

RECLASSIFICATION PETITION: Statistical Reviewer: Mel Seidman

I. INTRODUCTION:

The sponsor poses that published and unpublished information, since the original classification of these devices by FDA, now provides sufficient proof of the safety and efficacy of these designs to the degree that risks to patients can be adequately controlled by class II controls.

The supporting evidence consists of summary reports from the literature, summary reports from the data from regulated prospective multicenter clinical trials, a summary of adverse events, a section that assesses known risks to patients, and how these risks can be adequately controlled via class II requirements.

II. STATISTICAL REVIEWER'S COMMENTS:

A. The sponsor's published information contains an extensive literature submission with summary clinical outcomes. There were no statistical (meta analysis) or clinical rationale as to why these articles are sufficient support in this reclassification petition. Further, we do not know how the published literature was searched or if the submitted articles are inclusive of all articles found from the search(es). Further, it is extremely important to have similar protocols and similar evaluation endpoints when using historical data in support of clinical claims. This similarity cannot be determined with this submission.

B. The sponsor also presents unpublished clinical results from four clinical trials (A, B, C, D) from three device manufacturers. Again, how these clinical trials were selected is important in our evaluation of this petition. I did review the reported results for the clinical trials and I have several comments as follows:

1. The sponsor says that the primary efficacy endpoint will be HHS score and radiographic observations described by Gruen or DeLee or Charnley. Safety will be evaluated via complications. However, the protocols do not appear to be consistent with each other in regards to these endpoints. Additional differences noted among the protocols include the following:
 - Study A does not specifically say HHS score as a measure. It says HIP and Pain will be rated. Are these from the HHS member? There were also two protocols, one for cemented and one for cementless usage. Are both protocols reported in the results? Should they be? Are the studies completed?
 - Study B had no control. However, the protocol says at one site the patients will receive a control? The duration of the study appears open ended. There is no specific mention of HHS score evaluation. Efficacy appears to be radiographic determination.
 - Study C was for cementless usage. Evaluation intervals were not included and it does not appear to be a complete protocol.

Protocols must be similar if we are to allow results from these studies to be combined in support of the reclassification petition.

2. The sponsor uses data from all four studies in support in Book#1 of 4 with summary results. Later, in Book#3 of 4 (Item 2a response) the sponsor states that study D would be considered adjunctive and studies A, B, and C will be considered as the "core data". It is not clear to me when study D is or is not considered "core"??
3. The sponsor's primary analysis used results from 24 or more months (24+) for each study (A, B and C). These results are from 123 metal/metal and 88 metal/poly cases.

However, these cases account for less than 50% of the total cases from these studies. Therefore, the potential for BIAS based on selected follow-up may not be acceptable.

4. If there were an upward or downward trend over time this would not be noted in the analysis as there was only one time measured.
5. The sponsor's response (item 2e) used mean HHS score at 24+ months to determine pooling between sites. We also require baseline scores for these parameters, and the analysis must look at each site for pooling comparisons as well.
6. Several device configurations are included on page 16 (Book#3), for studies A, B, and C. Are these configurations acceptable? Are the control configurations required?
7. The sponsor has included a key for data appraisal on page 17 (Book#3). If the definition for item #7 (percent missing) is correct, then the reported results in table #2 that follows are not correct. Note, for example on the next page the sponsor shows only 13% as percent missing at 24+ months. However, using the definition provided the percent missing is actually 63%. This potential discrepancy must be resolved.
8. Table 7 (Book #3) shows analysis of HHS scores. Due to missing values, only 163 observations out of 216 possible can be used in this analysis. Thus, we are left with a potentially biased sample of a biased collection. This is not statistically acceptable. Also, the GLM procedure used in the analysis did not fit very well. The R-Square reported was 0.061. Therefore, the model used does not fit the data well. The results that compare the 24+ month's results for HHS score for metal to poly are not significant (last pg. of Table 7). This supports the sponsor's reclassification petition.

III. CONCLUSION:

The sponsor has not shown sufficient statistical justification for this reclassification for cemented or cementless usage. The sponsor has not adequately shown HHS, radiographic or complication comparisons among or between studies A, B and C for the 24+ month time interval. The sponsor should update the data and respond to the above comments. The sponsor should consider using meta analysis for their historical publications.