

## **Fibrocell BLA 125348 Review Team Meeting - January 13, 2011**

### Attendees

Janette Alexander, Kim Benton, Wilson Bryan, Charles Durfor, Don Fink, Changting Haudenschild, Samsul Hoque, Shiojwen Lee, Agnes Lim, Randa Melhem, Raj Puri, Patrick Riggins, Stephanie Simek, Terrig Thomas, Lori Tull, Janet White, Celia Witten, Keith Wonnacott, Yao-Yao Zhu, Craig Zinderman

This was the first review team meeting since Fibrocell submitted their Type 2 resubmission on 12-21-2010. The meeting was called to discuss the timelines for the review and to identify key aspects of any outstanding issues.

Lori provided a list of timelines:

- Type 2 Resubmission received 12/21/10.
  - Action due **June 22, 2011**
  - Labeling- begin discussion with company by 4/22
  - Draft reviews to Branch Chiefs by 5/22
  - Summary Basis for Regulatory Action (SBRA) – 3 weeks prior to action
  - Final reviews to office director 2 weeks prior to action
  - Timing for notification to OCOD
  - Meeting to brief Dr. Witten on review progress will be in Feb.
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- Safety Working Group – notification of any Post Marketing Requirements (PMRs) or Risk Evaluation and Mitigation Strategies (REMS) by 4/22

Craig gave an overview of the OBE/DE evaluation prior to issuing of the CR letter. Based on the safety data presented in the original BLA, OBE recommended a post-licensure registry study to further define the risk of tumor formation be conducted as a PMR. That recommendation had been based on the theoretical risk of tumor formation associated with the product, as well as a case of basal cell cancer that developed on the face of one subject in the clinical trials.

OBE/DE considers the single adverse event of a Basal Cell Carcinoma in a 70 year old female patient to be a signal of a serious risk and meets the criteria for a PMR. OBE/DE understands that the sponsor has now completed an additional histology study that noted no problems with tumor formation, however, that study was limited in the number of patients (23) and the length of follow-up (3 months so far). The results of the histology study will need further review by OCTGT but they might not be sufficient to negate the previously identified potential risk. OCTGT can advise further on this point.

Dr. Witten asked what the process would be for implementing such a PMR, and this process was discussed. The basics of the PMR should be decided with the sponsor during the review (e.g., study design, risk to address, approximate size, follow-up time, and due dates for a final protocol and completion of the study). An approval letter would be drafted and presented to the SWG. After licensure (if the product is licensed), the sponsor would submit a final protocol.

The registry study would involve active follow-up with providers at specified time intervals; the length of follow-up has not yet been determined but would likely be between 3-5 years. Data on concomitant facial aesthetic treatments would be collected as potential confounders. Dr. Witten requested that Craig draft language describing the registry study (as it might appear in the approval letter). Dr. Witten also asked about the risks of keloids, hyperpigmentation/hypopigmentation in non-Caucasian subjects as stated in the original OBE/DE review memo. FDA could ask the sponsor to collect data within the registry on this AE, but this risk is not a serious event so it will not be the basis of the PMR. Charles Durfor suggested that there might be other “low level” AEs that could predict development of cancer later but could be detected early, although no specific AEs were discussed.

As injection site reactions were more frequent in azficel-T treated subjects than controls, Craig and Yao-Yao reminded the review team that the sponsor also proposes to require physician training to minimize the frequency and severity of injection site reactions. As these reactions are also not typically serious events, they would not be included in the PMR. When asked whether the training program may be considered for a REMS, Craig reminded the team that during the previous review cycle Bob Yetter had stated that a REMS would only be required if OCTGT would not approve the product without the training program; also the injection site reactions are not a serious risk.

- Pediatric Review Committee (PeRC) – Pediatric Research Equity Act (PREA) waiver was approved for azficel-T in December 2009 as the product does not represent a meaningful therapeutic benefit in these age groups.
- Advisory Committee – at present there is no reason to hold a second advisory committee meeting for issues related to the resubmission.
- DMPQ - the Establishment Inspection Report (EIR) from the inspection in September 2009 has been written, and is awaiting approval; Randa said that a second inspection will not be required if approval occurs by 6-22-2011 as this will be less than two years since the original inspection and there have been no major changes to the facility or the manufacturing process; a Compliance Status Check will be required 30 days before the final action.
- Review status updates
  - a. Clinical

Yao-Yao gave a brief overview of the clinical histology study submitted with the complete response. This was a single-blind (subject blinded and dermatopathologist blinded), intra-patient controlled study to evaluate the histology of cutaneous tissue treated with azficel-T, as compared to untreated tissue and tissue treated with sterile saline. Injections were in the cutaneous tissue of the upper arm and a total of 29 subjects were enrolled in the study; one received one treatment injection, 21 received two treatment injections, and seven received three treatment injections. All subjects underwent a biopsy of the treated areas three months after the last treatment.

Qualitative evaluation of the cutaneous tissue sample cell morphology and histology was performed three months following the last injection. Histological evaluation of tissue sections was conducted using; -----(b)(4)----- for morphology and the presence of inflammatory cells; -----(b)(4)----- stain for collagen fibers, and -----(b)(4)----- for elastin.

In general, the histology across all treatment groups represented normal healthy skin. There were no reports of abnormal fibroblast morphology, structural changes to the subcutis, dermis or epidermis, scarring, increased cellularity, overt thickening of dermal layers or evidence of underlying pathology. The findings most likely reflect a localized, resolving inflammatory reaction following autologous cell implantation.

b. CMC

Terrig provided a brief overview of significant points to arise from preliminary review of the responses to the CMC-related CR letter comments. The sponsor has repeated the stability study under actual shipping conditions and the product remains within specifications for 24 hours. They are proposing an expiry time of ----- (b)(4)----- which is not acceptable given the possibility of shipping to the west coast. An expiry -(b)(4)- would be more appropriate, similar to that -----(b)(4)----- The stability study also included a measure cellular collagen content, which increased over time. This indicates that the cells are metabolically active when they are injected into the patient, which is encouraging.