**DEPARTMENT OF HEALTH AND HUMAN SERVICES** Public Health Service

**Food and Drug Administration**
**Rockville, MD 20857**

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mary Holloway
[redacted] (Ex. 6)

**PROPOSAL TO DEBAR**
**NOTICE OF OPPORTUNITY FOR HEARING**
**DOCKET No. FDA-2009-N-0361**

Dear Ms. Holloway:

This letter is to inform you that the Food and Drug Administration (FDA) 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.

Conduct Related to Conviction

On June 18, 2009, the United States District Court for the District of Massachusetts accepted your plea of guilty, and on June 29, 2009, entered judgment against you for one count of distribution of a misbranded drug, a Federal misdemeanor offense under 21 U.S.C. 331(a), 333(a)(1), and 352(f). The underlying facts supporting this conviction are as follows.

From 1998 through in or about December 2006, you were employed as a regional manager of Pharmco, a corporation engaged, among other things, in the manufacture and sale of pharmaceutical drugs for human use. As a regional manager you supervised approximately 100 Pharmco sales representatives and district managers.

On or about January 15, 2001, Pharmco submitted a New Drug Application (NDA) seeking approval of a new drug Bextra in 10 mg, 20 mg, and 40 mg doses for all uses. On or about November 16, 2001, FDA approved Bextra 20 mg dose twice a day as needed for short term use for primary dysmenorrheal, and the 10 mg dose once a day for osteoarthritis, and adult rheumatoid arthritis. On or about December 4, 2001, you received a copy of FDA's letter raising safety concerns about Bextra, which you asked other Pharmco managers not to share with the sales representatives.

In or about October 2004, a second study of Bextra and parecoxib in CABG surgeries showed a statistically significant increase in adverse cardiovascular events in CABG patients taking Bextra and/or parecoxib. This resulted in FDA requesting and Pharmco adding a warning in Bextra's product labeling that Bextra was contraindicated for treatment of post-operative pain following CABG surgery. FDA additionally required a black box warning in Bextra's labeling about reports of

serious skin reactions, including Stevens-Johnson syndrome in patients using Bextra. Pharmco removed Bextra from the market in April 2005 after FDA determined that the safety issues relating to Bextra outweighed its potential benefits.

From in or about December 2001 through in or about April 2005, you promoted and caused the promotion of the sale and use of Bextra for a variety of uses and at dosages other than the uses and dosages approved by FDA. In promoting and causing the promotion of Bextra for unapproved uses and dosages, you and those acting at your direction routinely did not disclose that FDA had specifically declined to approve Bextra as safe and effective for these uses. In promoting and causing the promotion of Bextra for these unapproved uses and dosages, you and those acting under your direction routinely did not disclose that Pharmco's studies and FDA had both raised specific safety concerns about the use of Bextra for some of these unapproved uses and dosages.

Additionally, you caused your sales representatives to promote Bextra with false claims of safety, including representations that Bextra had no cardiovascular risks and that the drug had placebo-like side effects. You also caused your sales representatives to promote Bextra by telling physicians that it was safer and more effective than Vioxx, despite the fact that there were no head-to-head studies of Bextra and Vioxx for the approved uses of Bextra that showed it was safer or more effective than Vioxx.

Consistent with your instructions and incentives, your sales team promoted, drafted, and distributed to physicians written protocols, pain management pathways, and standing orders for Bextra for uses and dosages that you knew were not FDA-approved.

You instructed your sales team to claim that Bextra could be used before, during, and after surgery to reduce the risk of Deep Vein Thrombosis (DVT), even though you knew there were no studies of Bextra showing that it was safe or effective for this use. In promoting and causing the promotion of Bextra for the prevention of DVTs, you routinely did not disclose that FDA specifically refused to approve Bextra for pre and post-operative surgical pain and that FDA had noted that no decrease in side effects, such as DVTs, had been shown from Bextra's use in this context.

On or about April 24, 2002, you sent an email to sales representatives and managers in your division instructing them to promote the use of Bextra to reduce the risk of DVTs to surgeons, even though you knew that Bextra had not been approved by FDA to reduce the risk of DVTs.
Beginning as early as December 2001, and continuing until at least in or about April 2005, you did introduce, deliver for introduction, and cause the introduction into interstate commerce, quantities of Bextra, which was intended for use for the treatment of acute pain, surgical pain, other unapproved uses, and at unapproved dosages, which was misbranded within the meaning of 21 U.S.C. 352(a) and (f), in that Bextra's labeling lacked adequate directions for such uses.

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 introduced misbranded drugs into interstate commerce, in violation of sections 301(a) and 502(f) of the Act (21 U.S.C. 331(a) and 352(f)). FDA therefore finds that your Federal misdemeanor conviction for these violations relates to the regulation of drug products under the Act.

Specifically, you promoted Bextra for uses that were not approved by FDA, even though you knew that some of these unapproved uses were unsafe and others were not supported by studies demonstrating safety and effectiveness. FDA, therefore, also finds that this type of conduct, which served as the basis for your conviction, undermines the process for the regulation of drugs.

The maximum period of debarment under section 306(c)(2)(A)(iii) of the Act (21 U.S.C. 335a(c)(2)(A)(iii)) is five years. Section 306(c)(3) of the Act (21 U.S.C. 335a(c)(3)) provides several factors for consideration in determining the appropriateness and the period of a permissive debarment. The factors applicable here include: (1) nature and seriousness of the offense involved, (2) nature and extent of management participation in this offense, (3) nature and extent of voluntary steps 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.**

Based on your plea agreement, you were convicted of one count of distribution of a misbranded drug. Your conviction was based on your admission that you did introduce, deliver for introduction, and cause the introduction into interstate commerce, quantities of Bextra, a drug within the meaning of the Act, which was intended for use for the treatment of acute pain, surgical pain, other unapproved uses, and at unapproved dosages, which was misbranded in that Bextra's labeling lacked adequate directions for such uses. FDA finds that your conduct created a risk of injury to consumers, undermined the agency's oversight of the labeling of approved drug products, and potentially undermined the safety and effectiveness of Bextra. Accordingly, FDA considers the nature and seriousness of your conduct as an unfavorable factor.

**2. The nature and extent of management participation in any offense involved, whether corporate policies and practices encouraged the offense, including whether inadequate institutional controls contributed to the offense.**

While you were employed as a regional manager for Pharmco, you used your position of authority to direct your staff to promote the use of Bextra for uses not approved by FDA. FDA had specifically told Pharmco that it could not approve Bextra for these uses because the safety in these other uses had not been established. Specifically, FDA was concerned about the results of a study in which there was an excess of cardiovascular events in patients who had undergone coronary artery bypass graft surgery and used Bextra. You were aware of FDA's safety concerns, but you nonetheless had your sales staff promote Bextra for precisely the uses that FDA refused to approve. You trained and encouraged your sales teams to promote Bextra by obtaining protocols from doctors that instructed that unapproved dosages of Bextra be used for the pain of surgery, an unapproved use. You also instructed your staff to market Bextra for use before, during and after surgery to reduce the risk of deep vein thrombosis, even though you knew there were no studies showing that Bextra was safe and effective for this use. Finally, you encouraged your staff to make false claims about Bextra in order to sell the drug. Therefore, FDA considers the nature and extent of your management participation as an unfavorable factor.

**3. The nature and extent of voluntary steps to mitigate the impact on the public of any offense involved, including the recall or the discontinuation of the distribution of suspect drugs, full cooperation with any investigations (including the extent of disclosure to appropriate authorities of all wrongdoing), the relinquishing of profits on drug approvals fraudulently obtained, and any other actions taken to substantially limit potential or actual adverse effects on the**

**public health.**

You were aware of FDA's safety concerns about Bextra because you received a copy of the letter raising these concerns. You did not disclose these concerns to your sales representatives but rather forwarded it to other Pharmco managers and asked them not to share FDA's letter with the sales representatives. You promoted and caused the promotion of the sale and use of Bextra for a variety of uses and at dosages other than FDA approved uses and dosages. In promoting and causing the promotion of Bextra for unapproved uses and dosages, you and those acting at your direction did not disclose that FDA had specifically declined to approve Bextra as safe and effective for these uses, nor did you take any subsequent steps to mitigate the impact of these violative actions on the public. Further, your actions during the investigation of the offense fell short of full cooperation. Accordingly, FDA considers your failure to take effective voluntary steps to mitigate the offense you committed to be an unfavorable 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.

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 distributing a misbranded 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-2009-N-0361 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.

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,

Brenda Holman
RADM United States Public Health Service
Acting Director
Office of Enforcement
Office of Regulatory Affairs

cc:
HF-3/Judge Davidson
HFC-130/ Michael Rogers
HFC-300/ Jeffrey Ebersole
HFA-305 (Docket No. FDA-2009-N-0361)
GCF-1/ Seth Ray
HFD-1/Dr. John Jenkins
HFD-7/ Nancy Boocker
HFD-300/ Deborah Autor
HFD-310/Ann Metayer
HFD-600/ Guy Buehler
HFC-2/ Michael Verdi
HFC-230/Debarment File
HFC-230/CF