

# Meeting to Discuss Pharmacovigilance Planning, June 24, 2009 - Laviv

- The product's safety database was reviewed.
- The product shows efficacy with an acceptable safety profile overall.
- The follow up periods for the clinical trials (6 months to 1 year) were not long enough to reveal long term adverse events.
- Certain demographic categories were under represented in the clinical trials. (Non-Caucasians with darker pigmented skin, patients 65 years of age and older and males).
- The consensus was not to propose that the sponsor conduct a follow-up clinical study on these groups, since it may be difficult to recruit sufficient patients in these demographic groups for a meaningful study.
- CDRH require sponsors of dermal filler products to conduct open label post-marketing studies to look for adverse event profiles in the above groups. The results, to-date, show low rates of hypo or hyperpigmentation and keloids in darker skinned individuals. (Charles Durfor will forward the final reports on these studies for review).
- The clinical review team suggested that the labeling should emphasize the unknown safety profile in these groups.
- CDRH have required a long-term open label study with one of their products to collect data on adverse events, longevity of response, and whether the injected material migrates from the initial injection site.
- Bob Wise raised the concern of possible allergic reactions to the product, as there were two possible cases in prior UK experience, but no specific details are available.
- Concern was raised about whether repeated use of the product could lead to adverse events. Whereas the clinical trials involved multiple injections of the product, over a six week period, none of the trials studied repeat courses of treatment (a second course of 3 sequential injections). It was suggested that we ask the sponsor, if, in their prior market experience, patients returned for additional courses of treatment.
- Rachael Strong provided input on the FDAAA requirements for what is needed to allow FDA to impose a PMR or REMS, such as having a specific safety concern that needs to be addressed. She also noted that it would be a good idea to send our plans to the CBER Safety Working Group for review before we express concerns or propose any plans to the sponsor. It was noted that a PMR or REMS proposal could also be discussed by the Advisory Committee
- The sponsor's proposed post-marketing study includes a small number of subjects (100); sufficient detail on the methodology or purpose of the study was not provided to assess its' usefulness. The follow up period (12 months) is too short to evaluate potential long-term safety events such as overgrowth or malignant potential. A larger post-licensure safety study, with explicit enrollment and follow-up criteria, may be required to further assess the identified safety concerns such as pigmentation changes, allergic reactions, or other potential acute or sub-acute events not identified in the clinical trials.

## Possible PMC/PMRs and REMs

- Require the sponsor to conduct either an open label study or a registry to evaluate safety after-licensure in a larger population, including non-caucasian dark pigmented individuals. There should be a component of active follow up (e.g., direct contact with patients or their physician shortly after treatment and/or on a periodic basis).
- Consent to follow up could be gained as part of the consent for treatment.
- Incorporate questions related to allergic reactions and number of repeat uses of the product into any post-market studies conducted.
- Require a REMS including restricted distribution of the product only to physicians who have completed training on administration of the product. The safety concerns to justify this are the risks related to occlusion and/or embolization if the product is injected into a vessel and the unknown risks of malignancy related to cells procured in the biopsy.

## Action items:

1. OBE will write a draft summary of safety concerns and potential options for post-market safety studies to be circulated to the other meeting participants for comment.
2. Charles Durfor will send:
  - an example of a letter CDRH has used to notify a sponsor of a specific safety concern
  - an example of a 100 day letter
  - final reports of the post-marketing studies conducted by sponsors marketing dermal filler products.
3. Convene a second meeting on pharmacovigilance planning prior to the mid-cycle review meeting to further delineate proposed requirements and discuss possible need for a REMS.

## Participants:

Craig Zinderman  
Robert Wise  
Rachael Strong  
John Thomas  
Donald Fink  
Lori Tull  
Agnes Lim  
Yao-Yao Zhu  
Bruce Schneider  
Wilson Bryan  
Keith Wonnacott  
Kim Benton  
Raj Puri  
Stephanie Simek  
Celia Witten  
Janette Alexander

Shiowjen Lee