

BLA 125348 Resubmission

**CMC Review of Complete Response letter items (including
483 items) and additional information not contained in
original submission**

azficel-T (LAVIV®)

Fibrocell Technologies, Inc

**Division of Cellular and Gene Therapies, Office of Cellular,
Tissue, and Gene Therapies**

Reviewed by:

Signature

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EXECUTIVE SUMMARY

Recommendation: The CMC-related items (1 to 13 and 15) from the FDA Complete Response (CR) letter dated 12-18-2009 have been addressed adequately. There are no outstanding CMC concerns at this time. Therefore, we recommend approval of the BLA.

Product Overview: Azficel-T is an autologous cell therapy product for improvement of moderate to severe nasolabial fold wrinkles in adults. The active ingredient is autologous cultured fibroblasts. The fibroblasts are cultured, using standard methodologies, from three 3-mm punch biopsies (dermal and epidermal layers) taken from a subject's post-auricular area. Fibroblasts, due to their proliferative nature, expand more rapidly in culture than the other cell types present, such as keratinocytes. Fibroblasts represent more than 98% of the final product. Following *in vitro* expansion, the fibroblasts are harvested, quality control tests are performed, and the cell suspension is cryopreserved in vials at a defined cell concentration. When required for clinical use, a dose of cells is thawed, washed, formulated to $1.0\text{--}2.0 \times 10^7$ cells/ml and shipped to the clinical site at 2-8°C by overnight delivery. The cells are injected intradermally in three separate doses administered four to six weeks apart.

The mechanism of action of azficel-T has not been demonstrated. However, Fibrocell performs testing of each lot to determine that the product consists of viable fibroblasts that produce collagen. The potency of azficel-T is determined by the combination of cell count, viability, identity as fibroblasts and collagen content. The rationale for the choice of these characteristics for azficel-T potency is based on the premise that fibroblast survival and collagen biosynthesis following injection of azficel-T are likely to be important factors for improvement in the appearance of nasolabial fold wrinkles.

Previous Review findings:

The original BLA was submitted and reviewed in 2009. The review identified CMC deficiencies that were included in the CR letter sent to the firm in December 2009. Those deficiencies included:

- Specific deficiencies cited in the form 483 Pre-License Inspection report had not been resolved.
- Studies conducted to validate the stability of the cells during shipping over a proposed 48 hour time limit were not sufficiently robust to assure product quality.
- The validation study performed for the collagen assay was not adequate.
- Qualification of the -----(b)(4)----- had not yet been performed
- Photographic documentation of morphology was needed
- Tighter controls were needed to prevent over confluence of the cells in tissue culture.
- Specifications for hold times and passage rules during the manufacturing process were not adequate to assure the quality of the final product.
- Validation of the container closure system was inadequate
- Addition of the potency assay to the stability protocol was needed

- The characterization of cell types other than fibroblasts -----(b)(4)-----
----- present was needed.
- One of the assays used for culture media qualification was still under development and needed to be completed.

Each of these issues was addressed in this resubmission and associated amendments and the issues have all been resolved. A complete review of each of the responses is included in this review. In addition, we have reviewed the labeling for accuracy and after several revisions have found the labeling to be acceptable.

Nomenclature for azficel-T

Trade name	LAVIV®
United States Adopted Name (USAN)	azficel-T
NDC code assignment	75935-001-01
UNII code assignment	022461SR75

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SECTION 1: REVIEW OF COMPLETE RESPONSES TO DECEMBER 18, 2009 COMPLETE RESPONSE LETTER (CMC)

CR Item #1. Outstanding issues identified during pre-license inspection of your manufacturing facility conducted August 31- September 4, 2009 and detailed in form 483 have yet to be addressed.

Fibrocell submitted a complete response to the nine FDA Form 483 items on 8-27-2010 as amendment #27. Responses to 483 items 1 through 8 were reviewed by Drs. Gang Wang and Randa Malhem of DMPQ. Response to 483 item 9 was reviewed by Drs. Gang Wang (DMPQ) and Donald Fink (OCTGT).

483 item #1: The system for documentation of deviations and their subsequent investigation is inadequate. For the period of time between November 2006 and March 2009, a total of 370 logged deviations and investigations had not been completed and closed by Quality Assurance. Many remain open in various stages of completion while documentation for a number of events cannot be located in Quality Assurance binders.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 with a commitment to provide a review of the current deviations and investigations to the FDA. Subsequently, they submitted a follow-up response on December 8, 2009 (BLA Amendment No. 025) with an interim report stating that 178 of the 370 open deviations and investigation had been closed.

In the current response, Fibrocell completed their previous commitments and provided the final response to this observation. A final and comprehensive report regarding the closure of the 370 deviations and investigations is provided in Appendix 4 entitled Quality Systems Review Report: Open Deviation and Investigation Reports November 2006-March 2009, dated 30 July 2010. This Report summarizes the methods of investigation and closure of the historical deviations and investigations. The sponsor stated that none of the deviations or investigations resulted in product lot failures.

Reviewer Comment: Appendix 4 entitled Quality Systems Review Report: Open Deviation and Investigation Reports November 2006 – March 2009 was reviewed. Based on this report, as of March 19, 2010, the sponsor had closed 100% of the 370 combined deviations and investigations that were the subject of this FDA 483 observation. In addition, they have updated all Quality Assurance binders with completed documentation for all events. The pre-commercial Quality System has now been retired and the commercial Quality System that was phased in from July to August 2009 is now used to track, trend and resolve all deviations, investigations and CAPA. The commercial Quality System is operating in control and has substantially reduced the time to closure for reported deviations and investigations.

Reviewer Comment: *Appendix 9: General Technical Report: Full Process Media Fill Simulation of the Manufacturing Process for Azficel-T (EX-GTR-125B) was reviewed which showed that all of the final filled media units from -----(b)(4)----- EX-PRT-125v01 and EX-PRT-125v02 were negative for microbial growth, and therefore supported the Standardized Manufacturing Process used to produce azficel-T as an aseptic process. MIR-09-030 determined the root cause for the contamination of the waste units with spore-forming organisms during EX-PRT-125v01, and the trial performed during EX-PRT-125v02 supported that -----(b)(4)----- could be handled aseptically once the contamination source was addressed. Both media fill runs demonstrated that even when contamination events are noted, media fill units remained free of contamination, indicating robust aseptic processing. I would agree with sponsor's assessment and conclusion on media fill simulation and consider this 483 issue has been resolved.*

483 item #3: Environmental monitoring (EM) conducted during the manufacturing processes performed -----(b)(4)-----
----- is inadequate. Viable and non-viable particulates were not monitored -----(b)(4)-----.
EM was performed for -----(b)(4)----- of the aseptic production -----(b)(4)-----.

Response:

Fibrocell submitted an initial response to this observation on September 17, 2009 that included a commitment to revise all relevant Master Batch Records (MBRs) and two EM SOPs to include EM testing of -----(b)(4)----- process. The current response included the final response to this observation to complete the commitment.

Fibrocell stated that they have updated all relevant MBRs and EM SOPs to include EM testing of -----(b)(4)----- commercial process. This includes SOP-EM-003v03, Viable Environmental Monitoring Program (Appendix 10) and SOP-EM-009v02, Non-Viable Airborne Particulate Monitoring (Appendix 11). Viable and non-viable EM is now conducted throughout the entire manufacturing process inside the -----(b)(4)-----, including viable ----(b)(4)---- and non-viable particulates monitoring throughout any product manipulation during the entire aseptic production process.

Finally, all other relevant MBRs and SOPs have been updated to reflect this improvement to EM. Revisions to the documents implementing EM throughout the entire aseptic production process conducted within the -----(b)(4)-----
Drug Substance – Cryovial and Drug Product – Injection lots have been manufactured. The continuous EM data collected during these operations has demonstrated assurance of aseptic processing, with no alert or action level excursions.

Reviewer Comment: *The responses are acceptable.*

483 item #4: Proper aseptic technique was not strictly followed during manufacturing of the PLI campaign lots. Specifically:

- a. Operators were observed using the same pipettes to repeatedly collect and dispense the -----(b)(4)-----.
- b. While waiting for the cell count result from the QC lab, the operator responsible for performing the --- (b)(4) --- was observed leaving the Cleanroom --(b)(4)-- and was not present when results were received from the QC lab.
- c. The same bottles of -----(b)(4)----- were used on multiple occasions to prepare cryopreservation solution for formulating different Drug Substance lots.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 (Appendix 1) with commitments to:

- 1) Change the practice of using the same pipettes to repeatedly collect and dispense the -----(b)(4)-----.
- 2) Increase personnel levels and dedicate a member of the manufacturing team outside of the Cleanroom areas to facilitate material transfers, cryopreservation activities, and communications between Manufacturing and QC.
- 3) ----- (b)(4) ----- process and to update relevant MBRs to reflect this practice.

In the current response, Fibrocell completed their previous commitments. Fibrocell has changed the practice of using the same pipettes to repeatedly collect and dispense ----- (b)(4) ----- (483 item #4a). The relevant pages from MBR-013v08, Harvest and Cryopreservation of Fibroblasts from ----- (b)(4) ----- have been revised (Appendix 12). Fibrocell has increased the number of trained personnel in the manufacturing department from --(b)(4)-- to assure that a trained staff member is available during manufacturing and to facilitate communication between manufacturing and QC lab (483 item #4b).

Fibrocell now ----- (b)(4) ----- (483 item #4c).

Reviewer Comment: The responses are acceptable.

483 item #5: Cleaning validations for the ----- (b)(4) ----- Cleanrooms have not been performed.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 that included the following two commitments to:

- 1) Demonstrate the adequacy of the established cleaning regimen during execution of EX-PRT-126, entitled Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones.
- 2) Perform effectiveness testing for cleaning procedures for media spills in the ---(b)(4)----, as part of EX-PRT-126.

In the current response, Fibrocell completed their previous commitments. Fibrocell performed the cleaning validation of the -----(b)(4)----- Cleanrooms under EX-PRT-126v01, entitled Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones (Appendix 15). Results from the study demonstrated established cleaning procedures. A summary of the cleaning validation testing performed and the data collected from testing conducted May-June 2010 is provided in EX-GTR-126v01 entitled Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones (Appendix 16). Based on the results obtained from this validation study, Fibrocell concluded that the results from viable and non-viable EM performed as an evaluation of worst-case locations are considered additional supporting data to the results obtained in previous HVAC PQ Protocols, EX-VAL-087, EX-VAL-044 and EX-VAL-045.

Reviewer Comment: Appendix 16: Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones EX-GTR-126 was reviewed. The results indicated a low occurrence of exceeded alert and action level events as compared to the number of tests performed over the course of the study (1.9% and 0.2%, respectively, out of --(b)(4)-- tests conducted). Fibrocell proposed several follow-up actions regarding performance of additional testing in the routine EM program, modification to the cleaning and disinfection schedule and specific trends to be monitored over a longer period of time. Both the cleaning, disinfection and EM programs will be evaluated over the next year under increasingly dynamic production conditions and the seasonal cycle to capture the full trend impact.

Based on the information submitted and the results presented this cleaning validation study was adequately designed and executed and the results to be acceptable. This 483 issue has been resolved.

483 item #6: Performance qualification of EM in the -----(b)(4)---- Cleanrooms is inadequate in that the worst-case locations for viable and non-viable particulates have not been identified. In addition, the viable and non-viable particulates were----- (b)(4)----- static and dynamic conditions.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 that included commitments to:

- 1) Perform EX-PRT-126, entitled Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones, a performance qualification of the EM procedures to be conducted over -----(b)(4)----- dynamic conditions.

- 2) Determine worst case EM locations as part of the EX-PRT-126 study.
- 3) Update EM procedures with the worst case sample locations identified during the study.

In the current response, Fibrocell provided technical report EX-GTR-126v01, entitled Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones (Appendix 16) to fulfill their previous commitment.

With regard to conducting the PQ study of EM in the ---(b)(4)--- cleanroom, Fibrocell performed the PQ, per protocol EX-PRT-126: Requalification of Cleanroom Heating, Ventilation and Cooling (HVAC) Zones, -----(b)(4)----- under both dynamic and static conditions. .

With regard to establishing and testing worst case locations, Fibrocell has identified the probable worst-case EM sampling locations. These locations were sampled during the execution of the protocol in addition to the locations previously established. The action levels for viable particulates and control limits for non-viable particulates, established in SOP-EM-003v02 and SOP-EM-009 are presented. Fibrocell stated that the results from demonstrate a successful PQ of the EM procedures in place for the -----(b)(4)----- Cleanrooms.

Reviewer Comment *The additions of identified “worst case” sites to the EM sampling and testing program, in combination with continued trending of EM results, will improve Fibrocell’s control over the Cleanroom environment. As summarized in comments to 483 item #5, the overall results of this PQ study appear acceptable and the cleanrooms appear to be adequately qualified. Based on the information submitted and results presented, this 483 issue has been resolved.*

483 item #7: The qualification smoke study for---(b)(4)--- conducted under dynamic conditions is inadequate in that the actual conditions of product manufacturing were not simulated. Maintenance of adequate airflow has not been demonstrated under such conditions.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 that included a commitment to conduct additional airflow visualization studies under dynamic conditions using the maximum amount of materials used in actual production in the -----(b)(4)-----.

In the current response, Fibrocell provided information on the completion of their previous commitment. -----(b)(4)----- was contracted to conduct qualification smoke studies simulating the actual conditions of product manufacturing. -----(b)(4)--- conducted smoke testing for airflow testing, filmed the testing, and provided raw data results to the sponsor for review. -----(b)(4)----- evaluated in the airflow visualization studies are all located in the -----(b)(4)----- . To replicate dynamic conditions, the study was conducted while an operator at the -----(b)(4)----- . This manufacturing step uses more supplies and materials within the (b)(4) than any other step in

the production process. To simulate “worst case” conditions, the (b)(4) workspace was filled with the maximum amount of materials and consumables that could be required during the execution of this MBR.

In order to meet acceptance criteria for the airflow visualization studies, a (b)(4) must pass all (b)(4) airflow tests, including -----

----- (b)(4) -----

----- The results showed that all (b)(4) tested passed all (b)(4) airflow tests. No dead spots or reflux were noted. No deviations from the protocol occurred during the study. Video footage from this testing was not provided in the submission, but is available upon request.

Reviewer Comment: The responses are acceptable.

483 item #8: Sanitization effectiveness of the disinfectants used for cleaning the Cleanrooms and manufacturing equipment has not been performed.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 that included a commitment to conduct disinfectant effectiveness studies on the disinfectants intended for use during commercial manufacturing operations in accordance with ----- (b)(4) ----- and FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice. Fibrocell have now submitted their final responses with the disinfectant effectiveness study. The sanitization effectiveness of all disinfectants used for cleaning and sanitizing the Cleanrooms and manufacturing equipment has been demonstrated. The testing performed and the data obtained are summarized below:

----- (b)(4) ----- conducted bacterial and fungal disinfectant effectiveness studies on the disinfectants intended for use during Fibrocell’s commercial manufacturing operations. These studies were defined in protocols EX-PRT-128v00 entitled Disinfectant Effectiveness Study (Appendix 17) and EXPRT-128v01 entitled Disinfectant Effectiveness Study (Appendix 18). Currently used chemicals were challenged against a collection of representative microorganisms and environmental isolates identified from the aseptic processing area. The challenges were performed on representative surfaces such as ----- (b)(4) -----
----- Each disinfectant and sporicide was subjected to time kill studies for microorganisms ----- (b)(4) ----- in accordance with ----- (b)(4) ----- and FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice. The data obtained during the study are provided in EX-GTR-128v00, entitled Disinfectant Effectiveness Study (Appendix 19), which were executed per protocols EX-PRT-128v00 and EX-PRT-128v01. All disinfectants evaluated were qualified for continued use in routine disinfection practices as described in SOP-MA-012v03 entitled

Cleaning and Disinfection Program of Aseptic and Support Areas, with the limitations on use of -----(b)(4)----- surfaces. -----(b)(4)----- is effective against bacterial and fungal species when using the (b)(4) only technique.

In addition, the sponsor also conducted a validation study on viral inactivation effectiveness of the disinfectants. The study was performed per protocol EX-PRT-135v00: Disinfectant Effectiveness Study – Virucidal Activity (Appendix 20), and the results documented in EX-GTR-135v00: Disinfectant Effectiveness Study – Virucidal Activity (Appendix 21). Based on this validation study, all disinfectant agents tested, including -----(b)(4)-----, met the criteria for virucidal activity, -----(b)(4)------. This represents a minimum percent reduction of viral titer of --(b)(4)--. All (b)(4) chemicals are considered qualified for use in --(b)(4)-- clearance for purpose of viral load reduction when applied as tested in this study -----(b)(4)-----.

Based on these data, Fibrocell concluded that the sanitization effectiveness of the disinfectants and application techniques used for cleaning the Cleanrooms and manufacturing equipment has been successfully demonstrated.

Reviewer Comment: The studies appear to be adequately designed and executed and the results appear to be acceptable. Based on the information submitted and the results presented, this 483 issue has been resolved.

483 item #9: Currently, mycoplasma release testing of the Drug Substance-Cryovial is performed by the contract company -----(b)(4)-----.; however, the test method has not been validated by the contract company.

Response:

Fibrocell submitted an initial response to this observation in the submission dated 17 September 2009 that included a commitment to use ----(b)(4)---- for the mycoplasma assay until -----(b)(4)----- completed their assay validation.

Fibrocell submitted a follow-up response to this observation on November 24, 2009 (BLA Amendment No. 023), which included documentation to verify the competency of -----(b)(4)----- to perform Mycoplasma testing.

In the current response, Fibrocell provided the validation study on -----(b)(4)----- testing performed by ---(b)(4)-- to fulfill their previous commitment. ---(b)(4)-- has validated the mycoplasma release test method for Drug Substance – Cryovial by performing -----(b)(4)----- testing for the Drug Substance. The validation was conducted under protocol EX-PRT-133v00 entitled -----(b)(4)----- (Appendix 24). The report from this testing, EX-GTR-133v00, -----(b)(4)----- Testing Against Drug Substance – Cryovial per -----(b)(4)-----, is provided in Appendix 25. Data is presented demonstrating that---(b)(4)-- has successfully executed a

validation study and has verified the suitability of employing their --(b)(4)-- Assay for the detection of mycoplasma contamination in the presence of azficel-T Drug Substance – Cryovial. The --(b)(4)-- protocol uses the -----(b)(4)----- assay detailed in the FDA’s Points to Consider in the Characterization of Cell Lines Used to Produce Biologicals (May 1993).

Fibrocell supplied ---(b)(4)--- with (b)(4) lots of Drug Substance – Cryovial product for mycoplasma analysis, and each of the (b)(4) lots were negative for the inhibition of growth and detection of representative mycoplasma in both the -----(b)(4)----- portions of -----(b)(4)----- Mycoplasma Test. All test results from each lot were compared to the positive and negative controls of the ---(b)(4)-- mycoplasma test met all pre-determined acceptance criteria and were deemed valid. The results confirmed that ---(b)(4)-- and their Points to Consider method ---(b)(4)-- is a suitable contract testing facility for release testing of the sponsor’s Drug Substance – Cryovial.

The sponsor stated that they intend to use --(b)(4)-- for commercial mycoplasma testing. -----(b)(4)---- has also validated their mycoplasma release testing method for azficel-T and will be retained as an authorized alternate testing facility in the BLA.

Reviewer Comment: *The response is acceptable.*

Summary of response to CR letter item #1:

The responses provided by Fibrocell to the nine form 483 items have been adequately addressed and Fibrocell has adequately responded CR letter item #1.

Responses to CR Items 2 -11 Received as Amendment 28 on 11-1-2010

CR item #2: The data provided from the shipping validation studies EX-PRT-116 and EX-PRT-121 failed to support your proposed designation of 48 hour drug product stability under the current conditions of shipment. Data from additional validation studies are required to demonstrate that temperatures can stay within the specified ranges and that the product remains stable for 48 hours. These data should be obtained from studies under actual shipping conditions and include potential extremes of temperature that may be encountered during shipment in summer and winter months. The collagen content assay should also be included in evaluation of product stability in your shipping validation studies.

Response:

The manufacturer of the previously utilized shipping container, -----(b)(4)-----, has -----(b)(4)----- Fibrocell has decided to use the -----(b)(4)----- . The ---(b)(4)-- shipping system is described.

[(b)(4)]

----- (b)(4) -----

----- (b)(4) -----

----- (b)(4) -----

6 pages redacted due to (b)(4)

[(b)(4)]

----- (b)(4) -----

----- (b)(4) -----:

----- (b)(4) -----

----- (b)(4) -----

Consequently, the expiration date used on the injection vial must include the hour of expiry, which should not exceed 24 hours post-shipment.

TELECON: 2-16-2011

Based on the above comment a Telecon was held with the sponsor on 2-16-2011

FDA Telecon Item 1: (Response to CR comment #2)

Shipping Validation Studies: Based on the results of the shipping validation studies presented in the response to the CR letter, we do not agree to an expiration of ----- (b)(4) ----- met all release specifications after 24 hours, but one lot deviated with regard to cell count by a margin of ----- (b)(4) -----.

Consequently, based on these studies, we consider 24 hours to be the maximal time from shipping to administration of the product. As the proposed expiration of -----(b)(4)----- may exceed 24 hours, please be advised that the expiration used on the commercial injection vial must include the hour of expiry, which must not exceed 24 hours post-shipment.

FIBROCELL RESPONSE (received 2-28-2011 in amendment #34):

Fibrocell acknowledges that, based on the data collected in EX-PRT-143v00, 24 hours from shipment of drug product is an appropriate maximal time from shipping to administration of the product. Furthermore, Fibrocell agrees that use of -----(b)(4)----- as the Drug Product – Injection expiration may allow for use of the product beyond 24 hours after shipping. Therefore, Fibrocell has revised the expiration in SOP-MA-001v03, *Production and Release Criteria for the Azficel-T Manufacturing Process* to “24 hours from time of shipment.” -----(b)(4)-----, the expiration hour will be 6:00 PM EST/EDT the calendar day following the day of shipment.

An example of the proposed container label that will be adhered to each Drug Product-Injection vial is provided:

Container Label (1” X 2” Flag)

(One label placed on each vial)

Note: the label has been populated with mock patient information

azficel-T (LAVIV®)		1.0mL
Fibrocell Technologies, Inc.		
PIN #:	1234567	
DOB:	01JAN1950	
Initials:	ABC	
Expires:	01MAR2011 6:00 PM EST	
Lot #:	201010001-01	RMS 6XXxv00

Reviewer Comment

Having a 24hour time of expiry displayed on the Drug Product-Injection label is acceptable to address the concern

**CR item #3: The validation data submitted for the collagen assay conducted as part of the final drug product potency assessment does not support your conclusion that the assay is suitable for its intended purpose. The analytical test method for measurement of collagen content (ATM-004) consists -----(b)(4)-----
----- . You have designated the assay as a “limit test”, with an acceptance criterion of -----(b)(4)-- cells, and examined only limit of detection and specificity in your validation protocol. Due to the characteristics of this assay and its use as part of the potency measurement of the drug product, we expect validation of the 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.**

Response:

The collagen assay has now been validated in accordance with ICH Q2(R1) “Validation of Analytical Procedures: Test and Methodology” as a test for content/potency. The collagen assay was validated for Accuracy, Precision (Repeatability), Intermediate Precision, Linearity, Range,

Specificity and Robustness under protocols EX-PRT-118v02 , EX-PRT-118v03, and EXPRT-118v04, entitled, *Revalidation Of Analytical Test Method - ATM-004 Collagen Assay*.

A summary of each validation parameter and corresponding acceptance criteria are provided in Table 3 below.

4 pages redacted due to (b)(4)

**CR item #4: Please provide the data obtained from proposed study EX-PRT-124
“Qualification and Comparability of -----(b)(4)-----”.**

Response:

----- (b)(4) -----

----- (b)(4) -----:
----- (b)(4) -----
----- (b)(4) -----
----- (b)(4) -----

----- (b)(4) -----
----- (b)(4) -----
----- (b)(4) -----

----- (b)(4) -----.

[(b)(4)]

1 page redacted due to (b)(4)

CR item #5: During the Pre-License Inspection on 9-1-09 it was noted that morphologic assessment is performed by -----

-----**(b)(4)**-----

Response:

-----**(b)(4)**-----

---::

[(b)(4)]

-----**(b)(4)**-----

-----.

-----**(b)(4)**-----

-----.

-----**(b)(4)**-----

-----.

Reviewer Comment: This is acceptable

**CR item #6: During the preparation of Bulk Drug Substance, the SOPs require -----
----- (b)(4) ----- . However, during the
pre-license inspection dated August 31- September 4, 2009, 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 change the relevant SOPs to
avoid this possibility.**

Response:

Control limits, or “passage rules,” have been incorporated into the manufacturing process and are detailed in Table 6 below. The limits were set based on azficel-T manufacturing history and experience. SOP-MA-001, entitled *Production and Release Criteria for the azficel-T Manufacturing Process*, has been updated to include the criteria for the process steps, in-process controls and decision making (provided in Appendix 13).

[(b)(4)]

All relevant Master Batch Records (MBRs) listed in Column 2 of Table 6 have been updated to reflect the criteria outlined in Table 6. The MBRs are provided in Appendix 14, Appendix 15 and Appendix 16.

Fibrocell requests that the FDA consider the process controls presented in response to Item #6 as an amendment to the original BLA CTD Section 3.2.S.2.4, *Control of Critical Steps and Intermediates*.

Reviewer Comment: *The proposed “passage rules” are only acceptable if -----*
----- (b)(4) -----.

TELECON: 2-16-2011

A Telecon was held with the sponsor on 2-16-2011 to address this issue

FDA Item 3: (Re: CR comment #6)

----- (b)(4) -----

----- (b)(4) -----:

----- (b)(4) -----

----- (b)(4) -----

- ----- (b)(4) -----
 - ----- (b)(4) -----
 - ----- (b)(4) -----
- .

1 page redacted due to (b)(4)

CR item #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)-----
-----.

Response:

In response, SOP-MA-001, *Production and Release Criteria for the azficel-T Manufacturing Process* (Appendix 13), has been updated to provide:

- -----(b)(4)-----

- -----(b)(4)-----

- -----(b)(4)-----

Fibrocell requests that the FDA consider the process controls presented in response to Item #7 as an amendment to the original BLA CTD Section 3.2.S.2.4, Control of Critical Steps and Intermediates.

Reviewer comment: *This is an adequate response to address CR item #7*

CR item #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.

Response:

----- (b)(4) -----
-----.

A. Summary of EX-GTR-129v00, Validation of Time Limit for----- (b)(4) -----
Drug Substance

----- (b)(4) -----

- ----- (b)(4) -----
-----.
- ----- (b)(4) -----
-----.
- -----
-----.
- ----- (b)(4) -----

----- (b)(4) -----

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4 pages redacted due to (b)(4)

CR item #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 Drug Substance-Cryovial .

The review of this item was provided by Randa Malhem of DMPQ and was found to be acceptable.

Response:

In the original BLA submission, Container Closure Integrity Testing (CCIT) data (CTD section 3.2.P.2.4, *Container Closure*) was assessed using -----(b)(4)----- testing. -----
----- (b)(4) -----
-----; however, the sensitivity of the method was not validated.

----- (b)(4).

----- (b)(4)

----- (b)(4)

Fibrocell concluded that the container closure integrity is intact after being subjected to all parameters of the manufacturing process. In addition, they stated that their --(b)(4)-- method can detect a contamination of -----(b)(4)-----.

Reviewer Comment: *Fibrocell addressed the freeze-thaw of the vials and demonstrated the integrity of the container closure using -----(b)(4)-----. However, they did not demonstrate the sensitivity of the assay to demonstrate the smallest crack that could be detected. As the CCIT was performed using -----(b)(4)----- with no failures, and because the containers used are -----(b)(4)-----, the sponsor's responses are considered to be acceptable.*

CR item #10: The container closure failed -----(b)(4)----- in the initial and confirmatory testing. The cryovials tested -----(b)(4)----- specified limit of -----(b)(4)----- . Please explain 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.

The review of this item was provided by Randa Malhem of DMPQ and was found to be acceptable.

Response:

In the original BLA, Fibrocell reported, in Section 3.2.S.6.2, *Container Closure Suitability*, that -----(b)(4)----- met the acceptance criteria; however -----(b)(4)----- results were above the ----(b)(4)---- specified limit of --(b)(4)--. They concluded that ink on the vial label might be responsible for the -----(b)(4)-----.

- -----

- -----

1 page redacted due to (b)(4)

CR item #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.

Response:

The post-approval stability protocol outlined in BLA CTD section 3.2.S.7.2, *Post Approval Stability Protocol and Stability Commitment* for Drug Substance – Cryovial defined in SOP-MA-025 (*Commercial Stability Testing of Fibrocell Science Product*) has been updated to include the --(b)(4)- assay as a part of the testing regimen for Drug Substance – Cryovial stability testing.

[(b)(4)]

Reviewer Comment: *This is acceptable.*

CR item #12: The current identity/purity assay for fibroblasts and keratinocytes is based on independent analyses for the -----(b)(4)------. This 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)----- by adding a quality control test.

Response (received on 12-11-2010 as Amendment #30):

Fibrocell has conducted a study to evaluate the quantity and cell types other than fibroblasts and keratinocytes in the azficel-T Drug Product – Injection suspension. Other cells from the dermal and epidermal layers of skin were selected as candidates that could potentially constitute a minor cell population unlabeled by either -----(b)(4)------. The product was screened for the presence of minor cell populations by -----(b)(4)-----.

Table 1. List of Cell Types Included in Screening

Skin Layer	Cell Type	Description	Proportion of Cells <i>in vivo</i> (Kanitakis, 2002)
Epidermis	Keratinocytes	Keratin producing cells, predominant cell type in the epidermis.	90-95%
	Langherans Cells	Dendritic cells located in the epidermis.	3-6%
	Melanocytes	Melanin-producing cells located in the bottom layer of the epidermis.	One melanocyte per 4-10 basal layer keratinocytes
	Merkel Cells	Receptor cells located in the epidermis.	“Their density shows regional variations (being maximal in palmoplantar skin), but is generally low.”
	Epithelial	Classification of cells lining the outermost layer of skin aiding in protection, adsorption and secretion.	Not provided
Dermis	Fibroblasts	Synthesizes extracellular matrix proteins, located in the dermis.	“Fundamental cells of the dermis”
	Macrophages/ Monocytes	Immune cells. Monocytes eventually leave the bloodstream to become tissue macrophages.	Variable
	Mast Cells	Histamine-producing immune cells, located in skin adjacent to blood and lymphatic vessels.	“Sparsely distributed in the perivascular and periadnexal dermis”

According to available literature, three of the cell types listed in Table 1 are not likely to expand during the *in vitro* azficel-T manufacturing process due to the culture conditions used.

Langerhans Cells

Langerhans cells are unlikely to be passaged beyond the initial biopsy culture phase. Langerhans cells rapidly disappear *in vitro* under normal culture conditions (DMEM +15% FCS) unless media supplements are used (Czernielewski et al., 2004).

Melanocytes

Melanocytes are unlikely to expand in the culture conditions used (DMEM +15% FCS), since culture of primary melanocytes requires supplementation with other special supplements such as basic fibroblast growth factor (bFGF) or insulin (Hsu et al., 2005).

Mast Cells

Mast cells are very unlikely to survive or proliferate in culture under the conditions used without additional supplements to the medium (Yamada et al., 2003). Mast cells require either supplemental Stem Cell Factor (Dallman and Lamb, 2000) or co-cultivation with murine 3T3 fibroblasts (Irani et al., 1992) to proliferate *in vitro*.

Although the literature suggests that these cells are unlikely present in significant populations in the culture, each was included on the list of cells types to be screened. These cell types, as well as Merkel cells, epithelial cells and monocyte/macrophages could theoretically be present although at very low levels.

Assay Development

----- (b)(4) -----

-----.

6 pages redacted due to (b)(4)

FDA ITEM #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.

Response: (received as Amendment 31 on 12-15-2010)

Note: Review of Clinical Support Center Policies and Procedures with regard to commercial handling of biopsies and re-biopsies is provided under the clinical review section

Management of Post-Release Sterility Testing Failures (CSC SOP 010)

The SOP describes the procedures required of the Clinical Support Center (CSC) for the receipt and communication of post-release sterility tests. The CSC will be responsible for obtaining information from Quality Assurance (QA) regarding any post-release sterility testing results including failures and promptly reporting the results to the medical clinic.

In the event of a sterility testing failure:

- CSC will receive a copy of the completed form Notification of Drug Product – Injection Sterility Test Failures [Form: 029-SOP MA-F4]
- CSC will promptly contact the medical clinic to notify them of the sterility test failure and will provide the clinic with the identification of the microbial isolate which caused the failure
- The CSC will request that the medical clinic contact the customer immediately to determine if additional follow-up is required. Fibrocell Medical Staff will be available for consult on treatment management.
- CSC will provide further follow-up communication to the clinic at the direction of QA in the event of a sterility testing failure

1 page redacted due to (b)(4)

Compliance with 21 CFR 1271.290

- The CSC will be responsible for receiving calls from authorized providers (medical clinics) with a new order request for LAVIV® therapy
- As per CSC SOP 001 *Scheduling Biopsy Collection Dates*, the CSC will complete Part 1 of the Product Order Form [Form: 029-SOP-MA-F1] that includes the following customer information:
 - Customer Initials
 - Customer date of birth
 - Medical clinic site code
 - Medical clinic address
 - Medical clinic contact name & phone #
 - Customer desired biopsy collection date
- At the time of biopsy scheduling, a unique patient identification number (PIN) for the LAVIV® batch will be assigned to the customer.
- Upon receipt by Fibrocell Manufacturing, each biopsy is also assigned a unique internal lot number.
- All manufacturing intermediates will be labeled with the lot number.
- The Drug Substance and Drug Product vials are labeled with both the lot number and the PIN. The Drug Product vials also contain the patient's initials and date of birth.
- The CSC will communicate and coordinate LAVIV® treatment dates with the medical clinic once the customer's product has completed the manufacturing process and the release of the bulk drug substance has occurred.
- CSC records the customer information and desired injection dates in the Injection Scheduling Form [Form: 029-SOP-MA-F2]. The following information must be recorded:
 - Customer PIN
 - Manufacturing Part and Lot Number
 - Medical clinic site code
 - Medical clinic address
 - Medical clinic contact name & phone number
 - Customer desired injection dates
- Fibrocell Materials Management verifies the patient information prior to shipping, and Quality Assurance re-verifies this information.
- Quality Assurance will verify that the shipping container has been packed and labeled properly.
- Final verification to ensure that each patient receives a product that is derived from his/her own cells, is performed at the clinical site where the information (initials, date of birth and PIN) on the patient vial will be verified by the clinician against Form 006-SOP-MM-F1, *Injection Inventory Form*, and with the patient, prior to injection.

- Form 006-SOP-MM-F1 contains a duplicate of the product label. In addition, the Physician's Training Manual outlines the procedures for inspection of azficel-T material upon receipt by health care providers in accordance with 21 CFR 1271.290.
- In addition to tracking delivery of LAVIV® product to the medical clinic, the CSC will also will receive verification from the clinic that product has been administered as per CSC SOP 005, *Confirming LAVIV® Delivery and Administration*.

Reviewer Comment: *Fibrocell has demonstrated adequate Compliance with 21 CFR 1271.290*

A. Additional Stability Information

(b)(4)

[(b)(4)]

42

Reviewer Comment: *While the stability data are acceptable for up to –(b)(4)--, the recommended treatment regimen for azficel-T is three treatment sessions at 3-6 week intervals. Consequently, once sufficient cells are obtained for the proposed licensed indication, it is unlikely that azficel-T will require cryopreservation for -----(b)(4)-----.* *Fibrocell's proposed post-approval stability protocol and stability commitment will not be requested in the approval letter and is considered a voluntary action.*

B. Container and Package Labels (Amendments #42 (5-26-2011) and #44 (6-8-2011)):

Container Labeling

An example of the proposed container label that will be adhered to each Drug Product-Injection vial is provided:

Container Label (1" x 2")

(One label placed on each vial)

Note: the label has been populated with mock patient information

azficel-T (LAVIV®)	1mL
Fibrocell Technologies, Inc.	
PIN #:	1234567
DOB:	01JAN1950
Initials:	ABC
Expires:	01FEB2011 6:00PM EST
Lot #:	201010001
	RMS 5213v00

------(b)(4)-----
----- the expiration hour will be 6:00 PM EST/EDT the calendar day following the day of shipment.

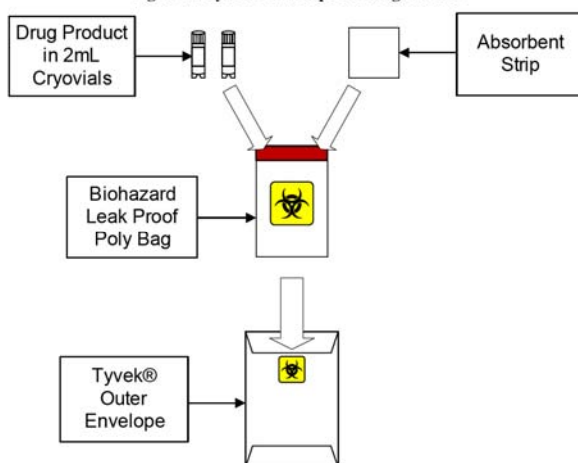
Reviewer Comment: Following discussions with the sponsor and APLB reviewers the above container label was found to be acceptable

Package Labeling

SOP-MM-006 (Packaging Procedure for Final Product) describes the packaging procedure using the -----(b)(4)-----.

For distribution and shipping, the container with azficel-T is placed inside a Biohazard leak-proof bag which is placed inside a Tyvek envelope and sealed.

Figure 7: Tyvek® Envelope Packing Scheme



The package label, containing information common and relevant to all lots of azficel-T, and the patient identification label are attached to the Tyvek envelope (shown below):

Package Label



Figure 6: Tyvek® Envelope Label Placement



Reviewer Comment: The above photograph shows older unacceptable versions of the package and patient identification labels and is displayed only to show the configuration of

the labeling on the Tyvek envelope. The patient identification label that is placed on the Tyvek envelope now contains a duplicate of the container label which the Agency considers to be acceptable.

Once verified, the Tyvek® envelope(s) is/are sealed and placed flat into the payload area of the shipper (see Figure 8).

----- (b)(4) -----

[(b)(4)]

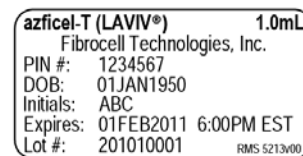
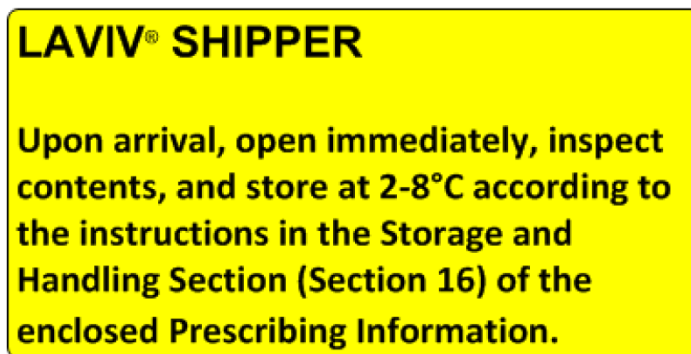
The ----- (b)(4) ----- Shipping Unit consists of an outer cardboard box and an inner shipping compartment formed by a laminated aluminum foil tray surrounded by a foam box. The lid of the inner carton contains the cooling mechanism. Prior to shipping, the -----
----- (b)(4) -----.

An adhesive envelope is placed on the inside of the outer box (see Figure 9) inside which are placed up to (b)(4) copies of the Package Insert -----(b)(4)----- and the original *Injection Inventory Form*. The Package Insert is folded so that the phrase “IMPORANT PERSCRIBING INFORMATION” is visible through the envelope.

[(b)(4)]

When all the items are present in the inner box, the cooler lid is placed on the package and the below label is adhered to the outside of the shipper.

Shipper Identification and Receipt Instruction Label



- The Injection Shipper Identification and Receipt Instruction label is a visual identifier to the Medical Clinic to differentiate the Drug Product shippers containing injection vials from the Biopsy Kits, and provides instruction to the addressee to immediately

- The Patient Identification label(s) alerts the site to the contents of the shipper by displaying the same label(s) as on the Tyvek envelope(s) and LAVIV injection vial.

The outer carton lid is closed and the shipper is taped closed in preparation for shipment to the Clinic. A courier shipping label is printed for the appropriate Clinic site, and compared to the Consignee label to ensure the addresses match. All shipments also include a requirement that the courier obtain an adult signature to deliver the package. Labels are placed on the top of the outside cardboard box according to standard requirements.

Reviewer Comment: Following discussion with APLB reviewers, the information provided on the package label is acceptable

C. Postmarketing Commitment

The nature of the product makes CBER lot release testing unfeasible and therefore the sponsor was given an exemption. -----

----- (b)(4) -----
-----.

On 26 May 2011, FDA and Fibrocell had a teleconference to discuss post-marketing reporting of CMC information.

On 5-27-2011, Fibrocell submitted a letter (amendment 43) providing a formal agreement to a post-marketing commitment for the annual reporting of CMC information as follows:

Each BLA annual report will include the following information:

- ----- (b)(4) -----
-----.
- ----- (b)(4) -----
-----.
- -----
----- (b)(4) -----
-----.

Fibrocell commits to providing the Agency with this information on an annual basis, in each BLA annual report.

Reviewer Comment: *This is acceptable and will be included in the approval letter*

SECTION III: APPENDIX ITEMS

Appendix A: List of amendments received from sponsor

Amend. No.	Date submitted	Topic	CMC	Clinical
1	7-20-2009	Additional study Case Report Forms (CRFs)		Yes
2	7-31-2009	Additional study Case Report Forms (CRFs)		Yes
3	8-13-2009	Response to 6-4-2009 telecon request for reformatted datasets		Yes
4	8-7-2009	Reformatted clinical datasets		Yes
5	8-17-2009	Response to 5-19-2009 letter		Yes
6	9-9-2009	Response to request for available long-term safety data from IT-R-005 and IT-R-006		Yes
7	9-10-2009	Briefing package for 10-9-2009 Advisory Committee meeting	Yes	Yes
8	9-17-2009	Chart records and photographs of subject ----(b)(6)----		Yes
9	9-17-2009	Response to form 483	Yes	
10	10-3-2009	Response to request for patient photographs		Yes
11	10-3-2009	Case report forms for selected patients in IT-R-002 and IT-R-007		Yes
12	10-7-2009	Patient Photographs and Assessments		Yes
13	9-17-2009	Response to form 483	Yes	
14	9-18-2009	Case report forms for patients with ongoing AEs		Yes
15	9-22-2009	Notification of sponsor name change to Fibrocell Technologies Inc		
16	10-14-2009	Addendum to advisory committee meeting package		
17	10-15-2009	Request of waiver of requirement for final container purity testing for pyrogenic substances using rabbit i.v. injections	Yes	
18	10-23-2009	Information to address questions raised at advisory committee meeting	Yes	Yes
19	10-31-2009	Notification of acceptance of USAN azficel-T		
20	10-30-2009	Response to information request		Yes

21	11-1-2009	Six month safety update	Yes
22	10-20-2009	Request for proprietary name Laviv	
23	11-24-2009	Response to CMC information request regarding -(b)(4)-contract testing facility	Yes
24	11-25-2009	Letters of authorization from -----(b)(4)-----	Yes
25	12-1-2009	Interim Pre-license inspection campaign report	Yes
26	12-8-2009	Quality Systems reports	Yes
27	12-23-2009	Letter of acknowledgement of receipt of 12-18-2009 CR letter and intent to file a resubmission to the BLA	
28	8-27-2010	Complete Response to Form 483 (CR item #1)	Yes
29	8-26-2010	Previous 483 response provided on 9-4-2009	Yes
30	11-01-2010	Response to CMC CR items #2-11 and 13	Yes
31	12-3-2010	Request for reconsideration of proposed trade name LAVIV Response to CR item #20	
32	12-11-2010	Response to CMC CR item #12	Yes
33	12-15-2010	Response to CR items #15-19	Yes
34	12-16-2010	Response to CR clinical item #14 completing the response to the CR letter	Yes
35	1-28-2011	Case Report Forms and Histology Report Forms for Study IT-H-001	Yes
36	2-25-2011	Response to CMC information request regarding CR items #2, 6 and 8	Yes
37	3-11-2011	6-month histology report forms for study IT-H-001	Yes
38	3-15-2011	6-month clinical study report for study IT-H-001	Yes
39	3-10-2011	Response to information request	Yes

40	4-7-2011	Response to 3-29-11 telecon regarding package insert labeling	Yes	Yes
41	4-21-2011	Response to 3-24-11 request for information regarding lab data for leucocytoclastic vasculitis SAE		Yes
42	5-26-2011	Response to 5-17-11 request for information regarding final product packaging procedure	Yes	
43	5-27-2011	Agreement to a PMC for CMC information to be submitted in annual reports	Yes	
44	6-8-2011	Revised labeling for container, package and shipper	Yes	
44	6-8-2011	Revised shipping, package and container labels	Yes	Yes