



Food and Drug Administration
Office of Device Evaluation
10903 New Hampshire Avenue
Silver Spring, MD 20993

Addendum to Denial Order

Date: December 2, 2013
To: The Record
From: Jismi Johnson, M.S., Lead Reviewer

Office: Office of Device Evaluation
Division: Division of Orthopedics
Branch: Restorative and Repair Devices
Branch

Re: P070023 Oxiplex®/SP Gel

Filed: August 21, 2007

Amended: October 4, 2007, November 21, 2007, November 23, 2007, February 27, 2008 (2), May 16, 2008 (6), July 7, 2008, July 18, 2008, February 25, 2009, July 29, 2009, October 19, 2009, June 8, 2010, June 11, 2010, January 6, 2011, October 17, 2011, October 19, 2011, March 13, 2012, July 23, 2012

Company Name: FzioMed, Inc.
Device Name: Oxiplex®/SP Gel
Product Code: MLQ

Decision: Denial

This document is an addendum to FDA's Denial Order, dated October 21, 2013, for FzioMed's premarket approval application (P070023) for Oxiplex®/SP Gel. The Denial Order contains the following statement in footnote 2 on page 3 concerning certain UK data:

Although you acknowledge that other OUS data were reasonably known (e.g., U.K. data), you have not provided these data to FDA, as required by 21 CFR 814.20(b)(8)(ii). As such, this information was not available to FDA at the time the decisions were made and is not included as part of the administrative record for this PMA.

Upon review of the Denial Order, the applicant notified FDA that six presentation slides referring to U.K. data were submitted in the bibliography of P070023. Accordingly, the statement quoted above from page 3 of the Denial Order is revised to read:

The U.K. data referred to in the PMA bibliography are not part of the administrative record of the denial decision for this PMA.

Jismi Johnson, M.S., Lead Reviewer

William H. Maisel, MD, MPH, Deputy Center Director for Science
Center for Devices and Radiological Health



Food and Drug Administration
10903 New Hampshire Avenue
Document Control Center – WO66-G609
Silver Spring, MD 20993-0002

By Registered Mail

John Krelle, President & CEO
FzioMed, Inc.
231 Bonetti Drive
San Luis Obispo, CA 93401

October 21, 2013

Re: P070023

FzioMed, Inc. Oxiplex®/SP Gel

Filed: August 21, 2007

Amended: October 4, 2007, November 21, 2007, November 23, 2007, February 27, 2008 (2), May 16, 2008 (6), July 7, 2008, July 18, 2008, February 25, 2009, July 29, 2009, October 19, 2009, June 8, 2010, June 11, 2010, January 6, 2011, October 17, 2011, October 19, 2011, March 13, 2012, July 23, 2012

Product Code: MLQ

Dear Mr. Krelle:

The Center for Devices and Radiological Health (CDRH or the Center) of the Food and Drug Administration (FDA) has completed its review of your premarket approval (PMA) application (P070023) for Oxiplex®/SP Gel (Oxiplex). You requested approval for this device to be indicated as follows:

Oxiplex®/SP Gel is indicated as a surgical adjuvant during lumbar laminectomy, laminotomy, or discectomy, for use in patients with preoperative leg pain and preoperative back pain, to improve outcomes by reducing postoperative leg pain.¹

¹ You modified the proposed indications for use several times during our review of your PMA application. This statement of the indications for use is the one that you last submitted on July 27, 2009 in P070023/A015 (referred to in this denial order as the Amendment 15 indications) before the issuance of the second Not Approvable letter on January 12, 2010. You subsequently submitted revised indications for use in your October 14, 2011 request for supervisory review of the not approvable decision and your November 5, 2012 petition for reconsideration: “The Oxiplex®/SP Gel is indicated use as a surgical adjuvant in adult patients with primary leg pain and severe baseline back pain undergoing first surgical intervention (i.e., open or endoscopic posterior lumbar laminectomy, laminotomy, or discectomy) for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy. The product is indicated for one-time use, up to 3 mL, after hemostasis during wound closure. Oxiplex is intended for use as an adjunct to primary surgical intervention to improve patient outcomes by reducing leg pain, back pain and neurologic symptoms” (referred to in this denial order as the revised “severe” baseline back pain indications). Although the revised “severe” baseline back pain indications were not part of your PMA submission, we nevertheless address them in this denial order because we considered them in our October 9, 2012 decision letter on your appeal under 21 CFR 10.75.

We regret to inform you that your PMA application is denied in accordance with section 515(d)(2) of the Federal Food, Drug, and Cosmetic Act (the Act) [21 U.S.C. § 360e(d)(2)]. This decision is effective immediately upon receipt of this letter.

Pursuant to 21 CFR 814.44(a), CDRH referred the PMA for Oxiplex to the Orthopaedic and Rehabilitation Devices Panel for review. On July 15, 2008, the Panel met and voted to recommend to CDRH that the PMA for Oxiplex be considered "Not Approvable." CDRH issued letters in accordance with 21 CFR 814.44(f) on September 15, 2008 and January 12, 2010, communicating that your PMA was determined to be not approvable because the evidence submitted for review was not sufficient to demonstrate a reasonable assurance of the safety and effectiveness of the device under the conditions of use prescribed, recommended, or suggested in the proposed labeling. *See* §§ 515(d)(2)(A), (d)(2)(B) of the Act [21 U.S.C. §§ 360e(d)(2)(A), (d)(2)(B)]. By letter dated October 14, 2011, and amended on March 13, 2012, you requested supervisory review by the Office of the Center Director of the not approvable decision. A letter issued on October 9, 2012, by Dr. William Maisel, on behalf of the Office of the Center Director, upheld the not approvable decision of January 12, 2010. You then chose to exercise the option provided under 21 CFR 814.44(f)(2) to consider the October 9, 2012 decision letter to be a denial of approval of the PMA under 21 CFR 814.45 and request administrative review under section 515(d)(4) of the Act [21 U.S.C. § 360e(d)(4)] by filing a petition for reconsideration under 21 CFR 10.33 on November 5, 2012.

Because you have petitioned for review under section 515(d)(4) [21 U.S.C. § 360e(d)(4)] by filing a petition in the form of a petition for reconsideration under 21 CFR 10.33, the Agency is hereby issuing an order denying approval of your PMA, as set forth in 21 CFR 814.45(e)(3). In accordance with section 515(d)(2) of the Act [21 U.S.C. § 360e(d)(2)], FDA has identified the reasons for denying the PMA and has identified, where practicable, the measures necessary to make the PMA approvable. In summary, you have not provided a reasonable assurance of the safety and effectiveness of the device under the conditions of use prescribed, recommended, or suggested in the proposed labeling. *See* §§ 515(d)(2)(A), (d)(2)(B) [21 U.S.C. §§ 360e(d)(2)(A), (d)(2)(B)]. The particular deficiencies in your PMA and the basis for this determination are summarized by the following:

Based on our assessment of the totality of evidence presented in your PMA application and your subsequent appeal of the not approvable decision, additional confirmatory clinical evidence of device performance for the requested indications for use is needed to establish a reasonable assurance of the effectiveness of the device. To establish a reasonable assurance that your device is effective, you must provide valid scientific evidence that, in a significant portion of the target 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. *See* 21 CFR 860.7(e)(1). Your US pivotal study failed to show a statistically significant and clinically significant difference in the overall treatment effect for Oxiplex. Therefore, we conclude that the data from the pivotal study are not adequate to support a reasonable assurance of effectiveness of the device for the Amendment 15 indications. We also conclude that the supplemental clinical data (described in more detail below) submitted are insufficient to establish a reasonable assurance of the effectiveness of the device for the Amendment 15 indications.

Additionally, you concluded from the US pivotal study that patients with “severe” baseline back pain may benefit from your device; however, this conclusion was based on your exploratory subgroup analysis of the pivotal study data. Accordingly, we conclude that there are not adequate data to support a reasonable assurance of the effectiveness of the device for the revised “severe” baseline back pain indications for use that you subsequently submitted in your October 14, 2011 request for supervisory review of the not approvable decision and your November 5, 2012 petition for reconsideration.

In response to our assessment that data from the US pivotal study were inadequate to demonstrate a reasonable assurance of effectiveness, you submitted data from two “confirmatory studies” that were conducted outside of the United States (OUS).² You provided additional detailed information on these two OUS studies at the request of Dr. Maisel during his review of your request for supervisory review of the not approvable decision, and we conducted further analyses of these data. However, the data from these two studies were found to be inadequate to provide a reasonable assurance of the effectiveness of the device, for the following reasons:

- None of the data from the clinical studies (the US pivotal study, Confirmatory Study #1, or Confirmatory Study #2) can be pooled because the studies have different subject populations, including different enrollment criteria, and different endpoints.
- Neither Confirmatory Study #1 nor Confirmatory Study #2 was sufficient to demonstrate a reasonable assurance of the effectiveness of the device for either the Amendment 15 indications or the revised “severe” baseline back pain indications.
 1. Confirmatory Study #1: With respect to the Amendment 15 indications, the overall treatment effect (the difference in leg pain improvement between the Oxiplex group and the control group) was minimal and not clinically or statistically significant at either the 30 day or 60 day endpoint. With respect to the revised “severe” baseline back pain indications, the study was not initially designed to assess the treatment effect in the “severe” baseline back pain subgroup, although you state a prospective statistical analysis plan was used. Additionally, a treatment effect from Oxiplex was not demonstrated for the quartile of patients with the most severe baseline back pain (baseline back pain VAS score ≥ 6.2), for either the 30 day or 60 day endpoint.
 2. Confirmatory Study #2: Although you describe this as a “randomized” study, the subject allocation was not truly randomized, and there are important baseline differences between the treatment and the control groups. The lack of randomization and differences in baseline subject characteristics preclude meaningful comparison of the treatment and control group data to support the Amendment 15 indications or the revised “severe” baseline back pain indications.

² Although you acknowledge that other OUS data were reasonably known (e.g., UK data), you have not provided these data to FDA, as required by 21 CFR 814.20(b)(8)(ii). As such, this information was not available to FDA at the time the decisions were made and is not included as part of the administrative record for this PMA.

In addition, even if these significant study conduct flaws were overlooked, few study subjects had back pain of comparable severity as defined in the exploratory subgroup of the US pivotal study, which limits meaningful interpretation of the data to support the revised “severe” baseline back pain indications.

We, therefore, find that additional clinical testing is necessary to demonstrate a reasonable assurance of the effectiveness of Oxiplex for the patient population described in both the Amendment 15 indications and the revised “severe” baseline back pain indications.

We also note that, the FDA’s Orthopaedic and Rehabilitation Devices Panel raised questions related to the safety of the Oxiplex device in the intrathecal space as well as the effect of Oxiplex on osteoid activity and local cytokine release during its July 15, 2008 meeting. In response to these questions, you stated at the panel meeting that there are primate data and other ongoing studies that would address these concerns. However, to date, you have not provided these data to FDA for review, as required by 21 CFR 814.20(b)(8)(ii). As such, this information was not available to FDA at the time the decisions were made and is not included as part of the administrative record for this PMA.

In summary, the information you submitted does not provide a reasonable assurance that the device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling. *See* §§ 515(d)(2)(A), (d)(2)(B) [21 U.S.C. §§ 360e(d)(2)(A), (d)(2)(B)]. You have not demonstrated that, in a significant portion of the target population, the use of Oxiplex 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. *See* 21 CFR 860.7(e)(1). You also have not demonstrated that the probable benefits to health from use of Oxiplex for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. *See* 21 CFR 860.7(d)(1).

The particular deficiencies in your PMA are discussed in further detail in the attached summary basis of denial.

Section 515(d)(2) of the Act [21 U.S.C. § 360e(d)(2)] requires FDA, if practicable, to identify measures necessary to place the PMA in approvable form. *See also* 21 CFR 814.45(b). To place your PMA in approvable form you must provide sufficient additional evidence demonstrating a reasonable assurance that the device is safe and effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling. To support both or either the revised “severe” baseline back pain indications and/or the Amendment 15 indications, this additional evidence may be in the form of additional clinical data that show a statistically and clinically significant treatment effect in the relevant patient population. The data may be from one multiple-arm study or from two separate studies, and should use a primary effectiveness endpoint of mean reduction from baseline pain to 6 month post-operative residual pain using a validated pain scale. To provide evidence of a reasonable assurance of effectiveness to support both or either indications, the study(ies) should demonstrate in the relevant patient population a statistically and clinically significant result of at least a 10% difference in the primary effectiveness endpoint, in favor of Oxiplex, when the mean difference between the groups is

divided by the treatment effect in the control group. This assumes at least a 50% reduction in baseline to 6-month residual pain in the control group. Other primary effectiveness measures may also be acceptable. If you plan to leverage any prior clinical data, we encourage an assessment of the final device formulations to ensure comparability across important specifications.

This letter completes FDA's review of your PMA. A notice of this denial will be placed on FDA's home page on the Internet and will be published in the Federal Register. *See* 21 CFR 814.45(d)(1). Should you choose to address the above deficiencies, FDA will consider that response a resubmission of the PMA and will assign it a new PMA number. All of the information contained in P070023 will be considered to be incorporated into the new PMA by reference in its entirety. Please do not resubmit any of those data unless requested to do so by FDA at a later date. Any resubmission of the PMA should clearly address how each of the above deficiencies was remedied. If you have any questions concerning this denial order, please contact Laurence D. Coyne, Ph.D., at 301-796-6450.

Sincerely,

William H. Maisel -S

William H. Maisel, MD, MPH
Deputy Center Director for Science
Center for Devices and Radiological Health

cc: Janice M. Hogan, Esq., Partner, Hogan Lovells US LLP

Attachments