DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Anastasios Pappas, MD
1913 S. Minnesota Ave.
Sioux Falls, SD 57105-2812

11-16-2010

PROPOSAL TO DEBAR
NOTICE OF OPPORTUNITY FOR HEARING
DOCKET No. FDA-2010-N-0441

Dear Dr. Pappas:

This letter is to inform you that the Food and Drug Administration (FDA or the Agency) is proposing to issue an order debarring you for a period of five years from providing services in any capacity to a person that has an approved or pending drug product application. FDA bases this proposal on a finding that you were convicted of a misdemeanor under Federal law for conduct relating to the regulation of a drug product under the Federal Food, Drug, and Cosmetic Act (the Act), and that the type of conduct that served as the basis for the conviction undermines the process for the regulation of drugs. This letter also offers you an opportunity to request a hearing on this proposal, and provides you with the relevant information should you wish to acquiesce to this proposed debarment.

Conduct Related to Conviction

On April 4, 2006, you entered a plea of guilty to a one-count information charging you with a misdemeanor offense of introducing and causing the introduction into interstate commerce of a misbranded drug. On August 14, 2006, judgment was entered against you in the United States District Court for the District of South Dakota, Southern Division for a misdemeanor violation of 21 U.S.C. §§ 352(o), 331(a) and 333(a)(1). The underlying facts supporting this conviction are as follows.

You were a licensed dermatologist in the State of South Dakota and a partner with Dakota Dermatology in Sioux Falls, South Dakota (Practice). Prior to 2009, BOTOX®/BOTOX® Cosmetic, a product manufactured by Allergan, Inc., was the only Botulinum Toxin Type A product licensed by FDA for use in humans for any indication, including for the temporary improvement in appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity, commonly described as the treatment of facial wrinkles.[1]

[1] On July 31, 2009, FDA approved a supplemental application to the license for BOTOX®/BOTOX® Cosmetic, which in relevant part changed the established, or proper name of the biological product from Botulinum Toxin Type A to onobotulinumtoxin A. See Letter fr. FDA to Allergan Inc. (July 31, 2009), available at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2009/103000s5209s5210ltr.pdf. This non-proprietary name change is not material to these purposes, and for the sake of consistency with the related criminal proceedings, the product will continue to be referred to in this letter as Botulinum Toxin Type A.

Between August, 2004 and November, 2004, in the District of South Dakota and elsewhere, you placed three orders for a total of six vials of Botulinum toxin Type A (TRI-Toxin) from Toxin Research International (TRI). Between September 2004 and November 2004, you administered TRI-Toxin to patients. TRI-Toxin was manufactured, prepared, propagated, compounded, or processed by TRI. TRI was not duly registered with the FDA and, therefore, the TRI-Toxin is deemed misbranded under section 502(o) of the Act, 21 U.S.C.§ 352(o).

You acknowledged that you committed a crime when you ordered non-FDA approved Botulinum Toxin Type A from a company not duly registered with FDA, and administered it to some of your patients.

These acts violated sections 502(o), 301(a), and 303(a)(1), 21 U.S.C. §§ 352(o), 331(a) and 333(a)(1).

FDA's Finding

Section 306(b)(2)(B)(i)(I) of the Act (21 U.S.C. 335a(b)(2)(B)(i)(I)) permits FDA to debar an individual if FDA finds that the individual has been convicted of a misdemeanor under Federal law for conduct relating to the regulation of drug products under the Act, and if FDA finds that the type of conduct that served as the basis for the conviction undermines the process for the regulation of drugs. You pleaded guilty to introducing and causing the introduction of a misbranded drug in violation of sections 502(o), 301(a) and 303(a)(1) of the Act (21 U.S.C. §§ 352(o), 331(a) and § 333(a)(1)). FDA therefore finds that your Federal misdemeanor conviction for these violations relates to the regulation of drug products under the Act. FDA also finds that this type of conduct, which served as a basis for your conviction, undermines the process for the regulation of drugs because the introduction and causing the introduction of a misbranded drug into interstate commerce are violations of the Act.

The maximum period of debarment under section 306(b)(2)(B)(i)(I) of the Act is five years. 21 U.S.C. 335a(c)(2)(A)(iii). Section 306(c)(3) of the Act (21 U.S.C. 335a(c)(3)) provides six factors for consideration in determining the appropriateness and the period of a permissive debarment. The factors applicable here include: (1) the nature and seriousness of the offense involved; (2) the nature and extent of management participation in any offense involved; (3) the nature and extent of voluntary steps taken to mitigate the impact on the public; and (4) prior convictions involving matters within the jurisdiction of FDA.

1. Nature and seriousness of the offense.

FDA regulates the manufacture and distribution of drugs in the United States. FDA also regulates the manufacture and distribution of biologic products, which includes toxins like Botulinum Toxin Type A. As noted above, only one Botulinum Toxin Type A product was licensed by FDA prior to 2009. FDA licensed BOTOX® in 1991, and approved a supplement for the indication of treatment of glabuller lines in 2002. Products for the latter indication are marketed and labeled as BOTOX® Cosmetic. TRI-Toxin has never been licensed or approved by FDA for any use. In your plea

agreement, you admitted to introducing and causing the introduction into interstate commerce of a misbranded drug.[2]

Specifically, in the sentencing memorandum filed by counsel on your behalf, you conceded that you received faxes and coupons at your office promoting the use of Botulinum Toxin Type A produced by TRI. Frustrated with the rising cost of FDA-approved Botox, you contacted TRI for information about their product and you were informed that TRI-Toxin was not approved and that it was in the process of being approved by FDA. You then ordered two bottles containing 500 units per bottle of the unapproved product and tested it on your dogs, your mother and yourself for safety and efficacy. You then contacted TRI and inquired about participating as a clinical investigator in trials of TRI Toxin; however, you were informed that the clinical trials had concluded. On the basis of having administered the product to your dogs, yourself, and your mother, you ordered two additional bottles of the unapproved drug in September, two additional bottles in October, and two additional bottles in November 2004, and administered it to your patients from September and November 2004. Some patients were informed the drug was unapproved, but not all patients were so informed.

FDA finds that your conduct created a risk of injury to consumers due to the use of an unapproved drug and demonstrated a disregard for the legal requirements for the conduct of clinical trials and the protection of human subjects. Furthermore, your conduct undermined the Agency's drug approval process, the Agency's oversight of approved drug products, and seriously undermined the integrity of the Agency's regulation of a drug product. Accordingly, FDA considers the nature and seriousness of your conduct as an unfavorable factor.

2. Nature and extent of management participation in any offense involved.

In determining the appropriate period of debarment, FDA also shall consider the nature and extent of your management participation in the offense, and whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense. You had a 25% ownership interest in the Practice and, as a licensed physician and owner, you held a position of authority where you directed the actions of the employees of the Practice. Your conduct also served as an example for the employees of the Practice. Therefore, the pattern of misbranding you engaged in is considered more serious than if you were an employee. Accordingly, FDA considers this an unfavorable factor.

3. The nature and extent of voluntary steps taken to mitigate the impact on the public.

FDA next will consider the nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including, among other things, full cooperation with any investigations and any other actions taken to substantially limit potential or actual adverse effects on the public health. You placed multiple orders for TRI-Toxin over a period of months and administered TRI-Toxin to your patients from September 2004 until November 2004. However, sometime after mid-November,

[2] FDA licensed BOTOX®/BOTOX® Cosmetic pursuant to the Agency's authority set forth in Section 351(a) of the Public Health Service Act (PHSA), 42 U.S.C. § 262(a). The misbranding provisions of the Act apply to products licensed under the PHSA. See 42 U.S.C. 262(j) ("[t]he Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) applies to a biological product subject to regulation under this section").

2004, you learned of an incident in Florida where four patients were paralyzed due to the administration of Botulinum toxin. Concerned that this incident involved TRI-Toxin, you did telephone TRI for comment, to no avail. You then discarded your remaining stock of the TRI-Toxin and began treating all of your patients with the approved Allergan's Botox. FDA considers this a favorable factor.

4. Prior convictions under this Act or under other Acts involving matters within the jurisdiction of the Food and Drug Administration.

FDA is unaware of any prior convictions. FDA considers this a favorable factor.

Weighing all factors, the Agency has determined that the facts supporting the unfavorable factors far outweigh those in support of the favorable factors, and therefore warrant the imposition of a five year permissive debarment in this case. You were a licensed physician entrusted with patient care and a partner in a professional practice. You acknowledged that you committed a crime when you ordered non-FDA approved Botulinum Toxin Type A from a company not duly registered with FDA, and administered it to some of your patients beginning in September 2004 and ending in November 2004. As discussed above, the conduct that formed the basis of your conviction created a risk of injury to your patients from the use of an unapproved drug and demonstrated a disregard for the legal requirements for the conduct of clinical trials, the protection of human subjects, the drug approval process, and the Agency's regulation of drug products.

Proposed Action and Notice of Opportunity for Hearing

Based on the findings discussed above, FDA proposes to issue an order under section 306(b)(2)(B) of the Act (21 U.S.C. 335a(b)(2)(B)) debarring you for a period of five years from providing services in any capacity to a person having an approved or pending drug product application. You were convicted of misbranding a drug, a Federal misdemeanor offense under the Act. As explained above, this offense relates to the regulation of drug products under the Act. Furthermore, the conduct that served as the basis for this conviction undermines the process for the regulation of drugs. Based on the factors discussed above, FDA proposes a five-year debarment period.

In accordance with section 306 of the Act and 21 CFR part 12, you are hereby given an opportunity to request a hearing to show why you should not be debarred as proposed in this letter.

If you decide to seek a hearing, you must file the following: (1) on or before 30 days from the date of receipt of this letter, a written notice of appearance and request for hearing; and (2) on or before 60 days from the date of receipt of this letter, the information on which you rely to justify a hearing. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for a hearing, information and analyses to justify a hearing, and a grant or denial of a hearing are contained in 21 CFR part 12 and section 306(i) of the Act (21 U.S.C. 335a(i)).

Your failure to file a timely written notice of appearance and request for hearing constitutes an election by you not to use the opportunity for a hearing concerning your debarment and a waiver of any contentions concerning this action. If you do not request a hearing in the manner prescribed by

the regulations, FDA will not hold a hearing and will issue a final debarment order as proposed in this letter.

A request for a hearing may not rest upon mere allegations or denials but must present specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. A hearing will be denied if the data and information you submit, even if accurate, are insufficient to justify the factual determination urged. If it conclusively appears from the face of the information and factual analyses in your request for a hearing that there is no genuine and substantial issue of fact that precludes the order of debarment, the Commissioner of Food and Drugs will deny your request for a hearing and enter a final order of debarment.

You should understand that the facts underlying your conviction are not at issue in this proceeding. The only material issue is whether you were convicted as alleged in this notice and, if so, whether, as a matter of law, this conviction permits your debarment under section 306(b)(2)(B) of the Act (21 U.S.C. 335a(b)(2)(B) as proposed in this letter.

Your request for a hearing, including any information or factual analyses relied on to justify a hearing, must be identified with Docket No. FDA-2010-N-0441 and sent to the Division of Dockets Management, Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. You must file four copies of all submissions pursuant to this notice of opportunity for hearing. The public availability of information in these submissions is governed by 21 CFR 10.20(j). Publicly available submissions may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

You also may notify the Secretary that you acquiesce to this proposed debarment. If you decide to acquiesce, your debarment shall commence upon such notification to the Secretary in accordance with section 306(c)(2)(B) (21 U.S.C. § 335a(c)(2)(B)).

This notice is issued under section 306 of the Act (21 U.S.C. 335a) and under authority delegated to the Director, Office of Enforcement within the Food and Drug Administration.

Sincerely,

Howard R. Sklamberg
Director
Office of Enforcement
Office of Regulatory Affairs

cc:
HF-3/Daniel J. Davidson

HFC-130/ Michael Rogers
HFC-300/ Jeffrey Ebersole
GCF-1/ Seth Ray
HFD-1/Dr. John Jenkins
HFD-300/ Deborah Autor
HFD-300/Douglas Stearn
HFD-310/Ann Metayer
HFD-600/ Gary Buehler
HFC-2/ Michael Verdi

HFD-45/Ball, Leslie
HFD-45/Lauren Iacono-Connor
HFV-200/Daniel G. McChesney

HFA-305 (Docket No. FDA-2010-N-0441)
HFC-230/Debarment File
HFC-230/CF
HFM-100 (CBER)
HFM-100
HFC-200/CF