

Draft FDA Panel Questions

Note to Panelists: *These are draft questions. The actual questions asked during the panel meeting may be different. Please be prepared to discuss the following issues. Panel deliberations provide FDA expert knowledge and experience on new devices, new issues or unanticipated safety and effectiveness questions. FDA values an open debate raising new ideas and fresh perspectives.*

1. The Oxiplex®/SP Gel is a gel applied during lumbar spine surgery designed to act as a physical barrier between tissues. The proposed indication for use states it is intended to be used as a surgical adjuvant during posterior lumbar laminectomy, laminotomy, or discectomy to improve patient outcomes by reducing postoperative leg pain, back pain and neurological symptoms. The primary endpoint was reduction in the composite leg pain score of Lumbar Spine Outcomes Questionnaire (LSOQ), and the secondary endpoints were composite back pain, leg weakness, physical symptoms, subject satisfaction, disability score, and activities of daily living. Please discuss the appropriateness of the primary and secondary effectiveness endpoints in the study conducted as supporting the proposed indications for use.
2. The sponsor provided biocompatibility, toxicity, and animal performance testing, and based support for chronic toxicity, carcinogenicity, and immunotoxicity on a rationale and literature search. The sponsor stated that due to the length of time Oxiplex remains in the body, based upon their preclinical animal studies and literature search, and use of components contained in Oxiplex (*i.e.*, CMC and PEO) in other medical device applications, chronic toxicity, carcinogenicity and immunotoxicity testing are not necessary. Please comment on the adequacy of the non-clinical testing and pre-clinical animal studies conducted by the sponsor. Please discuss whether the animal studies are expected to be predictive of the performance of the device for its proposed indications for use.
3. Some variability in patient outcomes among sites was shown in the unadjusted analysis on the 6-month leg pain change from baseline by site/pseudo-site on the Complete Cases populations. In the Generalized Estimating Equations (GEE) model on leg pain improvement, the treatment-by-site interactions were shown to be statistically significant ($p=0.034$ in Complete Cases population). Please comment on the validity of pooling data from different sites, taking into consideration the demonstrated site variability. Please discuss what impact this may have on the interpretation of the clinical data.
4. The sponsor included 19 covariates in its multivariate analysis of the primary effectiveness endpoint (*i.e.* composite leg pain) using the Generalized Estimating Equations (GEE) on the Intent-to-Treat (ITT) population. The sponsor's interpretation of this analysis is that it demonstrates the statistical significance of the primary endpoint based on the significance of treatment by baseline covariate interactions. Please discuss whether the sponsor's multivariate analysis is appropriate, and, to assist the FDA with the interpretation of whether the study met its primary endpoint, discuss this conclusion based upon the analyses conducted by the sponsor to determine statistical significance of the primary endpoint.
5. FDA requested that the sponsor calculate the simple mean difference of composite leg pain improvement (*i.e.* primary effectiveness endpoint) at 6-months between the Oxiplex and Control groups. This mean difference was 1.42 ($p=0.59$, t-test) on the 100-point LSOQ scale for the Modified Completed Cases population. Please discuss whether this mean difference between the Oxiplex and the Control groups is clinically meaningful.
6. The sponsor's primary effectiveness endpoint analyses screened 48 different covariates and their interactions with the treatment variable to be included in the statistical models. Some of these

treatment-by-covariate interactions had unadjusted p-values less than 0.044, which led to subgroup analyses. For example, for the subgroup of patients with baseline back pain scores greater than or equal to 63, Oxiplex patients had a 9.6 point advantage (on a 0-100 scale) over the Control patients in leg pain improvement at 6 months. This treatment effect had an unadjusted p-value of 0.012. Please discuss whether the observed significant treatment effect for some subgroup of patients could have happened due to chance, and how the sponsor's subgroup analyses may affect the interpretation of the safety and effectiveness of the device.

7. 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. Do the clinical data in the PMA provide reasonable assurance that the device is safe?
8. 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. Do the clinical data in the PMA provide reasonable assurance that the device is effective?

Note to Panelists: The inclusion of questions on labeling and Post-Approval Study should not be interpreted to mean that FDA has made a decision or is making a recommendation on the approvability of this PMA device.

Please consider the following potential questions:

Labeling

9. The sponsor provided Physician labeling/Instructions for Use for the subject device. The sponsor did not provide patient labeling because they consider the device an adjunct to surgical treatment and believe the patient is not involved in the choice of using the Oxiplex/SP gel. Please discuss:
 - a. The need for patient labeling.
 - b. The appropriateness and/or adequacy of the Physician labeling/Instructions for Use.

Post-Approval Study (PAS)

10. In the Post-Approval Study (PAS) outline, the sponsor proposes a non-inferiority design to compare the reduction in the number of disability days from baseline within 30 days of 6 months following surgery in subjects who will receive Oxiplex vs. the Oxiplex-treated subjects in the pivotal study. The sponsor also proposes tracking adverse events and re-operations over the 6-month follow-up period. Please discuss the following topics:
 - a. Whether the PAS study design is appropriate to address longer term device safety and effectiveness post-market;
 - b. Whether “reduction in disability days from baseline at 6 months” is an appropriate effectiveness endpoint to address the device effectiveness in the real-world settings; and
 - c. Whether 6-month follow-up after surgery is sufficient to address long-term safety of the device, and identify potential adverse events .