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## Inspections, Compliance, Enforcement, and Criminal Investigations

### Anulex Technologies, Inc. 2/11/11



Department of Health and Human Services

Public Health Service  
Food and Drug Administration  
10903 New Hampshire Ave.  
Silver Spring, MD 20993-0002

#### WARNING LETTER

#### VIA UPS EXPRESS

FEB 11 2011

P. Richard Lunsford  
President and CEO  
Anulex Technologies, Inc.  
5600 Rowland Road, Suite 280  
Minnetonka, MN 55343

Dear Mr. Lunsford:

This Warning Letter is to inform you of objectionable conditions observed during the Food and Drug Administration (FDA) inspection conducted at Anulex Technologies, Inc. (Anulex), from August 23, 2010, to September 22, 2010, by an investigator from the FDA Minneapolis District Office. The purpose of this inspection was to determine whether activities as sponsor of the clinical study "Randomized Study of Anular Repair with the Xclose™ Tissue Repair System" complied with applicable federal regulations.

The Xclose™ Tissue Repair System (Xclose) is a device as that term is defined in section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h) because it is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or is intended to affect the structure of function of the body. FDA cleared Xclose under Premarket Notification Submission (510(k)) K062307 for the intended use of soft tissue approximation for procedures such as general and orthopedic surgery. This letter also requests prompt corrective action to address the violations cited and discusses your written response, dated October 13, 2010, to the noted violations.

The inspection was conducted under a program designed to ensure that data and information contained in requests for Investigational Device Exemptions (IDE), Premarket Approval (PMA) applications, and 510(k)s are scientifically valid and accurate. Another objective of the program is to ensure that human subjects are protected from undue hazard or risk during the course of scientific investigations.

Our review of the inspection report prepared by the district office revealed serious violations of Title 21, Code of Federal Regulations (21 CFR) Part 812 Investigational Device Exemptions, and Section 520(g) (21 U.S.C. 360j(g)) of the Act. At the close of the inspection, the FDA investigator presented an inspectional observations Form FDA 483 for your review and discussed the observations listed on the form with you. The deviations noted

on the Form FDA 483, your written response, and our subsequent review of the inspection report are discussed below:

**Failure to submit an application to the FDA and obtain approval prior to allowing subjects to participate in an investigation. [21 CFR 812.20(a)(1) and (a)(2), 21 CFR 812.40, and 21 CFR 812.42]**

A sponsor is required to submit an IDE application to the FDA if the sponsor intends to use a significant risk device in a clinical investigation. In addition, a sponsor must not begin an investigation for which FDA's approval is required until FDA has approved the application. You failed to adhere to the above stated regulations. An example of your failure includes, but is not limited to, the following:

You failed to submit an IDE application to the FDA and ensure that an FDA-approved IDE was obtained before allowing subjects to participate in the "Randomized Study of Anular Repair with the Xclose™ Tissue Repair System." Specifically, you permitted the Xclose device, a significant risk device as defined in 21 CFR 812.3(m), to be implanted in **(b)(4)** of the 750 subjects enrolled in this study prior to submission to FDA and FDA approval of an IDE application. Anulex indicates on [clinicaltrials.gov](http://clinicaltrials.gov) that the endpoint classification for this study is an "efficacy study." The clinical investigation to determine the safety and/or effectiveness of a new intended use for the Xclose device requires an FDA approved IDE. 21 CFR 812.20(a)(2). We consider the annulus fibrosus repair indication to be investigational and outside the scope of your 510(k) clearance for Xclose. This claim represents a different intended use of the device. See 21 CFR 807.81 (a)(3)(ii). FDA considers devices marketed for an intended use of annulus fibrosus repair to be class III devices requiring a premarket approval application (PMA).

FDA considers annulus fibrosus repair to be a new intended use because it alters the therapeutic effect (i.e., tissue type, disease entity/target population, and effect on clinical outcomes), impacting safety and effectiveness.<sup>1</sup> In addition, the risk profile for a spinal implant contains additional risks that impact safety and effectiveness beyond those risks associated with suture use for "general and orthopedic" use. For instance, there are inherent risks in spinal surgery (e.g., neurological) that do not exist with orthopedic procedures such as ligament or tendon repair in the foot, ankle, etc. In addition, because the standard of care for disc herniation does not involve an implanted device, subjects in this trial are exposed to additional risks that are associated with device use (e.g., device migration, fracture, removal). Furthermore, the patient population for a ligament or tendon repair is significantly different from a herniation patient. Specifically, the assessment of reherniation does not exist in a "general orthopedic procedure," whereas prevention of reherniation is the primary endpoint for anular repair.

Your response is inadequate in that it fails to acknowledge that the clinical trial entitled "Randomized Study of Anular Repair with the Xclose™ Tissue Repair System" requires an IDE. FDA cleared the Xclose Tissue Repair System under 510(k) K091432, for the intended use of soft tissue approximation for procedures such as general and orthopedic surgery. As stated above, we consider the annulus fibrosus repair indication to be investigational and outside the scope of your 510(k) clearance for Xclose. A device used for the repair of the annulus fibrosus following spinal disc herniation is regulated as a class III device, requiring a PMA application supported by clinical data collected under an IDE. Accordingly, this device is required to have an approved PMA application in effect pursuant to section 515(a) of the Act, 21 U.S.C. 360e(a).

**Failure to comply with FDA regulations that prohibit promotion of an investigational device until after FDA has approved the device for commercial distribution and representation that an investigational device is safe or effective for the purposes for which it is being investigated. [21 CFR 812.7(a) and (d)]**

A sponsor, investigator, or any person acting for or on behalf of a sponsor or investigator shall not promote or test market an investigational device, until after FDA has approved the device for commercial distribution, and shall not represent that an investigational device is safe or effective for the purposes for which it is being investigated. You have failed to adhere to the above-stated regulations. Examples of your failure include, but are not limited to, the following:

o On your website, [http://anulex.com/anulex\\_technology/xclose.asp](http://anulex.com/anulex_technology/xclose.asp)<sup>1</sup>, assessed on September 17, 2010, in the section titled, "Xclose Plus Tissue Repair System for Efficient Soft Tissue Re-Approximation," the website includes the following statement, "The Xclose Plus Tissue Repair System provides a uniquely

simple method for treating the compromised soft tissue of the annulus fibrosus."

o FDA also reviewed your press releases dated November 10, 2009, and February 18, 2010, which were collected during our inspection, and are also accessed through Anulex's website. Both press releases state that "Xclose was cleared in September 2006 for use in soft tissue approximation for procedures such as general and orthopedic surgery. Xclose provides a simple, convenient method for treating the compromised soft tissue of the annulus fibrosus."

FDA considers these statements to promote Xclose for annulus fibrosus repair. As a result, you are in violation of FDA's prohibition against promoting an investigational device before FDA has approved the device for commercial distribution under 21 CFR 812.7(a). In addition, these claims could unduly influence potential physicians and study subjects in that they represent that the Xclose device is safe and effective for the purposes for which it is being investigated. These statements do not describe the additional risks associated with the implantation of your investigational device for the repair of the annulus. Therefore, you are representing that the Xclose device is safe and effective for the purposes for which it is being investigated in violation of 21 CFR 812.7(d).

Further, Anulex is promoting Xclose for annulus fibrosus repair, which is an intended use that the Agency has not cleared or approved. Such promotion renders Xclose adulterated under section 501 (f)(1)(B) of the Act, 21 U.S.C. 351 (f)(1)(B), because you do not have an approved application for premarket approval (PMA) in effect pursuant to section 515(a) of the Act, 21 U.S.C. 360e(a). The devices are also misbranded under section 502(o) of the Act, 21 U.S.C. 352(o), because you did not notify the Agency of your intent to introduce the devices into commercial distribution, as required by section 510(k) of the Act, 21 U.S.C. 360(k). For a device requiring premarket approval, the notification required by section 510(k) of the Act, 21 U.S.C. 360(k), is deemed satisfied when a PMA is pending before the Agency. 21 CFR 807.81 (b).

Your response is inadequate in that it fails to acknowledge that the use of the Xclose device for annulus fibrosus repair is investigational, and subject to the regulations of 21 CFR Part 812. Your response is also inadequate in that you incorrectly state the use of the Xclose device in anular repair poses no additional risks, or additional safety or effectiveness issues beyond those associated with the product's broader use.

**Failure to obtain adequate signed investigator agreements for each participating investigator. [21 CFR 812.43(c)]**

It is a sponsor's responsibility to obtain a signed agreement from each participating investigator. In addition, the agreement must contain, among other items, a commitment from the investigator to promptly update the financial disclosure information if any relevant changes occur during the course of investigation and for one year following the completion of the study. You failed to obtain the aforementioned information from participating investigators. Examples of your failure include, but are not limited to, the following:

o You failed to obtain investigator agreements from a total of **(b)(4)** investigators who implanted the Xclose device in a total of **(b)(4)** subjects.

o You failed to obtain a commitment from any of the investigators to update their financial disclosure information if changes occur during the investigation and for one year following the completion of the study.

In your response, you indicate the following corrective actions, including, but not limited to:

o Instituting methods to monitor investigator financial involvement in Anulex.

o Requesting signed clinical investigator agreements from those investigators who are still participating in the study.

o Ensuring financial disclosures include a provision whereby investigators are required to provide a financial interest update following changes in their financial interests in the company. You indicated that changes will also be included in clinical procedures to monitor compliance with this requirement.

In your response, please submit documentation that the changes indicated above have been implemented. Please be advised that, contrary to your response, and as previously stated in this letter, FDA considers your clinical trial entitled "Randomized Study of Annular Repair with the Xclose™ Tissue Repair System" to be an investigational device trial, subject to the regulations of 21 CFR Part 812.

The violations described above are not intended to be an all inclusive list of problems that may exist with your clinical study. It is your responsibility as a study sponsor to ensure compliance with the Act and applicable regulations.

Within fifteen (15) working days of receiving this letter, please provide written documentation of the actions you have taken or will take to correct these violations and prevent the recurrence of similar violations in current or future studies for which you are the study sponsor. Any submitted corrective action plan must include projected completion dates for each action to be accomplished. Failure to respond to this letter and take appropriate corrective action could result in the FDA taking regulatory action without further notice to you.

You have requested the opportunity to meet with FDA to discuss these inspectional observations. If you would still like to meet, in your written response to this letter you may include three proposed dates and times for which your corporate leadership will be available to discuss these issues either via teleconference or in person. Once your response is received, FDA will contact you to schedule the regulatory meeting.

Your response should reference "CTS # EC100567/E001" and be sent to:

Attention: Anne T. Hawthorn, J.D.  
Food and Drug Administration  
Center for Devices and Radiological Health  
Office of Compliance  
Division of Bioresearch Monitoring  
10903 New Hampshire Avenue  
Building 66, Room 3504  
Silver Spring, Maryland 20993-0002.

A copy of this letter has been sent to the Minneapolis District Office. 250 Marquette Ave.. Suite 600. Minneapolis, MN 55401. Please send a copy of your response to that office.

The Division of Bioresearch Monitoring has developed introductory training modules in FDA regulated device clinical research practices, which are available on the FDA website. The modules are for persons involved in FDA regulated device clinical research activities. These modules are located at the following website address:  
<http://www.fda.gov/Training/CDRHLearn/ucm162015.htm><sup>2</sup>.

If you have any questions, please contact Anne T. Hawthorn, (301) 796-6561, or [Anne.Hawthorn@fda.hhs.gov](mailto:Anne.Hawthorn@fda.hhs.gov).

Sincerely yours,  
/S/

Steven D. Silverman  
Director  
Office of Compliance  
Center for Devices and  
Radiological Health

<sup>1</sup> In your response, you reference several FDA guidances, including "Guidance for Industry on General/Specific Intended Use" (Issued November 4, 1998). After an evaluation of the criteria described in the General/Specific Intended Use guidance, FDA considers repair of the annulus fibrosus to be a new intended use that requires submission of a PMA to establish the safety and effectiveness of the device. A general discussion of these criteria, such as risk and endpoints, is included above.

**Links on this page:**

1. [http://anulex.com/anulex\\_technology/xclose.asp](http://anulex.com/anulex_technology/xclose.asp)
2. <http://www.fda.gov/Training/CDRHLearn/ucm162015.htm>