

## Draft Panel Questions

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 address the following questions:
  - a. Please discuss the clinical relevance of the 0.15 change observed from the baseline for the proposed indication for use.
  - b. Considering that the sample size of the study was originally sized to detect a difference of 0.297, yet the measured difference was 0.15 (according to the original analyses), please comment on the adequacy of the power of the study to determine whether the difference supports that a statistically-significant difference was observed.
2. The applicant originally provided an analysis of covariance (ANCOVA), fixed effects model for the analysis of their secondary endpoints. In response to FDA's deficiency letter, the applicant then performed a hierarchical sequential testing ordered method for the adjustment of type 1 error rate. Please comment on the adequacy of these analyses for the secondary endpoint.
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.
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.
5. Per the Outcome Measures in Rheumatoid Arthritis Clinical Trial- Osteoarthritis Research Society (OMERACT-OARSI) criteria, a patient is classified as a positive responder if at least 1 of the following two conditions is observed at the post-Baseline assessment:
  - In either pain (WOMAC A subscore) or function (WOMAC C subscore), a high improvement in the subscore, where high improvement in a subscore is achieved if there is both a > 50% improvement from Baseline and an absolute change from Baseline of > 20 normalized units (NU),  
OR
  - Improvement in at least 2 of the following 3:
    - Improvement in pain (WOMAC A subscore) defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU
    - Improvement in function (WOMAC C subscore) defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU
    - Improvement in PTGA defined as > 20% improvement from Baseline and an absolute change from Baseline of > 10 NU

Please address the following issues related to the responder analyses:

- a. Please comment on whether the OMERACT-OARSI criteria is appropriate and adequate to define a responder.

- b. Please comment on whether these criteria should replace the responder definition based solely on the pain reduction alone.
- c. For the responder rate analysis, please comment on how much pain reduction from the baseline through 26 weeks should be present on the WOMAC Pain Scale (VAS) from baseline in order to adequately define a responder.
- d. Please comment on what numerical difference in the proportion of responders between the two groups at 26 weeks is appropriate; and would represent a clinically meaningful difference in proportions of the rate of responders between the two groups.