

Review Team Meeting Minutes, May 21 2009

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Participants: Donald Fink, John Thomas, Yao-Yao Zhu, Gang Wang, Stephanie Simek, Shiohjen Lee, Changting Haudenschild, Allen Ou, Raj Puri, Lisa Stockbridge, Craig Zinderman, Atm Hoque, Keith Wonnacott, Kimberly Benton, Robert Wise, Lori Tull

1. Administrative

- eRoom update
 - an Isologen folder has been created in the “CBER-OCTGT-Regulatory Management Staff“ eRoom and all review team members now have (or soon will have) access.
- Day 74 Review Issues letter
 - Letter mailed 5-19-09. It was suggested that it also be faxed to the sponsor.
- Sponsor communication
 - Wait for sponsor’s response to Review Issues letter.
 - Except - DMPQ comment regarding aseptic processing validation. Gang, Lori and Terrig will set up a telecon date soon to discuss Isologen’s manufacturing status and proposed inspection date.

2. Review Status

- **Product:** The product review is going well and there are no major issues as yet.
- **OBE/DE:** There are concerns about the demographics represented in Isologen’s pivotal trials. The age range was weighted on the low end and ethnic groups other than Caucasian were under-represented.

OBE/DE would like to request a consult from CDRH to get feedback on how this was addressed for dermal fillers, post-marketing.

OBE/DE is reviewing the Pharmacovigilance Plan presented in the BLA. The sponsor intends to conduct a long-term safety follow-up in a subset of patients in the first 2 years after licensure but little detail was provided about this activity. This active follow up would be conducted via a registry or under protocol and will gather safety data from up to 100 patients at 6 months and 12 months after their last injection. Patient diary cards would be used for data collection.

Bob Wise mentioned the unknown risk for malignant growth after injection of autologous fibroblasts cells. A more rigorous plan for post-market safety studies, including a longer period of safety follow up, could be necessary.

OBE would also like input from CDRH on the possible length of post-marketing long term follow-up/pharmacovigilance studies based on their experience with dermal fillers.

OBE compiled a list of questions for directing the CDRH consultation, based on the issues raised above (attached)

- **Clinical:** The clinical review team would also like a CBER/CDRH consult.

Yao-Yao has compiled a list of questions for a Dermatology consultation (attached) and was referred to Dr. Jill Lindstrom (lead medical officer, Division of Dermatology and Dental Products at CDER) by Dr. Susan Walker (Division Director – Division DDDP).

- Lori suggested that any relevant sections of the BLA be prepared ready to send to the CDER/CDRH consult(s).
- Labeling: Steph brought a potential labeling issue for the group to consider. When a biopsy is taken from the patient for preparing the expanded fibroblast product, there is the possibility that insufficient cells will be obtained and treatment will not proceed. Wording to this effect will need to be included in the label.

3. **Advisory Committee (CTGTAC) Discussion**

- **Meeting date –**

Gail is polling the committee members for their availability for Sept. 25th- 30th and also for Oct. 2nd – 9th.

Based on who is and who isn't available for the two dates, the review team will decide which date has the most critical members available.

- *Since the meeting Gail has learned that a number of committee members are not available in late September. Most, but not all, are available for early October:*

- *Those **not** available in early October are indicated*

Savio Woo

Larry Kwak - Not yet known

Doris Taylor

Matthew Allen

Richard Chappell

Stan Gerson

Mahendra Rao

Eva Galantis - Not available (New member – Oncologist with GT expertise)

Peter Saltonstall

Evan Snyder

Steven Dubinett - Not available 10-5-09, but available 10-9-09 (New member - Pulmonologist with GT expertise)

- **Sponsor Notification Date**

- **Based on Gail's preferred timeline of 70 business days before the meeting, this will be middle to late June**

- **Committee Composition –**
 - It was agreed that the existing panel has sufficient expertise in cellular therapies and that an outside non-SGE expert on fibroblasts would not be required.
 - Based on recommendations by Drs. Witten and Simek, it was decided not to include a Bioethicist on the committee. Gail concurred that a Bioethicist is not often included on CTAGTAC.
 - It was agreed that an Epidemiologist would be required and the recommendations of Craig and Bob Wise would be taken into consideration.
 - It was agreed that a second Biostatistician would be beneficial to the committee.

- *In a subsequent e-mail communication with David Krause (Branch Chief, Plastic and Reconstructive Surgery Devices Branch at CDRH) he recommended **Ted Gooley**, who was on the CDRH Dermal Filler AC last November. Gail obtained the recommendation of **Steven Self** from the Vaccines and Related Biological Products AC. He will be used as an alternate Biostatistician if needed.*

- Regarding **Dermatology** expertise, there was discussion as to the need for dermatologists and plastic surgeons on the AC. Both medical specialties are involved in the application of dermal fillers, Botox, and related treatments for aesthetic purposes. It was suggested that there be at least one plastic surgeon and up to three dermatologists.

Drs. Michael Olding (plastic surgeon) and **Amy Newburger** (dermatologist) had been recommended previously by Dr. Witten. *These recommendations are also supported by David Krause at CDRH.*

It was noted that there is considerable dermatology expertise in CDER and Dr. Susan Walker (Division Director – Division of Dermatology and Dental Products) had been suggested as a point of contact at our previous meeting with Dr. Witten.

Dr. Walker was contacted and said that CDER could definitely provide some names. She will ask lead medical officer, Jill Lindstrom, to follow up on this.

Dr. Walker was excited to learn that CBER has a “wrinkle” product approaching licensure, and was very interested to know the endpoints being used for our product. She also expressed interest in discussing and reaching some form of Agency-wide consistency (CBER/CDER/CDRH) in evaluating outcomes for these products.

- **AC questions –**

- The questions posed to previous CDRH ACs for recommendation of various dermal fillers were provided as a starting point for discussion. It was agreed that there should be voting questions related to the safety and efficacy of the product, as well as other discussion questions.
- The questions were not discussed further at this time.

4. Inspections

DMPQ had previously indicated that late August would be the most likely time for the facility inspection. Gang indicated that having the CTGTAC meeting in late September or early October, instead of November, would be OK with regard to completing their review. *Following discussions between DMPQ and DCGT reviewers, the facility inspection is planned for August 30th to September 5th.*