

Isolagen BLA 125348 Review Team Meeting with Dr. Witten (7-7-09)

1. Administrative

- Mid-Cycle Review - date changed to August 13th to allow more time for 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 -----(b)(4)-----
- Lori contacted 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

The sponsor will try to provide a response asap. There had been a slowdown due to finances, (i.e. Isolagen filed for Chapter 11 Bankruptcy on June 16th), but they are back up to speed now (received court approved financing of -----(b)(4)-----).

3. Review Status

Product:

- While there were no major concerns, a number of issues will need to be addressed by the sponsor including:
 - *Proposed receipt capacity for the commercial process*
 - *Additional post-licensure stability studies to supplement the validation of cell count/viability post-shipment*
- Don is reviewing the Validation of Analytical Procedures sections with some additional assistance by Rabia, who has experience with validation protocols.

- A meeting is scheduled for 7-15-09 to discuss proposed CMC letter comments to the sponsor and will be included in the next Review Team meeting on 7-16-09.

DMPQ:

- Randa will provide a progress report and issues to be raised with the sponsor.
- Following Keith's suggestion, Terrig has sent his CMC review to Randa and Gang to try and minimize review overlap with DMPQ.

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
- Currently there is only a limited amount of 12 month safety data obtained from the earlier clinical studies (IT-R-001, IT-R-002, and 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.
 - Given the cosmetic indication and the added need to provide safety assurance prior to licensure, this data should now be available and submitted to the BLA.
 - It was suggested that the patients from the pivotal trials should continue to be followed post-marketing for both safety and efficacy.

OBE/DB:

- Review is progressing, no major issues.
- 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 held with Clinical review team, Rachael Strong, Charles Durfor (CDRH) and Jill Lindstrom (CDER) on 6-24-09.
 - Advice 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.
 - Craig will present a summary of the meeting

BIMO:

- ----Information withheld per Privacy Act-----
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- ----- Information withheld per Privacy Act -----
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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.

4. Advisory Committee (CTGTAC) update

- Meeting date – October 9th at Pooks Hill Marriott
- Sponsor has been notified and Gail has provided them with the necessary information regarding preparation for the AC
- Gail has sent out the AC timelines/deadlines
 - Final FR notice due August 24th (Plain English)
 - Final briefing document due Sept. 9th
- A meeting has been requested with Rani Tyler to talk to the group about 508 compliance of AC materials (Making web-based information accessible to people with disabilities).
- **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)*
 - Karen Burke - Dermatologist (on CDRH dermal filler AC panel last November)*

- Current Recruiting status:
 - Waiting to hear back from one CDER recommended Dermatologist SGE (Elizabeth Whitmore – John's Hopkins)
 - Five other SGEs and one non-SGE (Dr. Yamada) have been invited, but are not available
 - Invitations will continue to be sent out to other CDER recommended Dermatologist SGEs until six are confirmed.
- **AC briefing document/questions** – discussion of content and timelines
 - Review team has started drafting content of briefing document and possible questions which will be discussed at the next review team meeting on 7-16-09
 - 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

Participants

Gang Wang
 Janet White
 Craig Zinderman
 John Thomas
 Shiowjen Lee
 Donald Fink
 Bruce Schneider
 Patrick Riggins
 Agnes Lim
 Kimberly Benton
 Yao-Yao Zhu
 Keith Wonnacott
 Randa Melhem
 Lori Tull

Celia Witten
 Wilson Bryan
 Stephanie Simek
 Raj Puri