



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

**Addendum to Summary Basis for Denial**

**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

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This document is an addendum to FDA's Summary Basis for Denial dated October 21, 2013, of FzioMed's premarket application (P070023) for Oxiplex®/SP Gel. The Summary Basis for Denial contains the following statement on page 2 concerning certain U.K. data:

The applicant acknowledged other OUS data were reasonably known (e.g. U.K. data), but these data were not provided to FDA, as required by 21 CFR 814.20(b)(8)(ii) and are not included as part of the administrative record for this PMA.

A similar statement appears on page 24 in footnote 2 of the Summary Basis for Denial:

Although the applicant has acknowledged that other OUS data were reasonably known (e.g., U.K. data), the applicant has not provided these data 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 Summary Basis for Denial, 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 2 of the Summary Basis for Denial 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.

In addition, footnote 2 on page 24 is deleted from the Summary Basis for Denial.

Jismi Johnson -S  
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Jismi Johnson, M.S., Lead Reviewer

Christy L. Foreman -S  
2013.10.21 11:50:10 -04'00'

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Christy Foreman, M.S., Director, Office of Device Evaluation



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10903 New Hampshire Avenue  
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**Synopsis of Premarket Approval [PMA] Application Reviews and  
Summary Basis for Denial**

**Date:** October 21, 2013  
**To:** The Record  
**From:** Jismi Johnson, M.S., Lead Reviewer

**Office:** Office of Device Evaluation  
**Division:** Division of Orthopedics  
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**Re: P070023 Oxiplex®/SP Gel**

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**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

**Proposed Indications for Use:** 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.<sup>1</sup>

**Decision:** Denial

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**I. EXECUTIVE SUMMARY**

In accordance with the Food and Drug Administration's (FDA's) Premarket Approval program, FzioMed, Inc. has submitted a Premarket Approval (PMA) application (P070023) for Oxiplex®/SP Gel (Oxiplex). Oxiplex is a device designed to be implanted in the lower back to provide a physical separation of tissues after lumbar spine surgery. The product is an absorbable, clear, viscoelastic gel

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<sup>1</sup> The applicant modified the proposed indications for use several times during FDA's review of the applicant's PMA application, as discussed in further detail in the "Changes to Indications for Use" section on pages 23-24 of this summary basis for denial memo. This statement of the indications for use is the one that the applicant last submitted on July 27, 2009 in P070023/A015 (referred to in this summary basis for denial memo as the Amendment 15 indications) before the issuance of the second Not Approvable letter on January 12, 2010. The applicant subsequently submitted revised indications for use in its October 14, 2011 request for supervisory review of the not approvable decision and its November 5, 2012 petition for reconsideration (referred to in this summary basis for denial memo as the revised "severe" baseline back pain indications). Although the revised "severe" baseline back pain indications were not part of the applicant's PMA submission, we nevertheless address them in this summary basis for denial memo because we considered them in our October 9, 2012 decision letter on the applicant's appeal under 21 CFR 10.75.

applied to the dura and exiting nerve root, as well as the laminectomy/laminotomy site during lumbar spine surgery, immediately prior to closure. Oxiplex is comprised of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water.

A randomized, controlled pivotal study in the U.S. failed to show a statistically significant or a clinically meaningful difference in overall treatment effect for Oxiplex. The simple mean difference of the primary effectiveness endpoint (composite leg pain) between the two groups at 6 months was 1.42 on the 100 point chosen assessment scale. The applicant concluded from the U.S. pivotal study that a subset of patients with “severe” baseline back pain may benefit from Oxiplex; however, this conclusion was based on post-hoc exploratory subgroup analysis of the pivotal study data. While FDA concurs that the exploratory analysis of the US pivotal study was adequate to identify hypotheses for subsequent clinical trial designs, the analysis was not adequate to support a reasonable assurance of effectiveness for the subset of patients who were identified after conclusion of the clinical trial in an exploratory fashion.

In response to FDA's assessment that the exploratory subgroup analysis of data from the U.S. pivotal study was inadequate to demonstrate a reasonable assurance of effectiveness, the applicant submitted Amendment 15 to P070023 on July 29, 2009 containing data from two “confirmatory studies” that were conducted outside of the U.S. (OUS) – one conducted in China, the other conducted in Italy. The applicant acknowledged other OUS data were reasonably known (e.g., U.K. data), but these data were not provided to FDA, as required by 21 CFR 814.20(b)(8)(ii) and are not included as part of the administrative record for this PMA. The data from these two OUS studies were found to be inadequate to provide a reasonable assurance of the effectiveness of the device for several reasons. None of the data from the clinical studies (the U.S. pivotal study, Chinese study, or Italian study) can be pooled because the studies have different subject populations, including different enrollment criteria, and different endpoints. In addition, neither the Chinese study nor the Italian study is 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. Therefore, FDA determined 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.

FDA also notes that 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, the applicant stated that there are primate data and other ongoing studies that would address these concerns. However, to date, the applicant has not provided these data for review, as required by regulation per 21 CFR 814.20(b)(8)(ii). Therefore, 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.

## **DECISION**

After review of the original PMA, FDA 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 FDA that the PMA for Oxiplex be considered “Not Approvable.” A Not Approvable letter was sent to the applicant on September 15, 2008. FDA stated two grounds for its first Not Approvable decision:

- 1) The U.S. pivotal study did not meet its primary and secondary effectiveness endpoints, thereby failing to demonstrate that Oxiplex was more effective than the control treatment in the chosen patient population for the study. The applicant was asked to provide additional clinical data in a predefined population with appropriate indication(s) showing a statistically significant, as well as

clinically meaningful, difference between the Oxiplex and Control groups in the chosen primary endpoint. In addition, the applicant was asked to provide a scientific explanation of the physiologic mechanism for the effectiveness of the device in the target population for the additional clinical data set.

- 2) Because of concerns that the Type 1 error rate was not controlled for subgroup analyses performed on the data from the U.S. pivotal study, any results from such analyses would be considered exploratory findings and would need to be confirmed with additional clinical data. The applicant was asked to provide additional clinical data if the indications for use that were proposed *after* the panel meeting were to be sought (e.g., for use in patients with severe leg and back pain, to improve outcomes by reducing postoperative leg pain, back pain and neurological symptoms).

On July 27, 2009, the applicant submitted its response to the September 15, 2008 Not Approvable letter in the form of Amendment 15. In an attempt to confirm the subgroup findings from the U.S. pivotal study, this amendment consisted of retrospective data on Oxiplex from an Italian case series and a Chinese clinical study. After review of Amendment 15, a second Not Approvable letter was issued on January 12, 2010. The second Not Approvable letter stated the following grounds for the Not Approvable decision, among other scientific concerns:

Because the additional clinical data that were provided represented additional exploratory subgroup analyses and did not appear to be designed to confirm the exploratory subgroup effect from the pivotal study, the applicant was requested to provide additional confirmatory data from a new randomized controlled study which prospectively and consistently defines “severe” baseline back pain, in order to mimic the subgroup of patients in pivotal study who may benefit from the device.

In Amendment 19 (dated January 5, 2011), the PMA applicant voluntarily withdrew their PMA because the information requested in the Agency's January 12, 2010 not approvable letter could not be provided by the extended deadline.

In Amendment 20 (dated October 14, 2011), the PMA requested an internal agency supervisory review of the Not Approvable determination for Oxiplex, pursuant to 21 CFR 10.75. On April 11, 2012, the Center for Devices and Radiological Health (CDRH, the Center) and FzioMed met to discuss the appeal. On June 4, 2012, an interim response letter was sent to the applicant requesting submission of line-item clinical data on all patients enrolled in the two OUS studies in electronic format so that CDRH could conduct its own analysis. After review of the OUS clinical data, the Not Approvable decision was upheld by the Center Deputy Director for Science, on behalf of the Office of the Center Director, in a letter issued on October 9, 2012.

The applicant 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 by filing a petition for reconsideration under 21 CFR 10.33 on November 5, 2012. FDA's regulations provide that FDA will issue a letter denying approval of a PMA upon the filing of a petition under 21 CFR 10.33. See 21 CFR 814.45(e)(3). Therefore, FDA issued an order denying approval of P070023 on October 21, 2013.

## II. SUBMISSION BACKGROUND

### DEVICE DESCRIPTION

Oxiplex is an absorbable, clear, viscoelastic gel applied during lumbar spine surgery, immediately prior to closure. Oxiplex is comprised of sodium carboxymethylcellulose (CMC) and polyethylene oxide (PEO) in sterile water. Because the body rapidly absorbs CMC, PEO is added to the formulation to create stronger bonding between the two to enhance the residence time of the gel in the body. Calcium chloride (CaCl) is added for stability and sodium chloride (NaCl) is added for isotonicity. Oxiplex is non-pyrogenic and contains no animal or bacterial components. No color additives are used in the device.

Oxiplex is provided sterile in a 3mL (maximum dose) syringe, along with a sterile, flexible applicator for use in applying the gel during surgery.

The following represent the product specifications:

(b)(4)	(b)(4)
(b)(4)	(b)(4)
Color:	Colorless
Form/Shape:	Visco-elastic, flowable
(b)(4)	(b)(4)
Adhesiveness:	Tissue adherent
(b)(4)	(b)(4)
(b)(4)	(b)(4)
(b)(4)	(b)(4)

The following represent the ratio of different components present in the gel:

(b)(4)	(b)(4)

### Principles of Operation

Following the primary surgical procedure, after hemostasis is achieved and immediately prior to wound closure, Oxiplex is injected into the operative site surrounding the nerve root and coating the neural tissue. According to the Surgical Technique, Oxiplex is intended to coat the dura and exiting nerve root along all surfaces (dorsal, ventral, medial and lateral). Additionally, it is intended to be applied into the site of the laminectomy/laminotomy to fill the depth of the surgical site to the level of the ventral surface of the vertebral lamina. The device remains at the site of application for a period of time, and is intended to provide a physical separation (or temporary mechanical barrier) of tissues during the healing process. Oxiplex then clears from the body (through urine), is not metabolized, and does not require a second operation for removal. Pre-clinical animal testing showed that device resorbed by 30 days after implantation.

The original PMA submission discussed how CMC and PEO have each have been individually used to inhibit adhesion formation. Page 000022 of the submission provides: "The capacity of PEO to prevent the fibrin bridge progenitor between tissues, combined with its enhanced adherence to tissues with the addition of CMC, support the use of Oxiplex for use as an inhibitor of adhesion formation

(Schwartz, et al., 2005).” In Amendment 15, the applicant explained that Oxiplex works by reducing pain originating from the epidural space by acting as a physical barrier to shield against pro-inflammatory mediators that may cause sensitization of tissues, such as nerve roots; reduce epidural fibrosis; and reduce deposition of fibrin on the nerve root.

### **Marketing History**

Oxiplex received CE Mark in July 2001 and has been distributed under the brand names Oxiplex®/SP Gel (by DePuy Spine) and MediShield Anti-Adhesion Gel (by Medtronic Sofamor Danek) outside of the U.S. since January 2002. Despite their different names, Oxiplex/SP Gel and MediShield are identical products.

## **CLINICAL DEVELOPMENT OF OXIPLEX/SP GEL**

### **US Pilot Study Summary**

The applicant conducted a pilot safety study involving 35 subjects with herniated discs at four investigational sites between March 2001 to May 2003 to assess the safety of Oxiplex during single-level spinal discectomy and to determine, through assessment of clinical response and evaluation of enhanced magnetic resonance imaging (MRI), if the extent of peridural fibrosis and related symptoms may be reduced with use of Oxiplex. Clinical response was assessed via neurological function and radiculopathy and through self-assessment questionnaires relating to pain and activities of daily living, the Oswestry Disability Index Questionnaire (ODI) and the Lumbar Spine Outcomes Questionnaire (LSOQ) at 30 days, 3, 6 and 12 months. MRI was used to determine the extent of epidural scar formation at 3 months.

### **Indication Studied**

*Reduction of adhesions following lumbar surgery*

### **Intended Use**

*The intended use of the Oxiplex/SP Gel is as an adjunct to surgery during lumbar laminectomy, laminotomy, and discectomy procedures. The device is intended to inhibit the formation of peridural fibrosis and dural adhesions that might otherwise contribute to postoperative radicular pain and/or neurological dysfunction.*

### **Objectives**

The primary objectives of this pilot study were

1. To evaluate the safety of applying Oxiplex during single level spinal discectomy performed to eliminate or reduce symptoms associated with acute or subacute unilateral herniation of a lumbar intervertebral disc in subjects undergoing their first surgeries for such conditions
2. To determine if peridural fibrosis and consequent related symptoms may be lessened by the use of Oxiplex®/SP Gel, evaluated by assessment of clinical response between treated and non-treated subjects and with evaluation of enhanced MRI.

### **Study Design**

The pilot study was a prospective, randomized, single-blinded, clinical trial to evaluate the safety of Oxiplex when used to reduce postoperative peridural fibrosis and related symptoms following surgery for herniated lumbar disc at L4-L5 or L5-S1. Subjects were randomized 2:1 to the investigational or control group intraoperatively. The investigational group received Oxiplex around the dura and nerve roots, while the Control group underwent surgery for herniated disc without any additional treatment. All surgeries were performed using a posterior approach. The study was not powered to demonstrate statistically significant differences between the two groups.

The pilot study enrolled 23 investigational and 12 control subjects. One control subject withdrew prior to 3 month follow-up. All subjects received clinical evaluations at baseline and postoperatively at 1 and 3 months. All subjects were to complete ODI and LSOQ preoperatively, as well as at 1, 3, 6, and 12 months postoperatively. In addition to baseline MRI, all subjects were to receive follow-up evaluations at 3 months post-op for repeat MRI of the spine, with and without contrast. Two blinded MRI readers were employed to assess for the presence and extent of fibrosis/scarring.

### **Endpoints**

The primary endpoints of the clinical investigation evaluated the efficacy of Oxiplex in the reduction of postoperative pain and symptoms and peridural fibrosis on MRI and the safety of applying Oxiplex in lumbar disc surgery. The applicant measured pain reduction, as well as scar score reduction on MRI. The applicant considered a reduction in pain at any of the postoperative evaluations in the Oxiplex group compared to the control group of at least one unit in either the ODI or LSOQ to be clinically significant.

### **Key Inclusion/Exclusion Criteria**

The population studied consisted of adults scheduled to undergo a primary surgical intervention for diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

#### **Key Inclusion Criteria**

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level
- Radiological evidence of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms
- Involvement at the L4-L5 or L5-S1 level

#### **Key Exclusion Criteria**

- Previous spinal surgery at any level
- Treatment with any epidural steroids within four (4) weeks prior to the proposed surgery
- Treatment with any oral steroids within ten (10) days prior to the proposed surgery
- Treatment with aspirin or other non-steroidal anti-inflammatory drugs within seven (7) days prior to the proposed surgery

#### **Intra operative Exclusions:**

Subjects who met any of the following criteria were not eligible for enrollment:

- Dural entry during surgery
- Discovery of intraspinal tumor during surgery
- The need to involve more than one level
- Exploration of contralateral side
- Epidural fat placement
- Surgical determination that an hemostatic agent must remain at the surgery site
- Surgical determination of the need for any other device (that would interfere with interpretation of the study results) to remain at the surgery site

### **Surgical Procedure**

Subjects were randomized to receive surgery plus Oxiplex (Oxiplex group) or to receive surgery only (Control group), with both groups undergoing a posterior approach. The Control group was a standard surgery for herniated disc without any treatment. Patients in the Oxiplex group underwent an additional treatment with the investigational device, which was used to coat the dura and exiting nerve root along both its dorsal and ventral surfaces and applied to the site of the

laminectomy/laminotomy to fill depth of the surgical site to the level of the ventral surface of the vertebral lamina. The gel applied to the operative site was not to exceed 5 mL.

### **Results for the Pilot Study**

The adverse event rates in the Oxiplex and Control groups showed no statistically significant difference although the incidence of some parameters (e.g., back pain, buttock pain, hypoaesthesia and paresthesia) was markedly higher in the Oxiplex group versus the Control group. The results of the statistical analyses on the pilot study showed non-significant p-values when comparing the Oxiplex and Control groups in leg pain, symptoms, activity related pain index, functional disability, weakness in lower extremity, and radiculopathy score. Additionally, the MRI scar scores for the Oxiplex and Control groups at 3 months were comparable. It is important to recognize that this pilot study was not designed or powered to detect statistically significant differences between groups due to the small sample size.

### **US Pivotal Study Summary**

Based on the pilot study results, FDA allowed the applicant to initiate a new pivotal study to study the safety and efficacy of Oxiplex in a larger population.

### **Indications for Use**

The indications studied in the pivotal study, and those proposed in the original PMA, differ from the indications studied during the pilot study because the applicant removed inhibition of peridural fibrosis from the primary endpoint of the pivotal study:

*Oxiplex®/SP Gel is indicated 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.*

### **Study Design**

The applicant conducted a prospective, multi-center, randomized, third-party blinded, parallel group study. All subjects underwent lumbar disc surgery (standard laminectomy, laminotomy, and discectomy) and were randomized 1:1 to receive surgery plus Oxiplex (Oxiplex group) or to receive surgery only (Control group). Randomization occurred intraoperatively, immediately prior to wound closure. Subjects were not considered to be enrolled until they had met all eligibility criteria (preoperative and intraoperative), were randomized, and had received a study group assignment and subject identification number. The applicant stated that subjects and all evaluators of data were masked to the treatment assignment. Follow-up assessments were conducted at 1, 3, and 6 months.

There were 352 subjects (177 Oxiplex and 175 Control subjects) enrolled at 29 US investigational sites between October 2002 and October 2006 in order to obtain at least 334 evaluable subjects (those who completed the 6-month postsurgical follow-up visit). The final number of evaluable subjects was 334, referred to as Completed Cases (CC).

### **Objectives**

The primary objectives of the pivotal study were:

1. To evaluate the efficacy of Oxiplex/SP Gel in the reduction of postoperative pain and symptoms
2. To evaluate the safety of applying Oxiplex/SP Gel in lumbar disc surgery

### **Endpoints**

The *primary safety endpoint* evaluated the frequency and severity of adverse events categorized using the MedDRA coding system.

The *secondary safety endpoints* evaluated changes in laboratory results; physical and neurological exam and vital signs; re-operations at the lumbar level; and the use of concomitant therapies.

The *primary effectiveness endpoint* was the improvement in leg pain from baseline to follow-up visits (1, 3 and 6 months), as measured by the LSOQ. The LSOQ measures leg pain severity on a six-point rating scale for each of the six questions. The composite leg pain severity score ranged from 0 to 100, with higher scores indicating higher overall severity of experienced pain.

The *secondary effectiveness endpoints* were the improvements from baseline through 6 months, as measured by LSOQ, of the following endpoints: 1) back pain 2) leg weakness 3) physical symptoms 4) subject satisfaction 5) disability score and 6) activities of daily living. The order of these secondary endpoints was pre-specified for hierarchical closed testing procedure.

### **Key Inclusion/Exclusion Criteria**

The population studied consisted of adult males and females who were scheduled to undergo a first surgical intervention for a diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

#### **Key Inclusion Criteria**

- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level
- Significant pain and symptoms measurable by the LSOQ
- Radiological evidence (MRI Study or CT/myelogram) of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms
- Compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at the L4-L5 or L5-S1 level
- Subjects entering the Pivotal Study underwent a period of at least two weeks of non-operative treatment without resolution of pain, unless the surgeon decided the subject was experiencing intractable pain, or there was substantial progression of loss of neurological function

#### **Key Exclusion Criteria**

- Previous spinal surgery or chemonucleolysis at the lumbar level
- Treatment with any epidural steroids within 4 weeks prior to the proposed surgery
- Use of steroids perioperatively and/or intraoperatively

#### **Intraoperative Exclusions**

Subjects who met any of the following criteria were not eligible for enrollment:

- Dural entry during surgery
- Discovery of intraspinal tumor during surgery
- The need to involve more than one level
- Exploration of contralateral side
- Epidural fat placement
- Use of steroid solution
- Surgical determination that a hemostatic agent must remain at the surgery site
- Surgical determination of the need for any other device (that would interfere with

interpretation of the study results) to remain at the surgery site

### **Surgical Procedure**

Subjects were randomized to receive surgery plus Oxiplex (Oxiplex group) or to receive surgery only (Control group), with both groups having a posterior approach. The Control group was a standard surgery for herniated disc without any treatment. Patients in the Oxiplex group had additional treatment with the device, which was used to coat the dura and exiting nerve root along both its dorsal and ventral surfaces and applied to the site of the laminectomy/laminotomy to fill depth of the surgical site to the level of the ventral surface of the vertebral lamina. The gel applied to the operative site was not to exceed 3 mL.

### **Statistical Analysis Plan**

The pivotal study was designed to demonstrate superiority of the Oxiplex/SP gel compared to standard surgery alone.

The primary objectives of the pivotal study were to evaluate the safety of applying Oxiplex in surgery for herniated lumbar disc at L4-L5 or L5-S1 and to evaluate the effectiveness of the device in the reduction of postoperative pain and symptoms.

The study enrollment began in August 2002 and the interim analysis was conducted in April 2006. The revised statistical analysis plan was submitted to FDA in December 2006, and the PMA was submitted to FDA in August 2007.

### **Sample Size**

The sample size estimation was based on the mean comparison of two independently normally distributed variables with one interim analysis. Originally, 192 subjects per group were estimated with one interim analysis at 33% of the data. A protocol revision in May 2005 changed the interim analysis to 75% of the data, and the sample size was slightly increased to 394 with the goal of obtaining 334 evaluable subjects. At the end of the study, 352 subjects were actually enrolled and 334 subjects were evaluable at 6 months.

### **Randomization**

One-to-one randomization occurred intra-operatively, immediately prior to wound closure. Subjects were not informed of their group assignment until all data were analyzed. Randomization was stratified by study site and generated in block sizes of two and four.

### **Interim Analysis**

The applicant initially planned an interim analysis when 33% of total patients were completed. The timing of the interim analysis was changed from 33% of the data to 75% in May, 2005, after patient enrollment began (October, 2002). The actual interim analysis was conducted when 79% of the subjects had completed the 6-month LSOQ, with an alpha value of 0.0178 for terminating the study. When the interim analysis had been performed, the Data Safety Monitoring Board (DSMB) informed the applicant that the study did not meet the pre-specified alpha ( $p=0.0178$ ), and, thus, the pivotal study continued. Due to having conducted the interim analysis, a two-sided alpha value of 0.044 was determined to be necessary to achieve statistical significance on the final analysis using a group sequential method (alpha spending function was determined using the Hwang, Shih, and DeCani method with gamma value of -4).

### **Safety Analyses**

The applicant proposed a descriptive presentation and univariate analysis. The applicant planned to assess the frequencies and percentages of subjects with adverse events (treatment emergent, device-

related, serious adverse events, adverse events leading to study discontinuation and those related to surgery or wound site). The frequency of various adverse events was presented by MedDRA system organ class and preferred term relationship to the device and by severity. Differences between the treatment groups for system organ class were determined using Fisher's exact test and/or the Wilcoxon rank sum test. Statistical tests were only to be conducted for those adverse events with an overall incidence greater than 5%.

#### Primary Effectiveness Analyses

The primary effectiveness hypothesis tested was the following:

$$H_0: \mu_t = \mu_c \text{ vs. } H_a: \mu_t \neq \mu_c$$

where  $\mu_t$  is the mean change in LSOQ leg pain from baseline to 1, 3 and 6 months post-surgery in the Oxiplex group and  $\mu_c$  is the mean change from baseline in the control group.

The two-sided test was carried out using a multivariate Generalized Estimating Equations (GEE) model, including treatment, time, and baseline level and baseline by treatment interaction in the model. The required value of z adjusting for the interim analysis was 2.0098, corresponding to a 2-sided alpha level of 0.044.

The applicant planned to screen all clinically relevant baseline factors for inclusion into the multivariate model after performing the interim analysis. The list of possible covariates included, but was not limited to, age, weight, smoking history, surgical time, level of surgery (L4-L5 or L5-S1), surgery type (microdiscectomy or regular), baseline leg pain score, baseline back pain score, baseline lower extremity weakness score, baseline physical symptom score, baseline patient disability score, study site, and medical history variables. The applicant also planned to study covariate interactions with treatment.

#### Secondary Effectiveness Analyses

The applicant proposed a pre-specified closed-testing to control Type I error. With this method, the secondary effectiveness endpoints were to be tested sequentially in the pre-determined order (only after the primary effectiveness endpoint was met), and the first secondary endpoint had to be statistically significant before the next secondary endpoint could be considered. Similar to the primary effectiveness analyses, the treatment was to be considered statistically significant if the treatment effect or the treatment by time interaction was statistically significant at 0.044 level.

#### Study Success

The applicant set the success criteria of the pivotal study as an improvement of 15 points in composite leg pain score from baseline at 6 months on the 100-point LSOQ scale, when measured using longitudinal data analysis.

The FDA advised the applicant that in order for the study to be considered a success there should be a statistical significance, as well as a clinically meaningful difference in the chosen primary endpoint between the two treatment groups, *i.e.* a 20 point or 33% difference between the two groups in the mean LSOQ score reduction from baseline.

#### Results of Pivotal Study

The study was approved for up to 25 investigational sites and up to 394 total subjects. A total of 352 subjects were enrolled (177 Oxiplex and 175 Control) and underwent surgeries in the study.

### Patient Demographics

The study demographics are outlined below.

Table 1. Demographics and Baseline Characteristics

	Oxiplex (n=177)	Control (n=175)
	Mean	Mean
Age	41.8	41.7
Height (cm)	173.0	172.5
Weight (kg)	86.0	83.8
Gender		
Male	87	98
Female	90	77
Race		
Caucasian	152	153
African	9	4
Hispanic	8	11
Asian	2	3
Other	3	2

There were no statistically significant differences between the Oxiplex and Control groups in demographic characteristics at baseline.

### Patient Accounting

The table below identifies patient dispositions at 6 months of the Intent-to-Treat (ITT) population. Thirteen (13) randomized subjects withdrew from the study prior to 6 month follow-up visit, for reasons that include withdrawal of informed consent, protocol violation/noncompliance, death, and loss to follow-up.

Table 2. Patient Dispositions at 6 months

	6 Months	
	Oxiplex	Control
Enrolled (ITT)	177	175
Died	0	1
Withdrawn/Terminated	1	2
Lost to Follow-up	5	4
Modified Complete Cases <sup>1</sup>	171	168
Far beyond visit Window <sup>2</sup>	4	1
“Evaluable Population”	167	167
In-window Population	145	141

<sup>1</sup> At the request of FDA, the applicant included the 5 subjects that had 6-month visits far beyond the visit window in some analyses. This population is called “Modified Complete Cases” in this summary memo.

<sup>2</sup> Five (5) subjects had 6-month visits far beyond the visit window (> 365 days), and were excluded from the “Evaluable Population” by the applicant.

### Safety Results

All enrolled subjects (ITT) were included in the analysis of safety. The Clinical Evaluator (CE) was instructed to base Adverse Event (AE) reviews on medical judgment and to assume that a subject had received the device when assessing the relationship of the device to AEs. The applicant compared the AE rate in the investigational group to the control group. There were no statistically significant differences in the number of subjects having AEs or serious adverse events (SAEs) between the

Oxiplex and Control groups. There were no AEs leading to discontinuation of any subject from the pivotal study or discontinuation of the pivotal study. Five (5) patients in the Oxiplex group had AEs that were possibly or probably related to the device, whereas no patient in the Control group reported any AEs that were possibly or probably related to the device (p=0.061 in two-sided Fisher’s Exact test when combining possible-related and probable-related AEs).

Seven (7) subjects required a re-operation at or before the 3 month time point. Control subjects experienced higher rates of re-operations when compared to the investigational subjects (3.4% vs. 0.6%, respectively). Six (6) re-operations occurred at the same lumbar level as the initial surgery, and one Control subject had a re-operation at a different spinal level than the original surgery (L3-L4 vs. L4-L5).

The Oxiplex and Control groups were comparable with respect to the following variables: hematology, chemistry, urinalysis, abnormal physical examination at 1-month follow-up, abnormal physical examination at 6-month follow-up and postoperative neurology examination. There appeared to be a balance in concomitant therapies received by the Oxiplex and the Control groups.

### Effectiveness Results

#### Primary Effectiveness Endpoint

The applicant conducted a univariate analysis that showed there was no statistically significant difference in the composite leg pain score reduction from baseline to 6 months between the two groups (p=0.59). The simple mean difference of leg pain between the two groups at 6 months was 1.42 on the 100 point LSOQ scale (see Table 3 below), which could be explained by chance alone.

Table 3. Unadjusted Analyses on Leg Pain Improvement for Complete Cases at 1, 3, and 6 months for Modified CC

Visit	Oxiplex Mean Composite Leg Pain Intensity±Std (N <sup>1</sup> )	Control Mean Composite Leg Pain Intensity±Std (N <sup>1</sup> )	Oxiplex Leg Pain Improvement from Baseline Mean±Std (N)	Control Leg Pain Improvement from Baseline Mean±Std (N)	Oxiplex Improvement – Control Improvement = Treatment Effect (95% CI)	Unadjusted P-values for Treatment Effect (T-test <sup>2</sup> )	Unadjusted P-values for Treatment Effect (Wilcoxon Rank Sum Test <sup>3</sup> )
Baseline	67.5±15.2 (177)	67.7±14.1 (174)	N.A.	N.A.	N.A.	0.90 <sup>2</sup>	0.96 <sup>4</sup>
Month 1	18.8±19.8 (165)	18.5±20.8 (160)	48.8±23.3 (165)	48.9±23.9 (160)	-0.10 (-5.3, 5.1)	0.97	0.97
Month 3	15.7±19.0 (168)	15.5±20.3 (162)	51.8±22.9 (168)	51.4±24.9 (162)	0.44 (-4.7, 5.6)	0.87	0.97
Month 6 <sup>5</sup>	15.8±20.1 (171)	17.0±22.0 (168)	52.0±23.7 (171)	50.5±25.3 (168)	1.42 (-3.8, 6.7)	0.59	0.73

<sup>1</sup>Number of non-missing values.

<sup>2</sup>T-test assumes leg pain improvement is normally distributed.

<sup>3</sup>Wilcoxon Rank Sum test does not assume leg pain improvement is normally distributed.

<sup>4</sup>These are the p-values for baseline leg pain scores comparisons.

<sup>5</sup>The population at Month 6 (171 Oxiplex and 168 Controls) corresponds to the “Modified Complete Cases” population in which all subjects with 6-month visit were included, even if the visits were outside the normal visit window.

The applicant’s original primary effectiveness endpoint analyses on the ITT population screened at least 48 different covariates and their interactions with the treatment variable. This is analogous to conducting subgroup analyses in at least 48 different ways. The applicant found a subgroup of patients from the in-window population (with baseline back pain score  $\geq 63$ , 78 subjects for each treatment group) that had a nominally significant treatment effect for the composite leg pain reduction ( $p=0.0123$ , see Table 4 below). However, because at least 96 different subgroups were potentially analyzed, the probability of finding a significant treatment effect in at least one subgroup was quite high. Additionally, stratification of the composite baseline back pain scores into either  $<63$  or  $\geq 63$  to conduct subgroup analyses was not predetermined. The applicant did not provide a scientific justification for this cutoff other than that it was based on the median baseline back pain score of the pivotal study population.

The following table provides details of the subgroup analysis conducted by the applicant for composite leg pain for the in-window population at the 6-month visit.

Table 4. The subgroup analysis of Improvement in Leg Pain from Baseline at 6 Months by Treatment and Baseline Back Pain (in-window population) (Table 6.28 from Original SAR)

Treatment Group	Leg Pain Improvement at 6 Months Mean (SD)	
	For subjects with Baseline Back Pain Score $< 63$	For subjects with Baseline Back Pain Score $\geq 63$
Control	48.27 (20.05) (N=63)	52.47 (26.78) (N=78)
Oxiplex	42.69 (22.77) (N=67)	62.05 (19.91) (N=78)
P-value*	0.1412	0.0123

\*Two-sided t-test with adjustment for unequal variance as necessary, not adjusted for multiple comparisons.

In summary, there was no statistically significant difference or a clinically meaningful difference, *e.g.*, a reduction of 15 points between the two groups, when evaluating the applicant’s primary effectiveness endpoint. The applicant based effectiveness of the device on a subgroup of patients from the in-window population with baseline back pain score  $\geq 63$  who may benefit from Oxiplex; however, these subgroup analyses are considered exploratory and need to be confirmed with additional data.

Secondary Effectiveness Endpoints

The applicant analyzed several secondary effectiveness endpoints in the Complete Cases (CC) population, which included 167 Oxiplex subjects and 167 Control subjects. CDRH conducted a similar analysis on the “Modified Complete Cases” population (171 Oxiplex subjects, 168 Controls), that included all subjects who completed 6-month visits, including out-of-window visits (see Table 5 below for these individual outcome measures). The results are similar to those obtained from the CC population.

Table 5. Mean Differences in Improvement between Control and Oxiplex Groups at 6 Months and Confidence Intervals for Effectiveness Measures (All Subjects Who Completed 6-Month Visit Including Out-of-window Visits<sup>1</sup>)

Measures	Difference Of (Oxiplex - Control)	Control (N)	Oxiplex (N)	(95% Confidence interval) <sup>2</sup>	Statistical significance
Leg Pain	1.42	168	171	(-3.81, 6.66)	No
Back Pain	2.45	168	171	(-3.19, 8.10)	No
Leg Weakness	0.11	168	171	(-0.08, 0.31)	No
Physical Symptoms	3.88	168	171	(-1.20, 8.95)	No
Patient Satisfaction	0.11	168	171	(-0.19, 0.41)	No
Disability Days	1.62	168	171	(-0.28, 3.52)	No
Activities of Daily Living	0.98	156	160	(-0.68, 2.64)	No

<sup>1</sup>This analysis was conducted by FDA, which showed slightly different results from the applicant's analysis.

<sup>2</sup>Positive numbers indicate advantage of Oxiplex group.

In these unadjusted analyses, none of the secondary endpoints achieved statistical significance (all  $p > 0.05$ ), and all of their 95% confidence intervals included 0, indicating no statistically significant differences in means between the two groups.

The applicant's multivariate analyses on the secondary effectiveness endpoints screened at least 48 different covariates and their interactions with the treatment variable; this was analogous to conducting exploratory subgroup analyses.

## SUMMARY REVIEW OF EFFECTIVENESS AND SAFETY

The findings of the applicant's pivotal study showed that the adverse event profile for both study arms appeared to be comparable. In the pivotal study, there were 5 subjects/7 adverse events in the Oxiplex group in which the adverse event was classified as possibly or probably related to the device as compared to 0 cases in the Control group.

With respect to effectiveness, the US pivotal study failed to show a statistically significant and a clinically meaningful difference in overall treatment effect for Oxiplex. The post-hoc subgroup analysis conducted by the sponsor was not prespecified, significantly increasing the possibility that the finding does not represent a true treatment effect. Therefore, the applicant's exploratory subgroup analyses would need to be verified in a new study. Therefore, reasonable assurance of the effectiveness of the device was not established.

## ORTHOPAEDIC AND REHABILITATION DEVICES PANEL (JULY 15, 2008)

Following presentations by the applicant and the FDA, and after questioning the applicant and deliberating, the Panel voted (5-2-0) that the applicant's PMA be found "Not Approvable." Some Panel members generally believed that the device was safe, while others could not answer whether they considered the device to be safe when considering the potential benefit to risk ratio. Panel members believed that the device may be effective in certain subgroups, but not effective in the overall study population for the study's indications. The Panel believed that the results from the statistical analysis, which showed lack of a statistical significance of the primary and secondary effectiveness endpoints, did not show superiority of the device over the control of no treatment. Further, the Panel believed that the applicant had not provided a clear basis of physiologic efficacy

for Oxiplex. Panel members were also uncertain about the correlation between leg pain and back pain.

## **FDA DECISION**

Taking into consideration the Panel's input, a Not Approvable letter was issued to the applicant on September 15, 2008 requesting a new clinical study confirming the applicant's exploratory analyses and explanation of physiologic mechanism of effectiveness.

## **ADDITIONAL REVIEWS**

### **Informal Proposal (October 13, 2008)**

The applicant submitted an informal proposal (via email) to conduct a retrospective review of data from a U.K. study conducted from 2002-2006 to confirm the treatment effect in the subgroup identified by the exploratory analyses in the US pivotal study. Comments were emailed on November 23, 2008 to the applicant summarizing CDRH's concerns with the proposal (i.e., data quality, selection bias, single study site, blinding procedures, patient population). FDA recommended that the applicant contact FDA for further discussion on the proposed retrospective review of data or to submit an IDE submission for a prospectively defined study.

### **P070023 Amendment 15 (July 29, 2009)**

This amendment consisted of a response to the September 15, 2008 Not Approvable letter. The clinical data submitted in this amendment consisted of retrospective data on Oxiplex from a Chinese clinical study and an Italian case series in an attempt to confirm the subgroup findings from the U.S. pivotal study. The applicant reported in this PMA amendment the findings of a subgroup within each of the following two OUS clinical studies. The applicant stated a prospective statistical analysis plan was used to analyze the results of both clinical studies.

#### **Chinese Study**

This study was conducted in China at two sites between 2005 and 2007 on patients who underwent surgical intervention for unilateral herniation of the lumbar disc.

#### **Study Objectives**

The study objectives were to:

1. Evaluate the efficacy of Oxiplex in the reduction of post-operative pain and symptoms
2. Evaluate the safety of applying Oxiplex

#### **Sample Size**

70 subjects were to be enrolled to obtain 60 evaluable subjects (40 in the study treatment arm and 20 in the study control arm) at 2 investigational sites. The first subject was enrolled in October 2005 and the last subject was enrolled in August 2007 with follow-up completed in October 2007. The applicant provided information on a subgroup of 68 patients with back and leg pain, but the total number of patients in the Chinese study was not stated. Additionally, the applicant provided a summary of the study protocol, but the original, dated protocol was not provided.

#### **Key Inclusion/Exclusion Criteria**

The population studied consisted of adult males and females who were scheduled to undergo a first surgical intervention for a diagnosed unilateral herniation of lumbar intervertebral disc material associated with radiculopathy.

Key Inclusion Criteria

- Scheduled to undergo first surgical intervention for diagnosed (unilateral) herniation of lumbar intervertebral disc material associated with radiculopathy;
- Clinical signs and symptoms indicative of lumbar or lumbosacral radiculopathy, affecting one predominant nerve root level;
- Significant pain and symptoms as measurable by the Oswestry Disability Index;
- Radiological evidence (MRI or CT/myelogram) of compression of a nerve root, and/or confirmed existence of an extruded or sequestered disc fragment, at a level compatible with clinical signs and symptoms;
- Involvement at the L4-L5 or L5-S1 level;
- A period of at least two weeks of non-operative treatment without resolution of the pain, unless the surgeon decided the subject was experiencing intractable pain or substantial progression of loss of neurologic function;

Key Exclusion Criteria

Exclusion criteria outside of intraoperative exclusions were not identified.

Intraoperative Exclusion Criteria

The following unanticipated findings or events did not occur intraoperatively:

- Occurrence of a dural tear, multilevel herniation or the need to involve more than one lumbar level or the contralateral side
- Need to perform a spinal fusion or use any other device that was required to remain at the surgical site and would interfere with the interpretation of study results
- Discovery of an intraspinal tumor
- Use of any of the following:
  - Epidural fat graft placement
  - Steroid solutions
  - Hemostatic agents that were required to remain at the surgery site

Patient Randomization/Enrollment

- Randomization into treatment group (surgery plus Oxiplex) or control group (surgery without Oxiplex) on 2:1 basis (treatment: control)
- 3mL syringe was used; volume delivered was not to exceed 3mL, but amount of gel applied was not recorded so that the subject group assignment would not be compromised

Table 6. Baseline demographics, neurology, surgical level (Chinese Study)

		Oxiplex	Control	All
# of completed subjects		45	21	66
Gender	Male/Female (N)	27/18	12/9	39/27
Age - years	Mean (range)	40 (18-74)	39 (25-58)	40 (18-74)
Clinically Significant Neurology	Deep Tendon Reflexes/ Sensory (# of subjects with at least 1 event)	12/24	11/9	23/33**
Surgery Level	L4-L5/L5-S1 (N)	30/14*	8/13	38/27
*1 unknown – not specified				
**Total # of subjects with at least one (1) event in $\geq 1$ category: Oxiplex = 28 subjects;				

Control = 12 subjects

#### Assessments

##### Pre-operative (Baseline)

- Physical Exam
- Review Eligibility Criteria
- Perform quality of life questionnaires (Oswestry Disability Index (ODI) and Visual Analogue Scale (VAS))

##### Intraoperative

- Perform surgery
- Review Intraoperative Eligibility Criteria
- Perform necessary irrigation
- Remove all hemostatic agents
- Remove surgical drains

##### Postoperative

Subjects were evaluated for efficacy at 60 days post-op and for safety at 30 and 60 days post-op using ODI and VAS, wound assessment, neurological physical examination and documentation of adverse events (AEs) and serious adverse events (SAEs).

#### Safety Results

No AEs or SAEs were reported for either groups. No reoperations were noted to have occurred. It did not appear that patients enrolled in the Chinese study had more severe back pain than the general population of patients undergoing operative therapy.

#### Effectiveness Results

The applicant concluded that for the subgroup of patients identified, the device reduces VAS pain scores at 60 day follow-up.

The Chinese study data were pooled with Italian study data for a combined analysis. See “***Statistical Analysis*** and ***Conclusions from OUS Studies***” sections below for discussion of concerns with the pooled analysis.

#### Italian Case Series

This clinical study was reported in a journal publication:

Assietti, R et al. *Use of Carboxymethylcellulose/Polyethylene Oxide Gel in Microdiscectomy with Interlaminectomy: A case series comparison with long-term follow-up*; Spine 3.3(16) 2008 pp. 1762-1765.

This study was conducted in Milan, Italy between 2003 and 2006 on patients who underwent microdiscectomy with interlaminectomy, and consists of a case series comparison. When asked for the original clinical and statistical protocols for the Italian study, the applicant stated that they did not conduct the Italian study and do not have access to the protocol. The study methods outlined from the journal were provided.

#### Study Objective

The study objective was to compare safety, long-term pain, and disability scores with and without use of carboxymethylcellulose/polyethelene oxide (CMC/PEO) gel after microdiscectomy with interlaminectomy.

### Sample Size

The evaluation consisted of a consecutive, case series comparison of 70 patients with lumbar disc herniation undergoing microdiscectomy with interlaminectomy by one surgeon at one site between January and December 2003. Patients were treated at the end of surgery with Oxiplex/SP gel (n=35) or without gel, control (n=35).

### Inclusion Criteria

- Back pain irradiating to the lower extremity
- Demonstration of a positive Laseque sign (pain on straight leg raising)

### Exclusion Criteria

None stated.

### Patient Randomization/Enrollment

- A consecutive group of patients undergoing microdiscectomy with interlaminectomy between January and December 2003 were enrolled
- Randomization was performed by an independent member of the surgical team
- Patients with recurrent herniation were allocated to the CMC/PEO group, and all other patients in the series without recurrent disc herniation were allocated to surgery alone until the two study group numbers balanced, and 70 patients had completed surgery.

Table 7. Baseline demographics, neurology, surgical level (Italian Study)

	CMC/PEO	Control
Gender (f/m)	27/8	30/5
Age yrs (range)	54.8 (58-72)	57.1 (24-73)
Mean (SD) duration of symptoms (wks)	16.9 ( 14.5)	18.3 (14.7)
Type of disc (free fragment / intraforaminal / contained)	20/4/11	5/15/5
Neurology (motor/radicular)	17/18	13/22
Previous discectomy	10	0
Surgery level (L3-4/L4-5/L5-S1)	3/12/20	4/13/18

### Assessments

#### Pre-operative (Baseline)

Oswestry Disability Index (ODI) and Visual Analogue Scale (VAS) leg and back pain scores were taken.

#### Intraoperative

Type of disc (free fragment/intraforaminal/contained) and surgery level ((L3–L4/L4–L5/L5–S1) were recorded for each group.

#### Postoperative

Patients were followed-up at 30 days, 3 and 6 months, 1, 2 and 3 years. ODI and VAS was administered at 1, 2 and 3 years. The applicant states the patients were assessed post-operatively by a surgical team member unaware of initial treatment allocation.

### Safety Results

In the CMC/PEO group, there was one case of delayed wound healing compared to two cases in the Control group. There were two cases of late resolution of sciatica in both groups, but none of these

patients had a residual or recurrent disc herniation, and the symptoms resolved within the first 2 months.

#### Effectiveness Results

Both the CMC/PEO and Control groups demonstrated a reduction in disability measured by reductions in ODI and improved leg pain scores as measured by a reduction in VAS scores compared with pre-surgery at 1, 2, and 3 years. The reduction was significantly greater in the CMC/PEO group than the Control group at 3 years. The small additional reduction in back pain seen with the CMC/PEO group was not significant between the two groups.

This study suggested device use in patients with recurrent herniation undergoing reoperation may be an appropriate candidate population for Oxiplex; however, this study did not have a comparable control reoperation study arm. A comparable control group is needed to understand the benefits associated with device use in reoperation patients.

The Italian study data were pooled with Chinese study data for a combined analysis. See “*Statistical Analysis* and *Conclusions from OUS Studies*” sections below for discussion of concerns with the pooled analysis.

#### ***Statistical Analysis***

The applicant stated a prospective Statistical Analysis Plan was used to evaluate the clinical data presented in the Chinese and Italian studies. Primary effectiveness and safety endpoints were planned for the intent-to-treat (ITT) population with imputed data for missing patients, and supportive analysis of primary endpoints was planned for completed cases (CC) population.

#### Primary Objectives

1. To demonstrate that the patients treated with Oxiplex/SP Gel have a greater reduction in leg pain at the end of the trial than control patients with baseline back pain at or above the median level. The primary effectiveness endpoint is reduction in leg pain from baseline (change from baseline in leg pain = follow-up score visit minus baseline score).
2. To demonstrate that Oxiplex is safe for its intended use in low back surgery.

#### Secondary Objectives

To demonstrate that Oxiplex gel has a greater reduction in back pain at the end of the study than control patients with leg pain accompanied by baseline back pain that is at or above the median level.

The secondary effectiveness endpoint is the reduction in back pain (change from baseline in back pain = follow-up visit score minus baseline score).

#### Primary Safety Variable

The primary safety outcome to be evaluated is the frequency and severity of adverse events, including surgical complications.

#### Pooled Analysis

Data from both studies were pooled, and 66 patients from the Chinese trial (45 Oxiplex, 21 control) and 70 patients in the Italian study (35 each arm) were included in the analysis of the primary endpoint. These patients represent a subgroup of patients within the study population that had baseline back pain that was at or above the median baseline back pain value. The applicant stated the median baseline back pain was used as a cut-off to be consistent with the findings of the US pivotal study subgroup analysis. The median baseline back pain VAS was 5 and 2 for the Chinese and Italian

studies, respectively. Therefore, patients in the Chinese study that had baseline back pain VAS  $\leq 5$  were included in the subgroup analysis, and patients in the Italian study were grouped if they had baseline back pain VAS greater than or equal to  $\leq 2$ . The manner in which the applicant defined this subgroup appeared post-hoc because the severe baseline back pain score was not predefined, but defined after the applicant determined the median baseline back pain score for each study.

Although the applicant provided a basis for pooling across study sites and across studies (*i.e.*, all sites in both studies used protocols that had the same critical elements), there are differences between the two studies (e.g. patient populations, endpoints) that make pooling of the two data sets inappropriate. Additionally, in order to compare the U.S. pivotal study data to the two OUS studies, the applicant converted the LSOQ scores at 6 months from the U.S. pivotal study to scores on the VAS pain scale using regression analysis. The applicant did not demonstrate, however, that transforming one portion of a validated questionnaire to another distinct assessment tool is valid.

### **Conclusions from OUS Studies**

The confirmatory OUS clinical studies provided in Amendment 15 were intended to support the applicant's post-hoc subgroup analysis of the U.S. pivotal trial data suggesting that Oxiplex patients with back pain above the baseline median level of back pain had a statistically and clinically meaningful reduction in leg pain versus control patients. The patients enrolled in the two OUS studies, however, did not appear to have more "severe" back pain than the general population of patients undergoing operative therapy.

Because the OUS studies have different patient populations, including different enrollment criteria and follow-up time points, it is not appropriate to pool the OUS data. The fundamental study designs and analyses conducted on the OUS data were not sufficient to confirm the hypothesis identified by the exploratory subgroup analyses conducted on the U.S. pivotal study data.

A second Not Approvable letter was issued on January 12, 2010 for the following:

- Request for confirmatory study data from a new randomized controlled study that prospectively and consistently defines "severe" baseline back pain, in order to mimic subgroup of patients in pivotal study who may benefit from device
- Issues to be addressed if submitting retrospective data:
  - Providing data from all studies to minimize selection bias
  - Addressing challenges that compromise a prospective approach for evaluating exiting data
  - Providing prospective study protocols, analysis of all data and not just selected subgroups, etc.
  - Verification that device formulations used in additional studies are identical to that of the PMA device
- Lack of justification and identification of time for tissue healing and scar stabilization with the use of Oxiplex
- Outstanding panel questions related to the safety of Oxiplex (*i.e.*, effect of device on intrathecal space and potential interaction with drugs, and effect of device on osteoid activity and potential for re-herniations and foraminal stenosis)
- Request for summary of relevant literature supporting physiological mechanism of action

### **Pre-IDE I100885 (October 11, 2010)**

Several months after the issuance of the second Not Approvable letter, the PMA applicant submitted Pre-IDE I100885 to request feedback on their proposal to conduct a prospective, multicenter, single-arm, unblinded, historically-controlled confirmatory study to confirm the treatment effect of Oxiplex

in the subgroup identified by the exploratory analyses in the pivotal study. The subgroup in the control arm of the U.S. pivotal study would be used as a historical control for this proposed study; the applicant also planned to use a propensity score method to adjust between-group unbalances. CDRH provided feedback to the applicant, and a meeting with the applicant was held on December 6, 2010. During this meeting, the applicant proposed a new and different Bayesian statistical design than what was submitted in Pre-IDE I100885. After the meeting, the applicant held several discussions with CDRH/Division of Biostatistics regarding the appropriate statistical plan for a new confirmatory clinical study.

**P070023/A019 (January 5, 2011)**

The PMA applicant voluntarily withdrew its PMA because the information requested in the Agency's January 12, 2010 Not Approvable letter could not be provided by the extended deadline of January 12, 2011.

**G110085 (April 22, 2011)**

The applicant submitted IDE G110085 to obtain approval to initiate a confirmatory clinical study. The applicant proposed a study of 180 subjects to confirm exploratory subgroup analysis findings, which suggested that in subjects with severe back pain (LSOQ  $\geq 63$ ), Oxiplex may achieve a greater reduction in leg pain compared to the control. A Bayesian adaptive study approach to sample size was proposed. This IDE was disapproved on May 20, 2011 because the applicant did not specify a minimally significant clinical difference; no justification was provided for pooling subjects undergoing laminectomies, laminotomies and discectomies; there were concerns that post-op evaluations after the initial post-op evaluation were to be conducted via phone or email; and there were Informed Consent issues.

**10.75 Request for Supervisory Review (October 14, 2011)**

The PMA applicant requested an internal agency supervisory review by the Director of CDRH of the Not Approvable determination dated January 12, 2010 for P070023 due to scientific and procedural issues. The following five issues were disputed:

- The Agency's required threshold for clinical success was not scientifically justified.
- The Agency's assertion that the applicant's analysis was post-hoc was inaccurate.
- The submitted data provided reasonable assurance of safety and effectiveness.
- Foreign clinical data provided confirmatory evidence of safety and effectiveness and should be accepted in accordance with 21 CFR 814.
- Procedural inconsistencies during and following PMA review that adversely impacted the applicant.
  - The applicant claimed CDRH reverted to an old statistical model creating confusion among panel members.
  - The applicant claimed CDRH erroneously stated applicant's covariate analysis was entirely post-hoc after CDRH directed the addition of (up to 96) covariates.
  - The Panel was not appropriately constituted and included individuals who were unfamiliar with low back pain and would not use Oxiplex.
  - The CDRH clinical reviewer presentation was conducted in a confusing manner and did not adequately cover safety.
  - The CDRH assigned panel "homework" assignment inappropriately focused on adhesions.
  - CDRH inappropriately signaled that the device was "Not Approvable" by limiting post-approval study and labeling discussions.
  - CDRH changed its view from requesting a small confirmatory study to a new large randomized, controlled study.

On April 11, 2012, CDRH and the applicant met to discuss the appeal. On June 4, 2012, Dr. William Maisel, Deputy Director for Science at CDRH, sent an interim response letter, requesting the applicant submit line-item clinical data on all patients enrolled in the two OUS studies in electronic format so that CDRH could conduct its own analysis. On July 20, 2012, the applicant submitted the information requested in the interim response letter. On October 9, 2012, Dr. Maisel responded to the appeal on behalf of the Office of the Center Director and upheld the Not Approvable determination with modifications to the required threshold for clinical success. The following summarizes CDRH's response to the various issues in dispute in the Center-level appeal:

- Post Hoc and Other Panel Procedural “Inconsistencies”: Review of the Panel meeting transcript, administrative record, and appeal information confirmed that the conduct of the Panel meeting, the constitution of the Panel, and the interactions with the Panel were appropriate and in accordance with all relevant statutory and regulatory requirements.
- Acceptance of Foreign Clinical Data: Additional review of the OUS studies yielded the following conclusions:
  - *"Confirmatory Study #1 [referred to as Chinese study throughout summary memo] demonstrated no overall treatment effect but did show a statistically greater improvement in leg pain at 60 days in the Oxiplex group compared to the control group, for the subgroup with baseline back pain  $\geq 5$ . Few patients had back pain  $\geq 6.2$  and there was no evidence of a treatment effect among the patients with the most severe back pain."*
  - *"Confirmatory Study #2 [referred to as Italian case series throughout summary memo] has significant methodological shortcomings that severely limit its interpretation. The lack of randomization and differences in baseline subject characteristics preclude meaningful comparison of the treatment and control groups. Even if one were to overlook the significant study conduct flaws, few study subjects had back pain of comparable severity as defined in the US pivotal study, limiting meaningful interpretation."*
- Reasonable Assurance of Safety & Effectiveness: The information contained in the PMA administrative file and submitted during the appeal process were not sufficient to provide a reasonable assurance of safety and effectiveness for the device for its intended use, and additional clinical data would be necessary to confirm that patients with severe baseline back pain may benefit from treatment with Oxiplex.
- Required Threshold for Clinical Success: CDRH believed a confirmatory study should demonstrate a true, measurable Oxiplex treatment effect. Additionally, CDRH was willing to consider a study design that uses a primary effectiveness endpoint of mean reduction from baseline pain to 6 month post-operative residual pain using a validated pain scale. To show effectiveness, the study should demonstrate a statistically significant result, demonstrating at least a 10% difference in the above endpoint, in favor of Oxiplex, when the mean difference between the groups is divided by the treatment effect in the control group\*. Other primary effectiveness measures may also be acceptable. (\*Assumes at least a 50% reduction in baseline to 6-month residual pain in the control group.)

## **CHANGES TO INDICATIONS FOR USE**

The proposed indications for use was modified several times during the review of the PMA

application and in subsequent interactions. The following describes the history of the revisions made by the applicant to the indications for use:

### **September 2000**

Indications for Use proposed and studied in the U.S. pilot study:

*The intended use of the Oxiplex/SP Gel is as an adjunct to surgery during lumbar laminectomy, laminotomy, and discectomy procedures. The device is intended to inhibit the formation of peridural fibrosis and dural adhesions that might otherwise contribute to postoperative radicular pain and/or neurological dysfunction.*

### **March 2002**

Indications for Use proposed and studied in the U.S. pivotal study:

*Oxiplex/SP Gel is indicated 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.*

### **August 2007**

Indications for Use proposed in the original PMA application:

*Oxiplex/SP Gel 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. (emphasis added)*

### **July 2008**

Indications for Use proposed after the Orthopaedic and Rehabilitation Devices Panel meeting:

*Oxiplex is indicated as a surgical adjuvant during lumbar laminectomy, laminotomy, or discectomy, for use in patients with severe leg and back pain, to improve outcomes by reducing postoperative leg pain, back pain and neurological symptoms. (emphasis added)*

These indications were proposed based on the applicant's exploratory analyses of the U.S. pivotal study data from which the applicant concluded that patients with "severe" baseline back pain (baseline back pain score  $\geq 63$ ) may benefit from the device.

### **July 2009**

Indications for Use proposed in P070023/A015, which was considered a response to the September 15, 2008 Not Approvable decision:

*Oxiplex 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. (emphasis added)*

### **October 2011**

Indications for Use proposed in 10.75 Petition for Supervisory Review:

*Oxiplex is indicated for use as a surgical adjuvant in adult patients with primary leg pain and severe baseline back pain undergoing first surgical intervention (i.e., posterior lumbar laminectomy, laminotomy, or discectomy, open or endoscopic) 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. (emphasis added)*

## **November 2012**

Indications for Use proposed in 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. (emphasis added)*

The indications for use submitted in the October 2011 10.75 Petition for Supervisory Review and November 2012 Petition for Reconsideration are almost identical with the only differences being the placement of the words “open or endoscopic.” The applicant states that the “modifications reflect the population last discussed with FDA in pre-IDE and IDE interactions in late 2010 and early 2011. It was designed to reflect prior feedback from both the Advisory Panel and the FDA.” (pg. 12 of 10.75 Petition)

### **III. RATIONALE FOR 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 Oxiplex. To establish a reasonable assurance that Oxiplex is effective, the applicant 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). The applicant's US pivotal study failed to show a statistically significant and clinically significant difference in the overall treatment effect for Oxiplex. Therefore, the data from the applicant's pivotal study are not adequate to support a reasonable assurance of effectiveness of the device for the Amendment 15 indications. Additionally, 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.

The applicant also concluded from the US pivotal study that patients with “severe” baseline back pain may benefit from Oxiplex; however, this conclusion was based on the applicant's exploratory subgroup analysis of the pivotal study data. Accordingly, 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 the applicant subsequently submitted in its October 14, 2011 request for supervisory review of the not approvable decision and its November 5, 2012 petition for reconsideration.

In response to FDA's assessment that data from the US pivotal study were inadequate to demonstrate a reasonable assurance of effectiveness, the applicant submitted data from two “confirmatory studies” that were conducted outside of the United States (OUS).<sup>2</sup> The applicant provided additional detailed

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<sup>2</sup> Although the applicant acknowledged that other OUS data were reasonably known (e.g., UK data), the applicant has not provided these data to FDA, as required by 21 CFR 814.20(b)(8)(ii). As such, this information was not

information on these two OUS studies at the request of Dr. Maisel during his review of the applicant's request for supervisory review of the not approvable decision, and FDA 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 the applicant stated that 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  $\geq 6.2$ ), for either the 30 day or 60 day endpoint.
  2. Confirmatory Study #2: Although the applicant described 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. 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.

Additional clinical testing is, therefore, 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.

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, the applicant stated at the panel meeting that there are primate data and other ongoing studies that would address these concerns. However, to date, the applicant has 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 the applicant 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)]. The

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available to FDA at the time the decisions were made and is not included as part of the administrative record for this PMA.

applicant has 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). The applicant also has 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).

FDA issued Not Approvable letters to the applicant on September 15, 2008 and January 12, 2010. An October 9, 2012 response to a 10.75 request for supervisory review also upheld the Not Approvable decision.

The applicant petitioned for review of FDA's Not Approvable decision under section 515(d)(4) by filing a petition for reconsideration under 21 CFR 10.33. Pursuant to 21 CFR 814.45(e)(3), FDA issued an order denying approval of P070023 on October 21, 2013.

#### **IV. CONCLUSION**

FDA denied approval of this PMA, pursuant to 21 CFR 814.45(e)(3), upon the filing of a petition for reconsideration by the applicant following FDA's response to the request for supervisory review. Thus, the basis for this denial is the same as the basis for the decision of Not Approvable issued on September 15, 2008 and January 12, 2010, as well as FDA's response to the request for supervisory review issued October 9, 2012. FDA's grounds for its Not Approvable decision are based on the results of the U.S. pivotal study and OUS clinical study data, which do not provide sufficient evidence of effectiveness of Oxiplex in patients with preoperative leg pain and preoperative back pain or in patients with "severe" baseline back pain.

The applicant declined the opportunity to discuss a path forward with FDA after receipt of the appeal response letter, electing instead to pursue a petition for reconsideration under 10.33, filed on November 5, 2012. FDA issued an order of denial for P070023 on October 21, 2013.

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Jismi Johnson, M.S., Lead Reviewer

Christy L. Foreman -S  
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Christy Foreman, M.S., Director, Office of Device Evaluation