

Review Team Meeting, June 18, 2009 - Laviv

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, Gail Dapolito, Ashok Batra, Lori Tull

1. Administrative

- Mid-Cycle Review - date changed to August 13th to allow more time for review
- Lori will contact the sponsor to obtain a status report on responses to the comments sent with the day 74 Filing Issues letter on 5-19-09
 - Aseptic processing validation
 - Number of patients having biopsies but no treatment
 - Intra-rater and inter-rater variability assessments
 - Significance of product manufacture failure rates between IT-treatment and placebo groups
 - Reasons for patient withdrawals without treatment
 - Site(s) and patient (ID) errors that occurred when assigning treatments to patients
 - Submission of the original randomization lists generated prior to patient assignments
 - The current status of Isolagen's IRB
 - The status of the Proprietary Name Review

2. Sponsor communication

- Telecon held on 6-1-09 with DMPQ to notify the sponsor that the pre-license inspection will take place from August 31st – September 4th, 2009
- DMPQ requested and the sponsor agreed to perform the following manufacturing processes during the inspection:
 - Biopsy receipt/processing – -----(b)(4)-----
 - Harvesting of bulk Drug Substance – -----(b)(4)-----
 - Formulation of Drug Product-Injection – ----(b)(4)----- and final container filling procedures
 - A fully operational QC lab running various lot release tests
- *minutes are in the e-room*
- It was noted that the Isolagen facility is being brought back on-line only for the purpose of the inspection and that it may not represent a true day-to-day scenario. As DMPQ were not present at the Review Team meeting, Keith requested that we check that observing specific manufacturing operations in isolation is OK with them.

3. Review Status

Product:

- Terrig has completed his primary review of the CMC section. The review will be discussed with Keith and Don before the next Review Team meeting. While there were no major concerns, a number of issues will need to be addressed by the sponsor. This will be done in the form of letter comments.
- Don is reviewing the Validation of Analytical Procedures sections of the BLA and some additional assistance will be provided by Rabia, as she has experience with validation protocols.

DMPQ:

- Gang and Randa were not able to attend the meeting. Randa is reviewing the Facilities/Equipment and Container Closure System sections. She will provide a progress report at the next review team meeting.
- Keith suggested checking with the DMPQ reviewers to make sure there is minimal overlap in the review.

Clinical:

- CDER/CDRH consult progress
 - Questions for consult have been sent to CDER (Jill Lindstrom) and CDRH (Charles Durfor) for review
 - All relevant sections of the BLA have been scanned and sent to the consult reviewers

OBE/DB:

- Review is progressing
- It was noted that a few biopsied patients, subsequently failed the clinical trial inclusion criteria and were not treated. This has not affected the overall efficacy data.

OBE/DE:

- CDER/CDRH Consult progress
 - Questions have been sent out for review
- Meeting to discuss Pharmacovigilance Planning and possible REMS with Clinical review team, Rachael Strong, Charles Durfor (CDRH) and Jill Lindstrom (CDER) arranged for 6-24-09.
 - Advice will be sought regarding whether a phase 4 safety study is warranted in under represented populations and whether the sponsor's proposed PV activity constitutes a REMS.
- Currently there is only a limited amount of 12 month safety data obtained from the earlier clinical studies (IT-R-001, IT-R-002, IT-R-003A/B). The twelve month follow-up data from pivotal trials IT-R-005 and IT-R-006 were not available at the time of BLA submission. The sponsor has not indicated that the data will be submitted when available.
 - It was stressed that given the cosmetic indication and the added need to provide safety assurance, that this data should now be available and be submitted to the BLA. Lori will request this during the sponsor communication to follow up on day 74 letter comments.
 - It was suggested that the patients from the pivotal trials should continue to be followed post-marketing for both safety and efficacy.

BIMO:

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Labeling:

- Steph requested that the team look at the labeling information provided in the BLA that is relevant to each reviewer’s responsibility. A preliminary labeling discussion will take place during the mid-cycle review meeting.
- **Advisory Committee (CTGTAC) update**
- Meeting date – October 9th
- Sponsor notification – Due next week (70 business days before meeting).
- Gail will be sending out the AC timelines/deadlines next week
- **CTGTAC Committee** (current composition)
 - **Standing Committee** – (available members)

Stan Gerson - Chair

Savio Woo

Larry Kwak

Doris Taylor

Matthew Allen

Evan Snyder

Steven Dubinett

Richard Chappell (Biostatistician)

Mahendra Rao – Industry Representative

Peter Saltonstall – Consumer Representative

- **Temporary Voting Member SGEs** (confirmed as available)

Michael Olding - Plastic Surgeon (CDRH recommendation)

Amy Newberger - Dermatologist (CDRH recommendation)

Lynn Drake - Dermatologist (CDER recommendation)

- Current Recruiting status:
 - Temporary voting member SGE (invited but not yet confirmed)

Robert McCauley – Plastic Surgeon (CDRH recommendation)

- It was noted that three other SGEs and one non-SGE (Dr. Yamada) have been invited, but are not available
- As six Temporary Voting Member SGEs are preferred for the panel, the CVs of three additional Dermatologist SGEs recommended by CDER will be forwarded to the clinical review team for consideration

- Epidemiologist - OBE/DE decision- not required
- Second Biostatistician – OBE/DB decision – not required

- **AC briefing document/questions** – discussion of content and timelines
- Gail will provide a complete list of timelines
 - Draft FR notice – early August
 - Final FR notice to Gail by August 24
 - Final FDA briefing document to Gail by Sept. 9th
- Review team requested to begin drafting content of briefing document and possible questions for discussion at the next review meeting
- It was decided that there would probably be no need to invite any outside speakers to present at the AC meeting. Having CDRH present an overview of marketed dermal filler products may be an option.
- Product and Clinical will each provide presentations focusing on issues pertinent to the AC questions