

# Panel Questions

# Panel Question #1

Based on the mean difference observed between Synvisc-One and the Phosphate-buffered Saline (PBS) control for the primary endpoint of the study (WOMAC A Subscore) as shown in Table 18 (based upon the Applicant's original analyses), the difference between the groups was 0.15 out of the 5-point Likert Scale. Please discuss the clinical relevance of the 0.15 in the least square mean difference in the change of scores from the baseline between the two groups for the proposed indication for use.

## **Panel Question #2**

Multiple secondary endpoints were tested without adjusting for multiple comparisons. Please comment on the adequacy of the applicant's analyses for the secondary endpoints in light of there being no pre-specified multiplicity adjustment to control the overall Type 1 error rate.

# Panel Question #3

Under CFR 860.7(e)(1), effectiveness is defined as reasonable assurance that, in a significant portion of the population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, will provide clinically significant results.

Considering the study design and endpoints discussed today, please discuss whether the clinical data in the PMA/Supplement provide reasonable assurance that the device is effective.

# Panel Question #4

Under CFR 860.7(d)(1), safety is defined as reasonable assurance, based on valid scientific evidence, that the probable benefits to health under conditions of the intended use, when accompanied by adequate directions for use and warnings against unsafe use, outweigh any probable risks.

Considering the adverse events for the device, please discuss whether the clinical data in the PMA/Supplement provide reasonable assurance that the device is safe.

# Reminder

- The discussion of a Post-Approval Study (PAS) prior to a formal recommendation on the approvability of this PMA should not be interpreted to mean FDA is suggesting the Panel find the device approvable.
- The plan to conduct a PAS does not decrease the threshold of evidence required to find the device approvable.
- The premarket data submitted to the Agency and discussed today must stand on its own in demonstrating a reasonable assurance of safety and effectiveness in order for the device to be found approvable.

# **PAS Panel Question #5**

The applicant did not provide a Post-Approval Study (PAS) plan in the original PMA/Supplement. However,

- 1) The clinical study supporting this PMA/Supplement was conducted in Europe and patient's characteristics may be associated with the treatment effects of the device;
- 2) The follow-up of this PMA study was 26 weeks for the initial phase and 4 additional weeks for the repeat phase, while intra-articular injection of similar devices has demonstrated the treatment effects extended to 12 month after the injection;
- 3) The literature has suggested that compared to sodium hyaluronate, cross-linked hylan G-F 20 used by Synvisc may be associated with increased risk of severe acute inflammatory reaction, the exact mechanism of this association and its long-term consequences remain unclear.

# **PAS Panel Question #5 (continued)**

Please comment on the following:

- 1) Whether there is the need for a Post-Approval Study in the US patient population.
- 2) If a Post-Approval Study is recommended, please discuss the following:
  - the objectives
  - clinical endpoints, including the need to assess the risk of severe acute inflammatory reaction
  - study size
  - comparison group
  - duration of follow-up of study subjects
  - other specific issues that you would like to be addressed in PAS