewed your submission dated October 20, 2009 to your biologics license application (BLA) for azficel-T requesting a proprietary name review. In consultation with CBER's Advertising and Promotional Labeling Branch (APLB) we conclude that under the Federal Food, Drug, and Cosmetic Act and applicable regulations, your proposed proprietary name, Laviv, is acceptable at this time. We will perform another proprietary name review of Laviv closer to the time of the action due date of your BLA resubmission to ensure that we have not approved a conflicting proprietary name for another product in the interim.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the application; (2) notify us of your intent to file an amendment; or (3) withdraw the application.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our "Guidance for Industry: Formal Meetings With Sponsors and Applicants for PDUFA Products," dated February 2000. This document is available on the internet at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079744.pdf> or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm>, or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the application. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the application within the extended time period may also be considered a request for withdrawal of the application.

We acknowledge receipt of your amendment(s) dated December 1 and 8, 2009. Please be aware that we have stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response. You may cross reference applicable

sections of the amendment(s) dated December 1, and 8, 2009 in your complete response to this letter and we will review those sections as a part of your complete response.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Lori Tull, at (301) 827-5102.

Sincerely yours,

Stephanie Simek, Ph.D.
Deputy Director
Office of Cellular, Tissue and Gene Therapies
Center for Biologics Evaluation and Research