

Ms. Toni Kingsley
Zimmer, Inc.
P.O. Box 708
Warsaw, Indiana 46581-0708

Re: Reclassification Petition for Mobile Bearing Knees
Docket Number 2003P-0409/CP 1

Dear Ms. Kingsley:

The Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) has completed its review of your petition on behalf of the Orthopedic Surgical Manufacturers Association (OSMA) for the reclassification of mobile bearing knee prostheses that are intended for use in the replacement of a knee joint, or part of a knee joint.

In order to reclassify mobile bearing knees into class II, it is necessary to demonstrate that the proposed class of devices has sufficient regulatory controls to provide reasonable assurance of safety and effectiveness for their intended use. Although you have listed some of the common risks associated with both fixed and mobile bearing knees, we believe there are certain risks unique to mobile bearing knees. In particular, these relate to dislocation of the insert and specific wear patterns related to design and the mobility of the bearing surface. In addition, each of the different types of mobile bearing knees within this class may have its own risks related to the specific design and bearing surface. For each of the different type of mobile bearing knee designs, special controls must be identified to address their attendant risks. We do not believe you have provided these special controls which address the specific risks unique to mobile bearing knee prostheses.

In order to address these issues, please provide following additional information.

Device Description and Characterization

1. Based on the information you have provided in this application and a review of literature, FDA believes that the individual clinical performance is not only influenced by the particular design kinematics, but also by contact stress distribution, articulating

surface finish of the components, and the quality and quantity of polyethylene wear particles. Because these parameters are different

for each kind of mobile bearing knee design, we do not believe that designs with varying degrees of conformance and types of motion perform the same biomechanically or clinically, or can be grouped together as one group having similar characteristics. This is born out by the clinical outcomes. For example, revision rates vary between 2-30%, clinical function and range of motion are varied for different device designs, and complications show that different devices have different risks and complications associated with them.

- a. You have stated that test data from peer-reviewed journals indicates that the polyethylene wear rate is lower in mobile bearing knees compared to fixed bearing knees. However, you have provided data comparing the wear characteristics to Charnley *hip* systems, and some references you provide (Callahan, 2001) dispute that the rates are different than well functioning fixed bearing knees. In this discussion you have not sufficiently characterized the wear characteristics and ensuing risks associated with mobile bearing knees in relation to proposed special controls (i.e., those used for fixed bearing knee implants).

Although you have provided summaries of studies done with these devices as a group (i.e., MBK), you have not provided summaries which link the preclinical biomechanical and wear properties for each different type of mobile bearing knee (listed in table in 1c, below) to their clinical results (i.e., explain how bench test results correlate to clinical results).

We are aware that there are several preclinical and/or explant evaluations which characterize both mobile bearing (e.g. Parks and Engh, 1998) and fixed bearing total knee components (e.g. Jacobs, et al. 1994; Shanbhag et al. 2003) on the bench and as a result of in-vivo use. Please include this in a discussion regarding backside stress and wear of the various tibial insert designs, which was omitted from your petition, and has been identified elsewhere as a risk in both fixed and mobile bearing devices. This information is necessary to demonstrate that proposed special controls are sufficient to establish the safety and effectiveness for each of the different mobile bearing device types, without the need for additional special controls or clinical data.

- b. Based on the risks identified above, please describe appropriate special controls for each device type identified in the table below (1c) and how these proposed controls will provide reasonable assurance of safety and effectiveness for the given intended uses. Please also incorporate these special controls into the table.
- c. Please use the table below, which lists the different type of mobile bearing knee designs, to summarize the device characteristics, biomechanical advantages and

disadvantages, survival rates, risks, and proposed controls for each group of devices so that we can interpret the effects on clinical outcome.

Type of MBK	Representative Devices	Potential Biomechanical Advantages	Potential Biomechanical Disadvantages	Mean Survival /Yrs (range)	Complications common risks associated with device	Special Controls which address the associated risks
Platform						
Meniscal Bearing - total						
*Tricompartmental (patellofemoroltibial)						
*Bicompartmental (femorotibial – total)						
Unicompartmental Meniscal Bearing						
Cone-in Cone						
Tibial Tray Post						
Longitudinal Curved Sliding tracks						
Stops						
Constrained						
Semi Constrained						
Unconstrained bearing						
Congruent						
Partially Congruent/Gait congruent						

* We recommend that the categorization of the total condylar mobile bearing knees be further divided into sub groups of bicondylar and tricondylar at this time because the risks of patellar mobile bearing components are unique to the tricondylar devices.

- d. Although you have provided tables which summarize individual studies relating to the clinical outcomes for each of multidirectional knees, rotating platforms, meniscal bearing devices, and unicondylar meniscal bearing devices, you have not summarized the clinical characteristics of each group of devices based on these studies and made a comparison to fixed bearing devices to show that clinical outcomes for each group of mobile bearing knees are similar to those of fixed bearing knees. This information is necessary to write special controls, such as labeling, for these devices. Therefore, please provide a summary table of the data from the tables you have previously provided, and use this to summarize these particular groups of devices in a comparison with fixed bearing devices. Include in this summary the means and ranges of (where appropriate) patient age, diagnoses, postoperative pain improvement, range of motion, function improvement, survival rate, and common complications. Also provide this information for fixed bearing knees in a separate column or row.

- e. You have provided a study which has characterized the function of mobile bearing knees by looking at patients who were supine (Bradley, ref. # 14). However, this characterization is incomplete. We are aware that there are studies which evaluate some of the mobile bearing knees designs with patients' weight bearing and completing the gait cycle (Dennis, Steihl). In order to be complete, please provide/summarize any studies which characterize the range of motion or contact stress in a weight bearing and/or gait cycle.

Statistical Considerations Related to the Meta-Analysis

2. We acknowledge that you have provided a meta-analysis for mobile bearing knee replacement devices and compared this meta-analysis with one previously done for a sample of fixed bearing devices. FDA believes some additional information regarding the meta-analysis needs to be addressed to better understand the inferences regarding the difference between the effects of the two treatments (fixed vs. mobile). Please address the following which relate to your analysis:
 - a. Are there any other inclusion/exclusion criteria for the meta-analysis not reported in the submission?
 - b. Table 3, page 69, Section VIII, Volume 1, depicts the comparison of mobile bearing versus fixed bearing meta-analysis results. Please provide the publication year for each study used in this meta-analysis. Please also provide the data of follow-up years.
 - c. Please discuss in detail your method of calculation for 'weighted mean' (Table 3, page 69).
 - d. Does the number of cohorts mean the number of studies that meet the inclusion criteria (paragraph 4, page 68, Sec. VIII, Vol. 1)?
 - e. Are all the studies, mobile bearing and fixed bearing, controlled studies? If yes, please provide a summary from the control group for each study.
 - f. Please define "survival estimates", are they related to Kaplan-Meier method? If yes, please provide all 111 survival estimates discussed on page 70, Sec. VIII, Vol. 1.

- g. Please discuss the following statement, “weighted least squares (WLS) was performed on the survival estimates using the natural logarithmic transformation of the product of the number of cases (knees) and the mean

length of follow-up as the weighting variable (log knee-years)” (p. 70, Sec. VIII, Vol. 1), in detail. A numerical example would be very helpful.

- h. Please discuss the rationale for using the bootstrap procedure to calculate the confidence interval for the survival differences (p. 70, Sec. VIII, Vol. 1).
- i. Please discuss and provide computation details of the bootstrap resampling procedure used for generating confidence intervals and estimating the P-value for the differences between mobile and fixed bearing device survival (pages 70-71, Sec. VIII, Vol. 1; p. 284, App. 5, Vol. 2), and also for the bootstrap procedure used to generate confidence intervals for the difference in patient outcomes (% good to excellent and mean % improvement, in global knee rating score) following mobile bearing knee replacement (page 275, App. 4, Vol. 2).
- j. In regard to Appendix 4: Meta-Analysis - Patient outcomes following mobile bearing knee replacement, in Volume 2, what are the primary patient outcomes; range of motion and stability, or some other endpoint?
- k. Please provide a table of survival times for this submission. The table can be structured as follows:

Study	Survival	MBK	
		Failed	Withdrawn
1 follow-up time (months)	x (# knees)	x (# knees)	x (# knees)

- l. Does Table 3 on page 69, Sec. VIII, Vol. 1, contain the same information as the “Data Synthesis” section on page 272 of Appendix 4, Vol. 2?
- m. Please provide the rationale for the combined summary scale of pain, function and the range of motion (eighth line from the top of page 274, Appendix 4, Vol. 2). Are they weighted in this combination? Did all the studies use the same global knee rating scale?
- n. Table 11, page 279, Appendix 4, Vol. 2, depicts the values for outcome variables of interest from the mobile bearing knee literature. You have reported that 5 studies were imputed of the good or excellent global outcomes rating scores and 8 studies were imputed of the improvement in global rating scale. Imputed value was defined as “weighted least square regression-weighted by number of knees

operated on". Please provide details of the computation of the least squares model for the two outcomes

and show the result of R^2 for % good to excellent and % improvement in global rating scale.

- o. The discussion of the “Meta-Analysis” section on page 284, Appendix 5, Vol. 2, was too vague. Please define survival estimate and show an example how this can be derived from WLS (weighted least square). Please also refer Table 20, page 287, Vol. 2.
- p. Your table, Table 19, page 287, Appendix 5, Vol. 2, depicts the homogeneity analysis. Please provide an example to show the computation of using an F-Statistic, page 286, comparing the residual error from a “full” model which consisted only of an intercept. None of p-values in Table 19 are significant except N knee for FB p-value 0.0142. Please explain its clinical meaning.
- q. Please add one column to Table 22, page 293, Appendix 5, Vol. 2, to show whether the study is controlled. If yes, please indicate the control device.
- r. Please provide computation to show how the p-value of 0.992 was derived for the difference in implant survival between mobile bearing and fixed bearing devices (last sentence, page 287, Appendix 5, Volume 2).

In addition to answering the above questions please provide the following:

- s. A table that summarizes all the individual studies from the literature search. The total number of devices and number of failures for treatment and control groups for each study are requested. Failure should be defined based on the purpose of meta-analysis study. Control device should be identified for each study.
- t. Define the treatment difference used in the meta-analysis for future discussion of the hypothesis testing of the treatment difference.
- u. Provide a test of heterogeneity across studies.
- v. A justification for the selection of a fixed effect model verses a random effect model.
- w. The meta-analysis results and individual study estimates of treatment difference and their confidence interval graphically.
- x. Decision, based on item w, above.

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If you have any questions concerning this letter, please contact Mr. Peter Allen, at (301) 594-2036.

Sincerely yours,

Daniel G. Schultz
Director
Office of Device Evaluation
Center for Devices and Radiological Health

cc:

Robert W. Churinetz
Vice President, OSMA

cc: HFZ-401 DMC
HFZ-410 Division
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