

September 2007

MEDICAL DEVICES

FDA's Approval of Four Temporomandibular Joint Implants





Highlights of [GAO-07-996](#), a report to congressional requesters

Why GAO Did This Study

It is estimated that over 10 million people in the United States suffer from jaw joint and muscle disorders. Artificial temporomandibular joint (TMJ) implants have been used to replace the jaw joint in some patients in an effort to decrease pain and increase jaw function. The safety and effectiveness of these implants, like other medical devices, is overseen by the Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS). Two implants used in the 1970s and 1980s that were later removed from the market caused severe side effects for some patients. In 1998, FDA began to require certain TMJ implant manufacturers sponsoring these devices to demonstrate the implants' safety and effectiveness before receiving approval. Since 1998, four TMJ implants from three sponsors were approved.

In response to your request, GAO described (1) the types of concerns raised by FDA and how it addressed these concerns for the implants approved since 1998 and (2) how FDA has monitored sponsors' compliance with conditions of approval. GAO examined documentation related to the four TMJ implants approved by FDA since 1998 and sponsors' annual reports, which FDA uses to monitor compliance with conditions of approval. GAO also interviewed FDA officials, TMJ implant sponsors, and patient advocacy groups.

www.gao.gov/cgi-bin/getrpt?GAO-07-996.

To view the full product, including the scope and methodology, click on the link above. For more information, contact Marcia Crosse at (202) 512-7114 or crossem@gao.gov.

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What GAO Found

FDA officials raised concerns during the approval process that were similar for all four TMJ implants. These concerns generally involved the adequacy of the sponsors' clinical study protocols, patient follow-up, engineering testing, and other matters, such as device labeling. FDA addressed many, but not all, concerns upon approval. Some concerns were addressed by obtaining additional information from sponsors to clarify and supplement data contained in their device applications before approval. Other concerns were addressed when FDA approved the implants but required sponsors to comply with certain conditions of approval, such as continuing clinical studies postmarket and collecting patient data. Because FDA staff, who review the device applications, and FDA management, who approve the devices for marketing, held differing views as to whether the implants' health benefits outweighed its risks, they did not agree on the approval decisions of two of the four TMJ implants. FDA management acknowledged that the concerns raised about the implants were legitimate. However, they ultimately concluded that the benefits provided by these two devices outweighed the concerns and approved both devices to help patients obtain relief from chronic pain.

FDA monitored sponsors' compliance with conditions of approval by evaluating information contained in their annual reports. FDA often required additional actions by the sponsors to resolve questions that were raised through its review of these reports. However, GAO found that not all annual reports were received by FDA. At the time GAO conducted its work, FDA had only received 13 of 18 required reports. One implant sponsor did not submit 5 of 7 required annual reports. FDA has requested these reports and has issued draft guidance on annual report submissions to all medical device sponsors. In addition, when reviewing the available annual reports to determine if sponsors were complying with conditions of approval, many of the submitted reports did not provide FDA with sufficient information to assess compliance. FDA required these TMJ implant sponsors to provide additional information to address this lack of sufficient information. In most instances, once FDA received additional information from the sponsors, the annual reports were considered adequate. However, one sponsor submitted several annual reports for both of its devices that FDA said lacked sufficient information regarding patient follow-up and also underreported problems experienced by patients associated with the devices. FDA notified the sponsor that it must address these concerns, but the sponsor repeatedly provided inadequate responses. This situation ultimately led FDA to inspect the sponsor's records and file an administrative complaint for civil monetary penalties against the sponsor for failure to file certain reports with FDA. On July 6, 2007, an administrative law judge ruled in favor of FDA.

In commenting on a draft of this report, HHS provided clarification on postmarket requirements for approved devices and updated information on the administrative complaint for civil monetary penalties.

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Abbreviations

FDA	Food and Drug Administration
HHS	Department of Health and Human Services
MAUDE	Manufacturer and User Facility Device Experience Database
PMA	premarket approval
TMJ	temporomandibular joint

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United States Government Accountability Office
Washington, DC 20548

September 17, 2007

The Honorable Edward M. Kennedy
Chairman
Committee on Health, Education, Labor, and Pensions
United States Senate

The Honorable Tom Harkin
United States Senate

The Honorable Herb Kohl
United States Senate

The National Institutes of Health report that over 10 million people in the United States suffer from temporomandibular joint (i.e., jaw joint) and muscle disorders. Although most people have relatively mild forms of these disorders, others experience long-term persistent and debilitating pain. Artificial temporomandibular joint (TMJ) implants have been used to replace the jaw joint in an effort to decrease pain and increase jaw function for this latter group.

The Food and Drug Administration (FDA), an agency within the Department of Health and Human Services (HHS), is responsible for overseeing the safety and effectiveness of medical devices, including TMJ implants. Beginning in 1976, medical devices, including TMJ implants, were allowed to enter the market without the submission of safety and effectiveness information to FDA if the devices were determined to be “substantially equivalent” to previously marketed devices.¹ Many patients who received certain TMJ implants—one that was on the market prior to 1976 and one that entered the market in 1983 and was deemed substantially equivalent to a pre-1976 device—faced severe consequences associated with the materials contained in the implants. These included chronic pain, bone degeneration, and implant fragmentation or displacement. In 1991, one device was recalled by FDA, and in 1993, the

¹Medical devices may be deemed substantially equivalent to devices marketed prior to 1976 through the premarket notification process, referred to as the 510(k) process, which does not require the submission of additional information on the safety and effectiveness of the device. Substantial equivalence means, for example, that a device has the same intended use and same technological characteristics as a marketed device.

other was voluntarily discontinued by the manufacturer—who is also known as the sponsor—of the implant.

On December 30, 1998, FDA issued regulations requiring certain TMJ implant sponsors to submit a premarket approval (PMA) application. Applications were required for TMJ implants marketed prior to May 28, 1976, and for such implants deemed substantially equivalent to a device marketed prior to May 28, 1976. The PMA process requires sponsors to demonstrate the safety and effectiveness of their devices before receiving approval. To demonstrate safety and effectiveness of these devices, sponsors conduct clinical studies and perform engineering tests on the implant, such as testing the implant's strength, and include the results in the PMA application submitted for FDA's review. As part of the PMA process, FDA staff evaluate these studies through a review of the implant applications, and FDA management makes decisions regarding approval for marketing the implants. Since the implementation of these requirements, four TMJ implant applications from three sponsors have been submitted for approval. FDA conditionally approved all four devices—meaning the sponsors had to comply with specific conditions established by FDA, following approval. For example, these sponsors were required to conduct postmarket studies, among other conditions. Given your concerns for patients with temporomandibular joint and muscle disorders, you expressed interest in FDA's safety requirements for, and oversight of, TMJ implants.

This report examines (1) the types of concerns raised by FDA and how it addressed concerns raised during the TMJ implant approval process since December 30, 1998, when it began requiring data on implant safety and effectiveness and (2) how FDA has monitored TMJ sponsors' compliance with conditions of approval.

To determine how FDA addressed the concerns raised during the PMA process, we reviewed documentation provided by FDA for each of the four TMJ implants approved since December 30, 1998: (1) TMJ Concepts implant, (2) TMJ Implants, Inc., total joint implant, (3) TMJ Implants, Inc., partial joint implant, and (4) Walter Lorenz implant.² We identified FDA's concerns related to safety and effectiveness and the methods used to

²The TMJ Concepts implant PMA application was approved in July 1999, the TMJ Implants, Inc., total joint implant PMA application was approved in January 2001, the TMJ Implants, Inc., partial joint implant PMA application was approved in February 2001, and the Walter Lorenz implant PMA application was approved in September 2005.

address these concerns through a review of internal documents, such as the approval review package. Among other documents, this package includes results of FDA's reviews of the PMA application, a recommendation regarding approval, and final decisions for each implant. Throughout our review we considered concerns addressed by FDA as those in which the agency identified an issue concerning safety and effectiveness of an implant and dealt with the issue by contacting the sponsor. We also reviewed FDA's correspondence with the TMJ implant sponsors. In addition, to further understand FDA's concerns, we examined summaries of meetings held by FDA's dental products panel—an advisory body of external experts convened to provide advice to the agency—on each of the four PMA applications. An FDA official indicated that although the agency may not have documentation of all concerns raised during the PMA process, the documents we reviewed contained the most complete information possible to address our objectives. Therefore, it is possible that other relevant documents existed that we were unable to review. We grouped concerns raised during the PMA process into broad categories, such as study protocol, patient follow-up, and engineering testing.³ In addition, we further sorted these categories to provide additional explanations on the types of concerns we identified. We also identified actions taken by FDA such as whether FDA approved the device with conditions to address certain concerns. We discussed our determinations of whether and how concerns were addressed with FDA officials to gain their confirmation. However, we did not evaluate the appropriateness of FDA's approval decisions for each of the implants or its assessment of the medical, scientific, or engineering data provided by the sponsors. To better inform our discussion of concerns raised during the PMA process for TMJ implants, we contacted the three TMJ implant sponsors⁴ and several groups representing patients with temporomandibular joint and muscle disorders, including the TMJ Association, the TMJ and Orofacial Pain Society of America, and the Jaw Joints & Allied Musculo-Skeletal Disorders Foundation, Inc.

To determine how FDA has monitored TMJ implant sponsors' compliance with the conditions of approval, we reviewed annual reports, which FDA required from the three TMJ implant sponsors as a condition of approval.

³Study protocol and patient follow-up concerns relate to the clinical studies sponsors must conduct to prove that their devices are safe and effective. Engineering testing refers to testing that is conducted on the TMJ implant to ensure it can withstand daily jaw activity.

⁴One of the three sponsors, TMJ Implants, Inc., declined to speak with us.

Among other things, these annual reports provide the sponsors an opportunity to update FDA on the status of their required conditions of approval. We discussed the status of conditions of approval with FDA officials to obtain their views on sponsors' compliance with these conditions and collected related documentation. In addition, we gathered information related to FDA's overall efforts to collect and review annual reports. With the exception of FDA's review of annual reports, this report focuses on how FDA addressed concerns raised during the PMA process and excludes FDA's postmarket oversight activities.⁵

Through our interviews with FDA officials and our examination of documents provided, we determined that the data we used were sufficiently reliable for purposes of this report. We conducted our review from October 2006 through August 2007 in accordance with generally accepted government auditing standards.

Results in Brief

FDA officials raised similar concerns for all four TMJ implants' PMA applications. We grouped these concerns into four main categories: study protocol, patient follow-up, engineering testing, and other concerns, such as device labeling. For example, FDA found that all the studies supporting the four PMA applications had deficient patient follow-up, which made it difficult to determine outcomes over time, such as improvement in patient symptoms. FDA used two methods to address many, but not all, concerns upon approval. FDA addressed some concerns raised in the approval process by obtaining additional information from sponsors to clarify and supplement data contained in their PMA applications before approval. FDA addressed other concerns by approving the TMJ implants but requiring sponsors to comply with certain conditions of approval. As a condition of approval, FDA required the sponsors to continue their clinical studies postmarket and to collect data on patients for all four implants for at least 3 years. Because FDA staff, who review the device applications, and FDA management, who approve the devices for marketing, held

⁵We included FDA's monitoring of the conditions of approval, through the use of annual reports, in the scope of our work because these conditions relate to concerns raised in the PMA process. We excluded other FDA postapproval issues unrelated to concerns raised by FDA during the approval process. Many of FDA's postapproval activities for medical devices were reviewed recently in an Institute of Medicine report: Marilyn J. Field and Hugh Tilson, *Safe Medical Devices for Children* (Washington, D.C.: The National Academies Press, 2006), <http://www.nap.edu/catalog/11313.html> (downloaded Oct. 16, 2006). In addition, FDA announced plans to improve postmarket programs for medical devices in November 2006.

differing views as to whether an implant's health benefits outweighed its risks, they did not agree on the approval decisions of two of the four TMJ implants, both sponsored by TMJ Implants, Inc. Ultimately, both devices were approved. FDA management acknowledged that the concerns raised about these implants were legitimate; however, they concluded that the need for the devices outweighed these concerns. According to FDA management, they approved the devices primarily because they play an important role in helping patients obtain relief from chronic pain and there did not appear to be a prohibitory risk associated with the devices.

FDA monitored sponsors' compliance with conditions of approval by evaluating information contained in their annual reports and often required additional actions by the sponsors to resolve questions raised through its review of the reports. Although a total of 18 annual reports should have been submitted to FDA at the time we conducted our work, only 13 had been received by the agency. One implant sponsor—TMJ Concepts—did not submit 5 of 7 required annual reports. FDA has since requested these reports and has issued draft guidance to all medical device sponsors, which outlines best practices for submitting annual reports. When reviewing the annual reports from all of the sponsors to determine if conditions of approval were met, we found that 7 of the 13 submitted reports did not provide FDA with sufficient information to assess compliance. To address the lack of sufficient data provided in these 7 annual reports, specifically with regard to patient history and patient follow-up, FDA contacted the sponsors and required them to provide additional information. TMJ Implants, Inc., submitted several annual reports for both of its devices that lacked sufficient information regarding patient follow-up. In addition, FDA said the sponsor also underreported problems experienced by patients—known as adverse events—associated with the devices. FDA issued letters to the sponsor asking it to resolve these concerns, yet the sponsor repeatedly provided inadequate responses. This situation ultimately led FDA to file an administrative complaint for civil monetary penalties against the sponsor, which resulted in a decision from an administrative law judge in favor of FDA on July 6, 2007. A separate decision is expected on the amount of the penalties to be assessed, after which either side may appeal.

In commenting on a draft of this report, HHS provided clarification on the postmarket requirements that apply to approved devices. In addition, it updated information concerning the administrative complaint for civil monetary penalties.

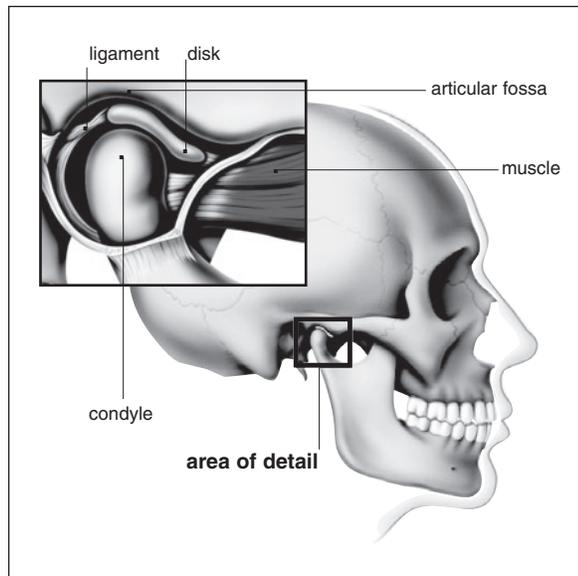
Background

Symptoms of temporomandibular joint and muscle disorders vary but typically include pain of the jaw joint and surrounding muscles. Other symptoms include limited or no movement of the jaw joint, clicking or grating in the jaw joint when opening or closing the mouth, headaches, and shoulder or back pain. According to the National Institutes of Health, most patients' symptoms improve significantly or disappear within weeks or months, while a smaller number of patients have significant long-term symptoms. Trauma to the jaw or jaw joint can contribute to temporomandibular joint and muscle disorders in some instances; however, the causes of most cases of temporomandibular joint and muscle disorders are unknown.

There are a range of treatments available for temporomandibular joint and muscle disorders; some are conservative and temporary while others are irreversible. Experts recommend that the most conservative treatment be used to relieve symptoms before irreversible treatments are used.

Conservative treatments can include taking pain medications, using a splint or bite guard, applying ice packs, or eating soft food. Irreversible treatments include grinding down the teeth to change a person's bite or surgical procedures such as replacing all or a portion of the jaw joint with TMJ implants. Total TMJ implants replace both the upper (articular fossa) and lower (condyle) portions of the jaw joint, whereas partial TMJ implants replace only the upper portion. (See fig. 1.) TMJ implants may improve the function of the jaw joint, however, pain, which is a chief complaint of many who suffer from temporomandibular joint and muscle disorders, is not always relieved.

Figure 1: Illustration of Temporomandibular Joint



Source: Reprinted with permission from the American Association of Oral and Maxillofacial Surgeons.

Medical devices, including TMJ implants, are regulated by FDA, through its Center for Devices and Radiological Health. TMJ implants are classified as Class III devices. Class III devices include those that present a significant risk of illness or injury to the patient.⁶

Prior to the marketing of most Class III devices, FDA must approve a PMA application.⁷ The PMA review requires sufficient and valid scientific evidence to assure that a medical device is safe and effective for its intended use. In making this determination, FDA officials—including FDA

⁶While TMJ implants designed to treat temporomandibular joint and muscle disorders are classified as Class III devices, those that are used for a temporary period, such as to treat cancer patients with bone plate restructuring, are classified as Class II devices. Such devices present less risk than Class III devices. Class II TMJ implants have an intended use of 1 year or less. This review only includes the four Class III TMJ implants approved since December 30, 1998.

⁷Submission of a PMA application is required for Class III devices unless the device was on the market prior to the enactment of the Medical Device Amendments of 1976 (Pub. L. No. 94-295) and FDA has not published a regulation requiring PMA submissions for the device. FDA issued regulations on December 30, 1998, requiring sponsors of all Class III TMJ implants to submit a PMA application for approval.

staff known as the review team⁸ and two levels of FDA management—must consider if there is reasonable assurance that the probable benefits to health of the device outweigh any probable risks. They must also consider whether the device is effective by evaluating data provided by the sponsor for “clinically significant results.”⁹ The review team examines clinical studies of the device involving human subjects, engineering testing performed on the device, and other aspects of the PMA application such as device labeling. It may also obtain input from one of its external advisory boards—in the case of TMJ implants, its dental products panel—for its evaluation and recommendation regarding approval. If the review team has concerns about the PMA application it contacts the sponsor for more information.¹⁰ In some cases the review team may determine that it needs significant additional information to complete the scientific review, in which case it issues a deficiency letter to the device sponsor indicating the information that is needed. The sponsor can respond by submitting an amendment to the original application. The review team can continue to issue deficiency letters and receive amendments from sponsors until it determines that it has the information needed to make a recommendation regarding approval.

Once the PMA review is complete, the review team makes a recommendation regarding approval. This recommendation is subject to review by the two levels of FDA management. Along with the recommendation, information provided by the sponsor and the review team’s assessment of the PMA application, including the individual reviews, such as engineering, clinical, and statistical reviews, and a team leader summary, are forwarded. The review team sends this package to the first level of management. If this level of management agrees with the review team’s recommendation, the review package is sent to the second

⁸Each review team includes an engineer, statistician, and clinician who assess the PMA application.

⁹FDA regulations do not define “clinically significant results.” See 21 C.F.R. § 860.7(e)(1). However, an FDA official stated such results indicate that use of the device would have a positive effect on the disease being treated according to the standards of care for the related field.

¹⁰For example, the review team may resolve application issues through meetings, phone calls, letters, or e-mails with the sponsor.

level for final review.¹¹ The second level of management may concur or override the decision made at the previous management level. Management can make a recommendation regarding approval even if some concerns regarding the PMA remain unaddressed; however, a device can only be approved for marketing if FDA concludes that its benefits outweigh its risks. If a member of the review team or the first level of FDA management disagrees with the final decision, an internal “respectful disagreement memo” can be written indicating the reason for the disagreement.¹²

FDA decisions regarding approval of devices can take four forms: (1) issuing an order approving the application, which allows the sponsor to begin marketing the device; (2) sending the sponsor an “approvable” letter indicating that the sponsor needs to provide more information; (3) issuing a “not approvable” letter informing the sponsor of the application’s weaknesses; or (4) issuing an order denying approval of the application.

Once a device has been approved, the sponsor must comply with postmarket regulations and restrictions that apply to the device. FDA may also impose postmarket approval or condition of approval requirements that apply specifically to the device that is the subject of the PMA. Conditions of approval can include requirements such as the continuation of a clinical study to collect additional data. Some conditions of approval do not expire, such as reporting adverse events and submitting annual reports, including a summary of all changes to the device.¹³ Others are time-limited, such as continuing a clinical study for a specified number of years after the approval of a device.

¹¹If the first level of management disagrees with the review team’s recommendation regarding approval, the manager prepares a different recommendation and includes it in the review package that is forwarded to the second level of management, which makes the final decision regarding approval.

¹²An FDA official told us that it is not uncommon for officials to write respectful disagreement memos when they feel strongly about their divergent views. He explained that this type of disagreement is an indicator of a healthy review process, in which officials are encouraged to think independently and thoroughly examine all aspects of a new device to help ensure its safety and effectiveness.

¹³The regulations require these reports to be filed at intervals specified by FDA, and FDA has required reports annually. See 21 C.F.R. § 814.82 (a)(7) (2006).

FDA Raised Concerns on All Implants and Addressed Many by Obtaining Additional Information and Establishing Conditions of Approval

In their review of the four PMA applications, FDA officials raised concerns that were similar for all four devices. FDA addressed many concerns raised in the approval process by obtaining additional information from sponsors to clarify and supplement data contained in their PMA applications. It also approved all four devices but required sponsors to comply with conditions of approval. However, some concerns were left unaddressed upon approval. In addition, the FDA review team and two levels of FDA management did not agree on the assessment of the safety and effectiveness of the two TMJ Implants, Inc., devices. Ultimately, according to FDA management, the primary justification for approving these devices was that the potential benefit to the patients outweighed the concerns raised and there did not appear to be a prohibitory risk associated with the devices.

FDA Raised Concerns That Generally Applied to All Four TMJ Implants

We grouped the concerns FDA raised during the PMA process into four main categories: study protocol, patient follow-up, engineering testing, and other concerns. These categories and types of concerns are shown in table 1.

Table 1: GAO Categorization of Concerns Raised by FDA during the PMA Process for TMJ Implants

Categories of concerns	Types of concerns included in categories
Study protocol	<ul style="list-style-type: none"> • Inadequate or inaccurate clinical study results, including: <ul style="list-style-type: none"> • Inaccurate measurement of data (e.g., problems with procedures used to measure pain over time)^a • Data not separated appropriately (e.g., results from different implants analyzed together)^a • Questionable conduct by sponsor (e.g., underreporting of adverse events)^a • Incomplete or insufficient data to draw conclusions^a • Lack of long-term data collection^a • Unsupported or poorly defined indications for use^a • Lack of patient history data, including: <ul style="list-style-type: none"> • Patients' clinical diagnosis unknown (e.g., rheumatoid arthritis, cancer)^a • Patients' treatment history unknown (e.g., first implant, multiple implants) • Original sample size of study too small
Patient follow-up^b	<ul style="list-style-type: none"> • Lack of patient follow-up, including: <ul style="list-style-type: none"> • Long-term data lacking due to poor follow-up^a • Number of patients in study too small due to poor follow-up^a
Engineering testing	<ul style="list-style-type: none"> • Inadequate wear testing, including: <ul style="list-style-type: none"> • Analysis of wear debris from implant lacking^a • No examination for wear of implants removed from patients^a • No analysis of wear on natural condyle^{a,c} • Inadequate fatigue testing^{a,d} • Other engineering testing inadequate^a
Other	<ul style="list-style-type: none"> • Inadequate device labeling^a • Unaddressed microbiology,^e packaging, and shelf-life issues • Incomplete sponsor manufacturing inspections

Source: GAO analysis of FDA documents.

Notes: This table applies to the four TMJ implants approved since December 30, 1998.

^aThese concerns were also raised by the dental products panel in its review of the PMA applications for the four implants.

^bPatient follow-up refers to the number of patients who remain in a study over time.

^cThe TMJ Concepts, TMJ Implants, Inc., total implant, and Walter Lorenz implants replace both the articular fossa (the upper portion of the temporomandibular joint) and the condyle (the lower portion). The TMJ Implants, Inc., partial implant only replaces the articular fossa, therefore there were concerns related to its effects on a patient's natural condyle.

^dFatigue testing refers to the amount of weight an implant can bear without breaking. Tests are conducted to ensure that the implant can withstand the weight that a functioning jaw joint would encounter during activities such as talking and chewing.

^eMicrobiology issues relate to the sponsors' processes to ensure the devices are sterile when shipped to the device user.

From FDA's review of the PMA applications, we observed similar concerns across most PMA applications. For example:

- All four PMA applications had incomplete or insufficient data to draw conclusions from the clinical studies. For example, FDA officials were concerned that because the Walter Lorenz clinical study was primarily conducted at one site, the physician at this site might have more expertise in implanting the device than a typical physician, potentially biasing the results. Officials were uncertain if equally favorable results would be obtained at other sites when the implant procedure was performed by less-experienced physicians.
- All four PMA applications had deficient patient follow-up information, which prevented a satisfactory evaluation of the study results, such as improvement in patient symptoms and survivability of the implant.¹⁴
- In three of the four PMA applications, concerns were raised about the lack of information specifying the clinical diagnosis of the patients included in their clinical studies. This made it difficult for the review team to interpret the types of clinical conditions for which the devices are appropriate.
- In three of the four PMA applications, concerns existed regarding inaccurate measurement of data. For example, neither TMJ Concepts's nor TMJ Implants, Inc.'s, total implant clinical data followed the same cohort of patients over time. This made it difficult for the review team to determine whether the device produced improvements in patients. The clinical data for TMJ Implants, Inc.'s, partial implant were compromised because medications used by patients were not documented in the study. Any use of medications could have affected patient outcomes.
- In three of the four PMA applications, the review team indicated that additional implant wear and fatigue testing needed to be conducted. For example, the team wanted TMJ Implants, Inc., (total implant) to conduct wear debris analysis. This analysis could help determine if material wears off the implant over time, which could be absorbed into the patient's body.

¹⁴Survivability of the implant refers to the implant's ability to function in the jaw as originally intended over time.

FDA Obtained Additional Information from Sponsors and Required Conditions of Approval to Address Most, but Not All, Concerns

FDA addressed the concerns it raised in its review of the PMA applications in two ways: (1) by communicating with sponsors and collecting additional information from them and (2) by approving the devices with conditions. FDA addressed many of its concerns by clarifying and collecting information for sponsors' PMA applications, before approving the devices. For example, FDA officials met with representatives of TMJ Concepts and TMJ Implants, Inc., (partial implant) to discuss concerns, such as unsupported indications for use of the device and inconsistent patient follow-up in the clinical studies. In addition, in many instances throughout the review process, FDA officials wrote the sponsors—highlighting problems with the applications—and reviewed their written responses. For example, FDA sent e-mails to Walter Lorenz regarding concerns related to the microbiology, packaging, and shelf life of its device. Walter Lorenz replied to FDA's questions and requests for information and these concerns were addressed. Correspondence between FDA officials and sponsors often continued for at least 3 months and in most cases longer until concerns were addressed.

The second manner in which FDA addressed concerns was by approving the four TMJ implants with certain conditions. A condition of approval common to all four TMJ implants included the requirement that a postmarket study be conducted, which would collect patient data for at least 3 years. This condition of approval addressed FDA's concerns regarding study protocol and patient follow-up. Other conditions of approval addressed concerns related to a lack of patient history data and inadequate wear testing, among others. TMJ Concepts and TMJ Implants, Inc., (total implant) were required to include patient history data in their postmarket studies. Further, TMJ Concepts and TMJ Implants, Inc., (partial implant) were required to conduct wear analysis in order to address concerns related to inadequate wear testing.

While FDA addressed the majority of concerns for each implant, we identified some concerns that remained unaddressed—concerns that were not offset or countered by a condition of approval or by FDA correspondence with the sponsor—upon approval. FDA officials examined these unaddressed concerns during the PMA process. However, they determined that the probable benefits of the devices outweighed the probable risks and therefore approved them. The unaddressed concerns for the devices were as follows and are expanded upon in appendix I:

- *TMJ Concepts*: The unaddressed concerns related to inadequate and inaccurate study results. For example, FDA officials indicated that data for

implants on the right and left sides of the jaw should have been analyzed separately, but the data collected did not allow for this type of analysis.

- *TMJ Implants, Inc. (total implant)*: The unaddressed concerns related to the category of other concerns—unaddressed microbiology, packaging, and shelf-life issues. For example, there was a concern regarding the procedures used for implants that will be shipped multiple times, which could occur if a physician shipped an unused implant back to the sponsor.
- *TMJ Implants, Inc. (partial implant)*: The majority of the unaddressed concerns related to inadequate and inaccurate study results and lack of patient history data. For example, there were concerns that the indications for use the sponsor cited in the device labeling were not supported by the clinical study. In addition, information about patients' treatment history was not included in the study, so it was unknown whether patients tried more conservative treatments before receiving the device. The remaining unaddressed concerns related to other topics—unaddressed microbiology, packaging, and shelf-life issues and outstanding manufacturing inspection matters.
- *Walter Lorenz*: The unaddressed concern related to lack of patient history data, specifically that the sponsor generalized the clinical study results to all patients, even though patients in the study had varying clinical histories.

Concerns Raised about Two Implants Resulted in Differing Opinions among FDA Officials Regarding Approval

Although FDA's review team and FDA management agreed that the TMJ Concepts and Walter Lorenz implants should be approved with conditions, there was disagreement among the review team and the two levels of management related to the approval of both TMJ Implants, Inc., devices. The review team recommended that the TMJ Implants, Inc., (total implant) application be considered not approvable. The team had concerns because it felt that the enrollment in the sponsor's clinical study was too small to draw significant conclusions related to the safety and effectiveness of the device. In addition, the review team believed the indications for use of the device were unsupported. However, the first level of FDA management recommended that the device be approved because it has a role in the treatment of TMJ and muscle disorders. The second level of management agreed with this recommendation. In its approval decision, FDA management acknowledged that there were concerns about the quality and quantity of clinical data provided by the sponsor. However, it stated that either good engineering data or good clinical data was acceptable to approve a device—not necessarily both—and that it deemed the

engineering data for the TMJ Implants, Inc., total implant to be satisfactory. Further, FDA management indicated that the clinical data were not expected to be of high quality because the sponsor was a small manufacturer, the data available at the time of approval did not indicate an extraordinary problem with the implanted devices, and the data provided appeared consistent and favorable. The total implant was approved with conditions to address the FDA review team's concerns mentioned above.

There was also conflict regarding the decision to approve the TMJ Implants, Inc., (partial implant) application. Although the second level of management ultimately approved the device for marketing with conditions, both the FDA review team and first level of management found that there was insufficient data to assure that the device was safe and effective. The review team recommended that the device be considered not approvable. The first level of management agreed with this recommendation for the following reasons:

- The data were limited due to lack of patient follow-up. For example, the group of patients with 2-year and 3-year follow-up data in the sponsor's clinical study was too small to draw significant conclusions about the device. Of approximately 100 patients with implants, only 29 completed the 24-month follow-up. Only 11 patients completed the intended 36-month follow-up.
- Outstanding concerns existed related to (1) questionable conduct by the sponsor in classifying and reporting adverse events, (2) lack of engineering testing to determine the long-term effect of the partial TMJ implant on the natural condyle, (3) unsupported indications for use of the device, and (4) lack of data on patients' clinical and treatment history.

While the second level of management recognized and agreed with the scientific concerns that had been raised, the sponsor was sent an approvable letter requiring minor application changes, such as revised device labeling, and the device was eventually approved. An internal memo outlining the second level of management's approval decision stated that there was a compelling argument in favor of approving the device. It argued that there appeared to be a small group of patients, although poorly defined, for whom the device seemed to provide an option for relief of chronic pain. In addition, it noted that there did not appear to be a prohibitory risk associated with the device in patients who are appropriately educated about all treatment alternatives, their disorder, and the device, and this information is provided in the implant's labeling. However, the approval memo also stated that the decision to approve the

partial implant did not imply that the previous concerns raised by the review team and first level of management related to the inadequacy of the data were reversed. Of these concerns raised, those related to engineering testing on the device's effect on the natural condyle were addressed through conditions of approval; the others remained unaddressed.

Upon the approval of the partial implant, two individuals—a member of the review team and an official from the first level of FDA management—wrote “respectful disagreement memos.” Their memos indicated that they did not agree with the second level of management’s decision to approve the TMJ implants, Inc., (partial implant) application for marketing. These memos outlined concerns raised during the PMA process related to the safety and effectiveness of the device. The concerns highlighted in these memos were that (1) lack of patient follow-up in the clinical study potentially biased the results, and consequently, the sponsor’s claim that the implant resulted in decreased patient pain was unsupported, (2) the clinical study protocol lacked scientific rigor, and (3) outstanding questions remained related to the indications for using the device. In addition, a member of the review team told us that the conditions of approval did not mitigate the concerns she highlighted in her respectful disagreement memo.

FDA Monitored Compliance through Review of the Sponsors’ Annual Reports It Received and Required Some Sponsors to Take Additional Action

In order to evaluate how the sponsors complied with the conditions of approval, FDA received and reviewed the majority of the required annual reports from TMJ implant sponsors. However, the review team had not received most of the required annual reports from one sponsor. Of the annual reports the review team evaluated, some of them were incomplete and FDA required sponsors to take additional actions to ensure compliance with conditions of approval. In addition, the FDA review team had concerns about one sponsor’s—TMJ Implants, Inc.—annual reports. FDA found that these reports lacked sufficient information that prevented them from monitoring safety and effectiveness. This eventually led FDA to investigate the sponsor, resulting in the subsequent filing of an administrative complaint for civil monetary penalties for the company’s failure to file certain adverse event reports with FDA.

FDA Reviewed the Annual Reports It Received, but Some Were Missing

FDA received and reviewed all required annual reports for TMJ Implants, Inc., total and partial implants between 2002 and 2006 and the Walter Lorenz implant in 2006. However, the review team was missing five of seven required annual reports between 2000 and 2006 from TMJ Concepts. It was not until we requested to review these reports that FDA contacted

the sponsor to obtain the missing information. In addition, FDA officials told us that they are developing an improved postmarket surveillance effort to assist sponsors with annual report submission. As part of this effort, FDA recently issued draft guidance on October 26, 2006, which outlines FDA's recommendations for submitting annual reports.¹⁵

Though many annual reports were missing from TMJ Concepts, FDA was able to review the two annual reports submitted by the sponsor in 2000 and 2004. For both reports, TMJ Concepts included information related to a number of conditions of approval, such as providing data on its postmarket study and including a patient quality of life question in that study. In 2000, the sponsor did not comply with the condition of approval to separate data by patients' clinical histories, but did complete this in its 2004 annual report. Therefore, in 2004, TMJ Concepts addressed all conditions of approval except one—submitting annual reports each year. Although all conditions of approval were not met and FDA was not able to review 5 years of annual reports, FDA found that the 2000 and 2004 annual reports provided adequate data and no additional information was required of the sponsor for those two reports.

FDA Required Some Sponsors to Take Additional Actions to Comply with Their Conditions of Approval

FDA evaluated information contained in the 13 annual reports it received and found that 7 reports—6 from TMJ Implants, Inc., (3 for the total joint implant and 3 for the partial joint implant) and 1 from Walter Lorenz—did not provide sufficient information to assess their compliance with conditions of approval.¹⁶ For 1 of the 7 annual reports, FDA directed TMJ Implants, Inc., to submit new information about changes to the approved labeling and to the manufacturing processes for its total implant. FDA sent deficiency letters to the sponsors regarding the other 6 annual reports. These deficiency letters required the sponsors to address questions regarding the lack of certain data that relate to the safety and effectiveness of the devices, including patient history, patient follow-up, and adverse events. For example, in its 2006 annual report, Walter Lorenz was required

¹⁵The draft guidance, which was available for public comment for 90 days after issuance, advises sponsors on how to best organize data and present the required information and what to expect from FDA in response to its annual report submission. This includes a new response format to standardize the review process and indicates that annual reports be reviewed by FDA within 90 days of receipt.

¹⁶FDA received a total of 13 annual reports from the four TMJ implant sponsors: 2 annual reports from TMJ Concepts, 5 annual reports from TMJ Implants, Inc., for the total implant, 5 annual reports from TMJ Implants, Inc., for the partial implant, and 1 from Walter Lorenz.

to submit data on its postmarket clinical study. During the review of these data, the FDA review team identified concerns about data that were included in the report and sent a deficiency letter to the sponsor to resolve this issue. FDA officials discussed the deficiency letter with the sponsor and are waiting for a response.

FDA took further steps to obtain compliance from TMJ Implants, Inc., which had not responded adequately to FDA's 2002 deficiency letter requesting additional information, following receipt of the sponsor's annual reports for its total and partial TMJ implants.¹⁷ Specifically, in 2002 FDA indicated that TMJ Implants, Inc. had not followed up with the required number of patients during its postmarket study. Also, the sponsor was not submitting adverse events, which it described in its annual reports, to FDA's Manufacturer and User Facility Device Experience Database (MAUDE).¹⁸ The sponsor reported that the reason for the implant removals was not specifically due to the failure of the implant and therefore concluded that they did not need to be reported as adverse events. However, after reviewing the 2003 annual reports where there was still a lack of adverse event reporting, FDA issued a deficiency letter. This letter informed the sponsor that all removed implants should be reported to the MAUDE system. In addition, supplemental data were required to be submitted for the conditions of approval related to patient follow-up and adverse event reporting. After FDA's review of the sponsor's 2004 annual reports, the outstanding concerns from the 2002 and 2003 reports remained. For example, issues regarding lack of patient follow-up were unresolved. At the time of the 2004 annual reports, the sponsor submitted data for 75 out of a total of 183 patients for whom data should have been provided. The sponsor maintained that the events related to the removed devices were not caused by device failure or function and concluded that they did not require reporting to FDA. Subsequently, FDA took action on the 2004 annual reports by sending another deficiency letter to the

¹⁷TMJ Implants, Inc., submitted two annual reports each year after approval; one for the total implant and one for the partial implant.

¹⁸Manufacturers are required to submit reports to FDA, which are included in its MAUDE database, whenever they receive information that reasonably suggests that one of their marketed devices (1) may have caused or contributed to a death or serious injury, or (2) has malfunctioned and that a recurrence would be likely to cause or contribute to a death or serious injury. Medical device user facilities and distributors also have responsibilities to report certain adverse events associated with medical devices or to maintain records of such events. In addition to these reports, FDA's MAUDE system includes reports that are voluntarily submitted by manufacturers, clinicians, and patients.

sponsor. In addition, FDA required that the sponsor submit a complete account of all patients to clarify its analysis of patients who were lost to follow-up.

According to FDA officials, the sponsor's response to these deficiency letters did not resolve the outstanding concerns. As a result, the review team raised the concerns with FDA's Office of Compliance and the sponsor was inspected from July 29 through August 11, 2003. During its inspection, FDA found that the sponsor's devices may have malfunctioned or caused or contributed to serious injuries. The inspection results also showed these adverse events had not been reported by the sponsor as required. In response to these findings, FDA issued a warning letter¹⁹ on February 24, 2004, requiring the sponsor to submit written medical device reports for specific adverse events detailed in the letter within 15 working days of receipt.²⁰ When the sponsor did not adequately respond to the warning letter, FDA filed an administrative complaint on July 14, 2005, for civil monetary penalties, which resulted in a decision from an administrative law judge in favor of FDA on July 6, 2007. A separate decision is expected on the amount of the penalties to be assessed, after which either side may appeal. The FDA's Office of Regulatory Affairs instructed the review team not to pursue any deficiencies found in the sponsor's annual reports until the matter is resolved. Therefore, the review team has reviewed TMJ Implants, Inc.'s, 2005 and 2006 annual reports, but decisions on the sponsor's compliance with the conditions of approval are pending.

¹⁹FDA may issue a warning letter to a sponsor if it believes that one or more of its products or practices violates the Federal Food, Drug, and Cosmetic Act, its implementing regulations, or other federal statutes. It is one of the principal methods used by FDA to achieve voluntary compliance with the applicable laws and regulations.

²⁰TMJ Implants, Inc., did not submit adverse event reports to the MAUDE database within 15 days of receiving the warning letter from FDA. However, from June 24, 2004, through March 27, 2007, 52 adverse events related to TMJ Implants, Inc., devices have been reported into the MAUDE database. Of those, 17 were reported by TMJ Implants, Inc., and all were determined by the sponsor not to be related to the device itself but to surgical complications, the surgeon, or other factors beyond the sponsor's control.

Agency Comments

In commenting on a draft of this report, HHS provided clarification on the postmarket requirements that apply to approved devices and updated information concerning the administrative complaint for civil monetary penalties. We revised our report to reflect these comments. It also provided technical comments, which we incorporated, as appropriate. HHS's comments appear in appendix II.

As arranged with your offices, unless you publicly announce the contents of this report earlier, we plan no further distribution of it until 30 days after its issue date. At that time we will send copies of this report to the Secretary of HHS, the Commissioner of the FDA, relevant congressional committees, and other interested parties. We will also make copies available to others upon request. In addition, this report will be available at no charge on GAO's Web site at <http://www.gao.gov>.

If you or your staffs have any questions concerning this report, please contact me at (202) 512-7114 or crossem@gao.gov. Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. GAO staff who made major contributions to this report are listed in appendix III.



Marcia Crosse
Director, Health Care

Appendix I: Concerns Left Unaddressed upon FDA Approval of TMJ Implants

While the Food and Drug Administration (FDA) addressed most concerns for each of the four temporomandibular joint (TMJ) implants we reviewed, we identified a number of concerns that were left unaddressed—concerns that were not offset or countered by a condition of approval or by FDA correspondence with the sponsor—upon approval. These unaddressed concerns fell into two of the four categories of concerns we identified previously: study protocol and other concerns. Table 2 lists the unaddressed concerns using the categories we established in table 1.

Table 2: GAO Categorization of Concerns Left Unaddressed by FDA during the Premarket Approval Process for TMJ Implants

Concerns left unaddressed by FDA, sorted by sponsor	Categories of concerns ^a	Types of concerns included in categories ^b
TMJ Concepts		
Data on the effectiveness and survivability of the implant over time are not reliable because of flawed analyses.	Study protocol	Inadequate or inaccurate clinical study results
Data on right and left side of the prostheses need to be analyzed separately; however, the sponsor did not provide data to allow for this analysis.	Study protocol	Inadequate or inaccurate clinical study results
TMJ Implants, Inc. (total implant)		
The data that demonstrate the performance of the implant will not diminish as a result of shipping and distribution are limited and questionable. In addition, there are specific concerns regarding the procedures that will be used for implants that will be shipped multiple times.	Other concerns	Unaddressed microbiology, packaging, and shelf-life issues
More information is needed related to shelf life and packaging of the implant.	Other concerns	Unaddressed microbiology, packaging, and shelf-life issues
TMJ Implants, Inc. (partial implant)		
Data that indicate the performance of the implant will not diminish as a result of manufacturing processes must be submitted.	Other concerns	Incomplete sponsor manufacturing inspections
The sponsor has not yet submitted data related to outstanding microbiology, packaging, and shelf-life issues for its total implant, which it must do before approval of the partial implant.	Other concerns	Unaddressed microbiology, packaging, and shelf-life issues
Clarification and definition of patient inclusion criteria for the clinical study is needed to understand the clinical conditions of patients who received the implant.	Study protocol	Lack of patient history data
The sponsor has not provided a summary of preoperative conditions of patients enrolled in the study.	Study protocol	Lack of patient history data

**Appendix I: Concerns Left Unaddressed upon
FDA Approval of TMJ Implants**

Concerns left unaddressed by FDA, sorted by sponsor	Categories of concerns^a	Types of concerns included in categories^b
The data do not indicate if patients enrolled in the clinical study have confounding conditions, which could affect results.	Study protocol	Lack of patient history data
The sponsor did not provide information on patients' past history, such as treatment history, to substantiate the use of an implant.	Study protocol	Lack of patient history data
The sponsor did not provide specific information about the nature of other treatments used with patients in the study.	Study protocol	Lack of patient history data
The use of broad diagnostic terms, such as internal derangement—displacement of the jaw joint—makes it impossible to adequately identify patients who are candidates for this surgical treatment.	Study protocol	Inadequate or inaccurate clinical study results
The sponsor needs to provide more clearly defined indications and support for these indications.	Study protocol	Inadequate or inaccurate clinical study results
The sponsor has not provided data on the adverse events associated with the device.	Study protocol	Inadequate or inaccurate clinical study results
Walter Lorenz		
The sponsor generalizes data for all study subjects when they have different clinical history indicators.	Study protocol	Lack of patient history data

Source: GAO analysis of FDA documents.

Notes: This table applies to the four TMJ implants approved since December 30, 1998.

^aWe categorized concerns raised during the PMA approval process into four categories: study protocol, patient follow-up, engineering testing, and other concerns.

^bThis column provides detail on the type of concern within the category to which the unaddressed concern relates. See table 1 for the four categories and the types of concerns we placed within these categories.

Appendix II: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Assistant Secretary
for Legislation

Washington, D.C. 20201

JUL 27 2007

Marcia Crosse
Director, Health Care
U.S. Government Accountability Office
Washington, DC 20548

Dear Ms. Crosse:

Enclosed are the Department's comments on the U.S. Government Office Accountability Office's (GAO) draft report entitled: Medical Devices: FDA's Approval of Four Temporomandibular Joint Implants (GAO 07-996).

The Department appreciates the opportunity to review and comment on this report before its publication.

Sincerely,


for Vincent J. Ventimiglia
Assistant Secretary for Legislation

GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON THE U.S. GOVERNMENT OFFICE ACCOUNTABILITY OFFICE'S (GAO) DRAFT REPORT ENTITLED: MEDICAL DEVICES: FDA'S APPROVAL OF FOUR TEMPOROMANDIBULAR JOINT IMPLANTS (GAO 07-996)

1. Replace the last two sentences of the summary cover page with the following:

This situation ultimately led FDA to inspect the sponsor's records and file an administrative complaint for civil monetary penalties against the sponsor for failure to file certain reports with FDA. On July 6, 2007, the Administrative Law Judge ruled in favor of FDA.

2. Replace the last paragraph on page 9 with the following:

Once a device has been approved, the sponsor must comply with postmarket regulations and restrictions that apply to the device. Postmarket regulatory requirements that apply to devices include adverse event reporting and compliance with current Good Manufacturing Practices. Devices subject to premarket approval must also comply with annual report requirements, which include the requirement to report a summary of all changes to the device. FDA may also impose requirements in the Premarket Approval order; such requirements, known as postmarket approval or condition of approval requirements, apply specifically to the device that is the subject of the PMA. Conditions of approval can include requirements such as the continuation of a clinical study to collect additional data. Some conditions of approval do not expire, such as the conditions of reporting adverse events and submitting annual reports, while others are time limited, such as continuing a clinical study for a specified number of years after the approval of a device.

3. On page 20, 6 lines from the bottom, replace "This matter has not yet ... issued shortly" with the following:

, which resulted in a decision from the Administrative Law Judge in favor of FDA on July 6, 2007. TMJ Implants has thirty days in which the company may appeal this ruling.

Appendix III: GAO Contact and Staff Acknowledgments

GAO Contact

Marcia Crosse, (202) 512-7114 or crossem@gao.gov

Acknowledgments

In addition to the contact named above, Geraldine Redican-Bigott, Assistant Director; Deirdre Brown; Cathy Hamann; Julian Klazkin; Michaela M. Monaghan; and Sari B. Shuman made key contributions to this report.

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