

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

FILED
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UNITED STATES OF AMERICA

) Criminal No.

U.S. DISTRICT COURT
DISTRICT OF MASS.

v.

)

) 21 U.S.C. §§ 331(a); 333(a)(1) and 352

MARY HOLLOWAY,

) (Introduction into Interstate Commerce of a

) Misbranded Drug)

Defendant.

09 CR 10.089. [REDACTED]
INFORMATION
09 CR 10.089.

The United States Attorney charges that:

GENERAL ALLEGATIONS

At all times material to this Information, unless otherwise alleged:

1. **MARY HOLLOWAY** (hereinafter "**HOLLOWAY**"), was an individual residing in Branchburg, New Jersey. From 1998 through in or about December 2006, **HOLLOWAY** was a Regional Manager of Pharmco, a corporation engaged, among other things, in the manufacture and sale of pharmaceutical drugs for human use ("**Pharmco**" hereinafter refers to **Pharmco** and its predecessor entities and subsidiaries). **HOLLOWAY** supervised approximately 100 **Pharmco** sales representatives, district managers and others in the Northeast region of the United States.

The FDA and the FDCA

2. The Food and Drug Administration ("FDA") was the federal agency of the United States responsible for protecting the health and safety of the public by enforcing the Federal Food Drug and Cosmetic Act ("FDCA"), 21 United States Code, Section 301, *et seq.* and ensuring, among other things, that drugs intended for use in humans were safe and effective for their intended uses and that the labeling of such drugs bore true, complete and accurate information.

3. The FDCA prohibited causing the delivery for introduction into interstate commerce of drugs that were not approved for use by the FDA. The FDCA also prohibited causing the delivery for introduction into interstate commerce of drugs that were misbranded. The FDCA also prohibited the doing of any act that caused a drug to be misbranded while it was held for sale after shipping in interstate commerce.

4. The FDCA, and its implementing regulations, required that before a new drug could legally be distributed in interstate commerce, a sponsor of a new drug product submit and obtain approval of a New Drug Application (“NDA”) from the FDA.

5. The FDCA required that the NDA include proposed labeling for the proposed intended uses of the drug that included, among other things, the conditions for therapeutic use. The NDA was also required to contain, to the satisfaction of FDA, evidence, such as data generated in well-controlled clinical trials, that demonstrated that the drug would be safe and effective when used in accordance with the proposed labeling.

6. An NDA sponsor was not permitted to promote and market the drug until it had an approved NDA, including approval for the proposed labeling. Moreover, if approved, the sponsor was permitted to promote and market the drug only for the medical conditions of use and dosages specified in the approved labeling. Uses not approved by the FDA, including dosages not approved in the drug’s approved labeling, were known as “unapproved” or “off-label” uses.

7. The FDCA, and its implementing regulations, required the sponsor to file a supplemental NDA (or “sNDA”), in order to label or promote a drug for a use or dosage different from the conditions for use and dosage specified in the approved labeling. The sNDA was required to include a description of the newly proposed indications for use, and evidence

consisting of well-controlled clinical studies, sufficient to demonstrate that the drug was safe and effective for the newly proposed therapeutic use. Only upon FDA approval of the sNDA could the sponsor promote the drug for the new intended use. Absent such FDA approval, the manufacturer promoting a drug for the new intended use caused the drug to become an unapproved new drug and misbranded under the FDCA.

8. The FDCA provided that a drug was misbranded if, among other things, “its labeling [was] false or misleading in any particular.” The FDCA also provided that a drug was misbranded if, among other things, the labeling did not contain adequate directions for use. Adequate directions for use could not be written for indications or uses for which the drug had not been approved and proven to be safe and effective through well-controlled clinical studies.

9. The FDCA prohibited the introduction and the delivery for introduction and causing the introduction and the delivery for introduction into interstate commerce of an unapproved new drug and of a misbranded drug. The FDCA also prohibited the doing of any act that caused a drug to be misbranded while it was held for sale after shipment in interstate commerce.

The Bextra Approval Process

10. Bextra was Pharmco’s trade name for the drug valdecoxib and was a so-called “Cox-2 Inhibitor.” At the time of Bextra’s approval in November, 2001, the “Cox-2” class of drugs included the previously released drug Celebrex, also marketed by Pharmco, and Vioxx, manufactured and marketed by another pharmaceutical company.

11. The Cox-2 class of drugs was designed to relieve various forms of pain and inflammation equal to the predecessor pain relievers (the so-called “non-selective NSAIDs”), but

without the negative gastrointestinal side effects often associated with these drugs. Thus, the major justification for switching a patient to the Cox-2 class of drugs over the non-selective NSAIDs was greater safety, not better efficacy.

12. Because many of the non-selective NSAIDs, such as ibuprofen or naproxen, were available as generic and over the counter drugs at the time the Cox-2 drugs were launched, the drugs in the Cox-2 class generally were much more expensive than the predecessor drugs.

13. On or about January 15, 2001, Pharmco submitted an NDA seeking approval of Bextra, which was a new drug within the meaning of 21 U.S.C. § 321(p) and 21 C.F.R. § 310.3 (h)(4) and (5). In that NDA, Pharmco sought approval to market Bextra at dosages of 10, 20 and 40 mg for the following uses:

- (1) the prevention and treatment of acute pain in adults. Preoperative administration of [Bextra] prevents or reduces post-operative pain. [Bextra] has an opioid sparing effect when used concomitantly with opioids;
- (2) for the treatment of primary dysmenorrhea; and
- (3) for relief of signs and symptoms of osteoarthritis and adult rheumatoid arthritis.

The FDA Approval and Non-Approval of Bextra

14. On or about November 16, 2001, the FDA approved Bextra to treat the signs and symptoms of osteoarthritis (“OA”), adult rheumatoid arthritis (“RA”) and primary dysmenorrhea (“PD”). Pharmco sought, but the FDA specifically declined in writing to approve, Bextra for general acute pain, for the preemption of the pain of surgery and for opioid sparing.

15. Moreover, although Pharmco had sought approval for the 10 mg, 20 mg and 40 mg doses for all uses, the FDA only approved the 20 mg dose twice a day as needed for short

term use for PD, and only the 10 mg dose once a day for OA and RA (hereinafter, these uses for Bextra will be referred to throughout this Information as the "Approved Uses and Dosages.")

16. The FDA never approved Bextra for any use other than the Approved Uses and Dosages.

17. The FDA informed Pharmco by letter that it was not approving Bextra for acute pain at least in part because of safety concerns about Bextra. Among the other concerns cited by the FDA were the results of a study of Bextra and its injectable form, parecoxib, used in patients undergoing coronary artery bypass graft surgery (the "CABG I" trial), in which there was an excess of serious cardiovascular events associated with the use of these drugs in connection with the CABG surgeries.

18. On or about December 4, 2001, **HOLLOWAY** received a copy of the FDA's letter raising these concerns and forwarded it to other Pharmco managers. **HOLLOWAY** asked these managers not to share the FDA's letter with the sales representatives.

19. In or about October 2004, the results of a second study of Bextra and parecoxib in coronary artery bypass graft surgery (CABG II) became public. This study showed a statistically significant increase in adverse cardiovascular events in CABG patients taking Bextra and/or parecoxib.

20. As a result of this study, in or about November 2004, the FDA requested, and Pharmco added, a warning in Bextra's product label that Bextra was contraindicated for treatment of post-operative pain following CABG surgery. At the same time, the FDA required a black box warning on Bextra's label about reports of serious skin reactions, including Stevens-Johnson syndrome, in patients receiving Bextra.

21. In addition, following a review of the safety of the Cox-2's and other anti-inflammatory drugs by an FDA Advisory Committee in the first quarter of 2005, the FDA determined that the safety issues relating to Bextra, including serious skin rashes, outweighed its potential benefits and asked that Pharmco withdraw Bextra from the market. Pharmco removed Bextra from the market in April 2005.

HOLLOWAY'S Promotion of Bextra by For Unapproved Uses and Dosages

22. From in or about December 2001 through in or about April 2005, **HOLLOWAY** promoted and caused the promotion of the sale and use of Bextra for a variety of uses and at dosages other than the Approved Uses and Dosages, including in the ways set forth in paragraphs 23 through 41 below.

23. In promoting and causing the promotion of Bextra for unapproved uses and dosages, including for the acute pain associated with surgery, both pre- and post-operatively, **HOLLOWAY** and those acting at her direction routinely did not disclose that the FDA had specifically declined to approve Bextra as safe and effective for these uses.

24. In promoting and causing the promotion of Bextra for these unapproved uses and dosages, **HOLLOWAY** and those acting at her direction routinely did not disclose that Pharmco's studies and the FDA had both raised specific safety concerns about the use of Bextra for some of these unapproved uses and dosages.

25. **HOLLOWAY** also caused her sales force to promote Bextra with false claims of safety, including that Bextra had no dose proportional increase in hypertension and edema, that Bextra had no cardiovascular risks and that Bextra had placebo-like side effects.

26. **HOLLOWAY** also caused sales representatives to promote Bextra by telling physicians that Bextra 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 that Bextra was safer or more effective.

Promotion of Bextra For Surgical Pain and With Pathways and Protocols

27. **HOLLOWAY** trained and directed her sales team to seek written surgical and pain management protocols, standing orders and pathways from physicians, hospitals, and other customers for use in pre- and post-operative surgical situations.

28. **HOLLOWAY** caused her assistant to circulate to her sales team an electronic template of a hospital-wide pain management pathway that provided for administration of Bextra for unapproved uses and at unapproved dosages and to give instructions on how to prepare such pathways for distribution in hospitals and institutions.

29. **HOLLOWAY** also encouraged her sales representatives to promote Bextra for unapproved uses and dosages by circulating examples of written protocols obtained by other representatives that called for unapproved uses and dosages of Bextra in certain surgical and pain management settings.

30. **HOLLOWAY** praised and rewarded representatives who obtained such surgical and pain management protocols for unapproved uses and dosages of Bextra.

31. Consistent with these instructions and incentives, **HOLLOWAY's** sales team promoted, drafted and distributed to physicians written protocols, pain management pathways and standing orders for Bextra for uses and dosages that they knew were not FDA-approved.

32. For example, in or about June or July 2002, a sales representative working under **HOLLOWAY** in Massachusetts drafted and recommended a written protocol for the unapproved use of Bextra to control pain in OB/GYN surgeries, including at unapproved dosages, to a physician in Massachusetts.

33. On or about July 19, 2002, **HOLLOWAY** sent an email to her sales team praising this Massachusetts sales representative for a “fantastic protocol” in six different areas of OB/GYN surgery, each an unapproved use for Bextra.

HOLLOWAY’s Promotion of Bextra to Prevent Blood Clots Known As “DVTs”

34. **HOLLOWAY** instructed her sales team to claim that Bextra could be used before, during and after surgery to reduce the risk of Deep Vein Thrombosis or “DVTs,” a form of life-threatening blood clots that can form during or after surgery, even though she knew there were no studies of Bextra showing that it was safe or effective for this use.

35. In promoting and causing the promotion of Bextra for the prevention of DVTs, **HOLLOWAY** routinely did not disclose that the FDA had specifically refused to approve Bextra for the treatment of pre and post-operative surgical pain and that the FDA had noted that no decrease in side effects, such as DVTs, had been shown from Bextra’s use in this context.

36. Specifically, on or about April 24, 2002, **HOLLOWAY** sent an email to sales representatives and managers in her division, including numerous representatives and managers in Massachusetts, and instructed them (with an attached script) to promote the use of Bextra to reduce the risk of DVTs to surgeons, even though **HOLLOWAY** knew that Bextra had not been approved by the FDA to reduce the risk of DVTs.

37. On or about October 18, 2002, acting under the direction of **HOLLOWAY**, a Pharmco representative promoted Bextra for pain and to reduce the risk of DVT's to a physician in Brooklyn, New York.

**HOLLOWAY'S Use of Medical Inquiries to Promote Bextra For
Unapproved Uses and Dosages**

38. **HOLLOWAY** caused the sales force to originate physician requests for medical information in order to send unsolicited information to physicians.

39. In or about June 2002, in or about November 2003, and at other times, **HOLLOWAY** instructed the sales force to send out unsolicited letters known as Medical Inquiry Letters (also known as the "Medical Letter" or "Medical Inquiry Response") to, among others, groups of physicians who prescribed a lot of Vioxx. These letters were issued by Pharmco as if they were responses to physicians' unsolicited inquiries.

40. **HOLLOWAY** instructed her sales team to send the Medical Inquiry Letters to top Vioxx prescription writers who had not made requests for the letters, including by instructing their teams to send them to "Every Vioxx Loyalist," even though **HOLLOWAY** knew it was contrary to company policy to send these letters unsolicited.

41. At the direction of **HOLLOWAY**, Pharmco sales representatives sent unsolicited Medical Letters promoting the use of Bextra for unapproved uses and dosages to physicians.

Interstate Distribution of Bextra

42. Pharmco manufactured Bextra in Puerto Rico and distributed Bextra into interstate commerce throughout the United States, including specifically into Massachusetts, from in or about December 2001 until approximately April 2005.

COUNT ONE

**(Distribution of a Misbranded Drug:
21 U.S.C. §§ 331(a), 333(a)(1) & 352(f))**

43. The allegations in paragraphs 1 through 42 of this Information are realleged and incorporated herein by reference.

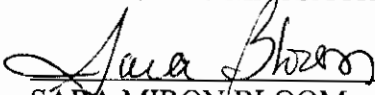
44. Beginning as early as in or about December 2001, and continuing thereafter until at least in or about April 2005, in the District of Massachusetts and elsewhere, the defendant,

MARY HOLLOWAY,

did introduce, deliver for introduction, and cause the introduction into interstate commerce, into Massachusetts and elsewhere, quantities of Bextra, a drug within the meaning of the FDCA, 21 U.S.C. § 321(g), 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.

All in violation of 21 U.S.C. §§ 331(a), 333(a)(1) and 352(f).

MICHAEL J. SULLIVAN
UNITED STATES ATTORNEY
DISTRICT OF MASSACHUSETTS



SARA MIRON BLOOM
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ASSISTANT U.S. ATTORNEYS

Dated: *March 30, 2009*