

UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA)
)
v.) Case Number: 09-cr-10089-JGD
)
MARY HOLLOWAY,)
)
Defendant.)

MARY HOLLOWAY’S SENTENCING MEMORANDUM

Introduction

Mary Holloway (“Ms. Holloway”) respectfully submits this memorandum in support of the government and her joint recommendation of a probationary sentence and fine for her misdemeanor violation of the Food, Drug and Cosmetic Act. As the Court is aware, the charge against her is based on the sale and marketing of Bextra, a pain relief medication, in a manner inconsistent with its FDA-approved indications. As explained herein, Ms. Holloway believed at all times that her actions in this regard as a Regional Sales Manager at Pfizer were lawful and indeed consistent with how Pfizer wanted her to promote and sell the product.

Personal Background Information

Ms. Holloway grew up in a middle-class suburb of Cleveland, Ohio, the sixth of seven girls in the family. She had a happy and stable childhood, with one notable exception; Ms. Holloway’s younger sister Janet, with whom she was very close, died of brain cancer at age 10. The death of her sister had a formative impact on Ms. Holloway’s career. After graduating college, Ms. Holloway’s first full-time job was working for the American Cancer

Society. Ms. Holloway's belief in the curative and life-enhancing power of drugs led her in 1988 to a pharmaceutical job. She has remained in that industry for the last two decades.

Ms. Holloway and her husband Dennis recently celebrated their twenty-first wedding anniversary, and enjoy spending time with their close family members and friends. In particular, Ms. Holloway feels very close with her seventeen-year old niece, whom Ms. Holloway recently cared for while she recovered from a traumatic brain injury. Both Ms. Holloway and her husband have also developed close ties in their New Jersey community, where they have lived for more than twelve years, and where Ms. Holloway currently volunteers at a local hospital.

Ms. Holloway takes great pride in her achievements as a pharmaceutical company sales representative and sales manager. In one period of seven years at Pfizer, she received four promotions, the last of which elevated her to Regional Sales Manager. In fact, Ms. Holloway has the distinction of being one of the first five females at Pfizer to be promoted to the position of Regional Sales Manager. In that capacity, she supervised approximately 100 sales representatives, district managers and others in the Northeast Region of Pfizer's Powers Division. She became a standout at Pfizer not only for her knowledge of Pfizer's products and leadership skills, but also for her concern for her employees and willingness to mentor them. In particular, Ms. Holloway served as a role model for women who were striving to succeed in their career while maintaining balance in their lives. By all accounts Ms. Holloway was a model employee and leader, praised for her job performance and appreciated for her guidance. Attached as Exhibit A to this memorandum is a sampling of the praise and expressions of

gratitude that Ms. Holloway has received over the years from superiors, peers and subordinates.

Sale and Marketing of Bextra

Bextra is Pfizer's trade name for the drug valdecoxib, a COX-2 inhibitor. COX-2 inhibitors relieve pain and inflammation without the negative gastrointestinal side effects of nonsteroidal anti-inflammatory drugs ("NSAIDs") such as aspirin and ibuprofen. In November 2001, the Food and Drug Administration ("FDA") approved Bextra to treat the signs and symptoms of osteoarthritis, adult rheumatoid arthritis, and primary dysmenorrhea, an acute premenstrual pain condition.

Doctors routinely prescribe medications for unapproved, so-called "off-label" uses where such a prescription would be beneficial to the patient. Although Bextra was approved by the FDA for only the three above-noted indications, physicians had good reasons to prescribe Bextra for a variety of off-label uses. For one reason, although Merck's competing COX-2 inhibitor Vioxx was approved for treatment of acute pain and Bextra was not, Bextra's FDA-approved labeling arguably reflected a safer cardiovascular profile than Vioxx's.¹

The instant Information focuses on three courses of conduct related to promoting unapproved uses and dosages of Bextra: promoting Bextra to prevent blood clots known as deep vein thromboses ("DVT") (§§34-37); promoting Bextra for surgical pain with protocols and standing orders (§§27-33); and using Medical Inquiry Letters to promote unapproved uses

¹ For example, Bextra's label stated that the incidence of hypertension in arthritis patients taking 40 mg of Bextra is not statistically different from that in arthritis patients taking 1,000 mg of the NSAID naproxen. In contrast, the Vioxx label stated that the incidence of hypertension was twice as high in arthritis patients taking Vioxx at 25 mg. (a dose comparable to Bextra's 10 mg. dose) as in arthritis patients taking 1,000 mg. of naproxen.

and dosages (¶¶38-41). Only one of these courses of conduct, the so-called “DVT Message,” was initiated by Ms. Holloway, and the DVT Message had a sound medical basis.

1. Promotion of Bextra to prevent blood clots, known as deep vein thromboses

The DVT Message was responsibly developed after consultation with prominent clinicians, including a Pfizer consultant. In April 2002, Pfizer, through Ms. Holloway, presented a \$100,000 research grant to a consultant whose Pfizer-sponsored research focused on the use of COX-2 inhibitors, instead of narcotics, for postoperative pain control in joint replacement patients. The underlying rationale for his study was that the sedative side effects of narcotics prevented joint replacement patients from early mobilization and ambulation after surgery. The inability to walk in turn promoted the occurrence of blood clots. By replacing narcotics with COX-2’s, the consultant aimed to reduce the administration of potentially hazardous medications and to increase patient ambulatory and rehabilitation potentials.

During a meeting, the consultant explained to Ms. Holloway the science underlying the study, and the benefits of incorporating COX-2 inhibitors into an overall DVT prophylaxis regimen. Shortly after this discussion, Ms. Holloway prepared a “DVT Backgrounder” that summarized the information gleaned from the meeting and internally circulated the document to her sales team. The Backgrounder covered general background information about DVT, such as common risk factors and prophylactic regimens, and explained how, as part of a multi-modal treatment plan, Pfizer’s COX-2 portfolio could help orthopedic surgeons reduce the risk of DVT in their joint replacement patients.

After her initial exposure to the DVT Message, Ms. Holloway initiated further contact with the Pfizer consultant to make sure she understood it. She also met with another

orthopedic surgeon for validation. Then, to ensure that the message was properly taught to her district managers and hospital representatives, Ms. Holloway arranged for the consultant to lecture them directly on the topic. As is evident, at all times, Ms. Holloway acted in good faith and with the clear intent to convey a truthful and scientifically grounded message.

In addition to being championed by medical experts, the DVT Message was consistent with medical literature. Total joint replacement procedures are frequently used to repair arthritic joints. By 2002, it was recognized that orthopedic surgical patients have an extremely high risk of developing DVT. At least one study concluded that patients undergoing a total joint replacement are particularly prone to thromboembolic complications with potentially life-threatening consequences.² Further studies have shown that, without preventive treatment, as many as 80 percent of orthopedic surgical patients would develop DVT.³ Clearly, DVT is a significant issue for orthopedic surgeons and joint replacement patients.

Stripped to its essence, the DVT Message was an early ambulation message. The message was not that Bextra or Celebrex treated or prevented the DVT disease state. Rather, the message was simply that incorporating COX-2 inhibitors into a prophylactic regimen helped address stasis by reducing pain and thereby getting frequently arthritic joint replacement patients out of bed.

Indeed, the company publicized such findings. In February 2002, Pfizer issued a press release boasting that a new study suggested that Bextra was an effective morphine-sparing analgesic in knee replacement surgery. That same day, another Pfizer regional sales manager

² Thomas P. Sculco, *Prophylaxis Against Thromboembolytic Disease in Patients Having a Total Hip or Knee Arthroplasty*, 84 J. of Bone and Joint Surgery, 466 (2002).

³ See American Academy of Orthopaedic Surgeons, *Deep Vein Thrombosis*, available at: <http://orthoinfo.aaos.org/topic.cfm?topic=a00219> (last visited June 1, 2009).

circulated a copy of the press release to Ms. Holloway, among others. The study referenced in the press release claimed that Bextra can be used successfully as part of a multimodal treatment strategy for pain management following knee replacement surgery, reducing opioid use, while providing improved pain relief and increasing patient satisfaction with analgesic treatment.⁴ Even more recently, a New York Times article published in January of this year highlighted the devastating consequences that often result from lack of ambulation after surgery.⁵

Ms. Holloway believed at the time, and the evidence she gathered indicated, that surgical patients could derive significant health benefits from taking Bextra before and after surgery. While she understands and accepts fully her responsibility for the impropriety of her conduct, Ms. Holloway highlights that she sought to help disseminate what she believed was a salutary message from the medical community. As such, she respectfully requests that the Court consider in imposing her sentence the overall context in which the DVT Message was disseminated.

2. Use of pain management protocols and standing orders

The circumstances surrounding Ms. Holloway's instructions with regard to hospital protocols are likewise worthy of the Court's attention. Protocols and standing orders are written instructions to physicians or other healthcare professionals that are not specific to a single patient. The benefit to a company in having its product on a protocol or standing order is obvious, because the product becomes the medicine of choice for all patients to whom the instructions apply. The implementation of a marketing plan to obtain Bextra protocols and

⁴ Lowell Reynolds, *The Cox-2 Specific Inhibitor, Valdecoxib, Is An Effective, Opioid-Sparing Analgesic in Patients Undergoing Total Knee Arthroplasty*, Journal of Pain and Symptom Management, Vol. 25, No.2 (Feb. 2003) at p. 140 (emphasis supplied).

standing orders was a company-wide initiative, not a Northeast Region initiative, and certainly not a Mary Holloway initiative.

Pfizer actively promoted the use of protocols as a means to grow market share. No later than 2002, Pfizer had instructed its regional managers to use protocols as a means to increase COX-2 sales. In 2003, regional managers were required to track protocols obtained in their territory and report back to the Company. As such, and no differently from any other, Ms. Holloway's region dutifully reported Bextra protocols attained for orthopedic, podiatry, urology, ob/gyn, ENT and dental indications, where much of the usage was off-label. Corporate tracked this information, and at no time did it inform Ms. Holloway that any of the reported protocols were inappropriate. Instead, the instruction was to get more protocols. Indeed, to ensure compliance with its corporate message, Pfizer sales representatives and sales managers were evaluated based on their ability to obtain protocols, and regions received positive recognition and public praise at Plan of Action ("POA") sales meetings for having obtained such protocols in their territory.

At one such meeting, Ms. Holloway and another Regional Manager gave a presentation that included a discussion of protocols and standing orders adopted by various medical practices and hospitals. (Notably, the majority of the protocols were from Portland, Oregon -- far from Ms. Holloway's region.) The packet of protocols was called "COX 2 Protocols and Standing Orders - Best Practices." Ms. Holloway did not create the protocols, nor did she instruct anyone to obtain off-label protocols during her presentation. In fact, every single page of the packet was clearly marked "not for detail," i.e. not to be used as sales material.

⁵ Gina Kolata, *A Tactic to Cut I.C.U. Trauma: Get Patients Up*, N.Y. Times, Jan. 11, 2009.

However, as part of her segment, Ms. Holloway spoke about Bextra protocols in the peri-operative setting, which included off-label uses.

As a clear sign of corporate endorsement, two of Ms. Holloway's superiors complimented her for the presentation. Moreover, one Pfizer Medical Director in attendance wrote to another Medical Director that "Mary Holloway was awesome" at the meeting. In accordance with Pfizer practice, Ms. Holloway forwarded adopted protocols to her regional sales force. This collection and dissemination of protocols was not limited to Ms. Holloway's Northeast region, but took place across the various sales regions.⁶ It was part of the Pfizer culture.

In following this practice, Ms. Holloway occasionally forwarded a protocol with off-label uses. The Information describes one such occasion in which Ms. Holloway praised the employee who obtained the protocol. (Information ¶33). However, Ms. Holloway was actually praising the employee's initiative in obtaining a protocol for multiple areas of surgery, not the fact that these uses were off-label.

Ms. Holloway did not prepare any of the forwarded protocols and had no control over the content. Rather, in adopting a protocol, each medical professional presumably exercised independent professional judgment to develop appropriate practices and procedures. Such professional judgment included the ability to legally prescribe a drug, such as Bextra, in an off-label manner.

⁶ According to one POA slide deck, Pfizer reported that as of January 2003, 42 protocols had been obtained in Dallas and another 137 protocols were obtained in the Great Lakes region. Furthermore, Pfizer produced a 36-page presentation of sample and actual protocols, most of which were obtained from the Portland, Oregon territory. Other protocols from Pennsylvania and Florida have also been identified.

Based on the foregoing and other interactions with senior management and in-house Pfizer physicians, Ms. Holloway believed that her territory's protocol efforts were consistent with the corporate strategy. In pursuing protocols, Ms. Holloway did so as a middle manager following corporate direction. At all times, she believed it was appropriate for her representatives to solicit protocols from health care professionals, and for her and other sales managers to circulate them.

3. Dissemination of Medical Inquiry Letters

"Medical Inquiry Letters" at Pfizer are descriptions of on-label and off-label product usage and disease states that are prepared by health care professionals and scientists. The Information alleges that Ms. Holloway caused her sales force to send unsolicited Medical Inquiry Letters to physicians containing information about off-label uses of Bextra. (Information ¶¶38-41). In particular, the charging document focuses upon a statement in a slide deck that "Every Vioxx Loyalist" should receive the "Medical Letter..." (*Id.* ¶40; *see also id.* ¶39.).

The slide deck at issue was a collective presentation of six Pfizer sales divisions, and the slide quoted in the Information may not even relate to Bextra. Moreover, the Information does not allege that Ms. Holloway played any role in creating the company's Medical Inquiry Letters, or that these letters contained false or misleading information about Bextra and its uses. The PowerPoint slide quoted in the Information states the following:

"Every Vioxx Loyalist Gets the Medical Letter

(Specialty = Pro/Powers/Searle, P C = Alta, Upjohn, Roerig)

Place in team notes when completed."

Pro, Powers, Searle, Alta, Upjohn and Roerig were all divisions within Pfizer at the time. Ms. Holloway was Regional Sales Manager for only one of these divisions, the Powers Division.

While Ms. Holloway does not recall how this particular slide deck was created, the practice for such regional presentations was that the regional managers of the various divisions would collectively adapt the company-wide message into a coordinated regional message. For consistency, one regional manager would act as a scrivener and prepare three or four slides summarizing the group message. Each regional manager would then comment on the slides and the group would eventually agree on a final slide deck. Therefore, the substance of any slide cannot fairly be attributed solely to Ms. Holloway.

Moreover, given the timing of the presentation and the content of the slide, the medical letter referenced in the slide was probably a Celebrex letter, not a Bextra letter. Unlike Bextra, Celebrex had FDA approval at the time for treatment of acute pain. Therefore, comparisons of Vioxx and Celebrex for the treatment of acute pain were not even inherently off-label.

The Information does not allege that any Medical Inquiry Letter created for Bextra contained false or misleading information. On the contrary, these letters provided important medical and scientific information to doctors. While FDA rules explicitly allow the dissemination of fair, balanced information about off-label uses only in response to unsolicited requests by medical professionals, one can fairly question whether this sentencing on a misdemeanor conviction can or should be the forum to decide to prohibit the dissemination of

accurate medical and scientific information, regardless of whether a health care professional initiates the request.

These three courses of conduct represent the basis for the instant Information. The parties stipulated to an adjusted offense level of 4: a base level of 6 and a two-level reduction under USSG § 3E1.1 for Ms. Holloway's prompt acceptance of personal responsibility for the actions described above. Pursuant to the Sentencing Guidelines in effect as of November 1, 2008, the fines for individual defendants facing an offense level of 4 should fall between \$250 and \$5,000. The maximum fine allowed by statute is \$100,000. Ms. Holloway agreed to a stipulated fine of \$75,000.

Cooperation With The Government

There is some irony in the fact that to date, Ms. Holloway has been singled out as the lone Pfizer sales manager to be charged with off-label promotion of Bextra. When Ms. Holloway heard in September 2004 that three sales representatives in one of her districts had deleted information from their computers, she immediately reported this information to her direct superior. Indeed, Ms. Holloway's good-faith action in reporting to her supervisor that employees in her region had allegedly deleted information from their computers likely led to the government investigation that focused on her region. This may be one reason why Ms. Holloway was ultimately singled out for off-label sales and marketing activity, although Ms. Holloway was not the only Pfizer employee engaged in this activity. Similarly, while represented by prior counsel, Ms. Holloway voluntarily testified before the federal grand jury investigating the Bextra case, without requesting immunity. Even after the government

focused on her, Ms. Holloway readily signed each tolling agreement requested by the government.

Unfortunately for Ms. Holloway, her cooperation did not dissuade the government from charging her in this misdemeanor case. However, this cooperation should be considered by this Court in imposing an appropriate sentence.

Respectfully submitted,
MARY HOLLOWAY
By her attorneys,

/s/ Robert L. Ullmann

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CERTIFICATE OF SERVICE

I hereby certify that on June 12, 2009, a true copy of the above document was electronically served on attorneys for the government and was served by hand on the U.S. Probation Office.

/s/ Robert L. Ullmann
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