CIRCUIT COURT OF OREGON

MARION COUNTY

IN THE MATTER OF:

PFIZER INC

Case No. 12C25574

ASSURANCE OF VOLUNTARY COMPLIANCE

1. This Assurance of Voluntary Compliance ("AVC") is an agreement between Pfizer Inc ("Pfizer") and the Oregon Department of Justice ("ODOJ") acting pursuant to ORS 646.632.

2. In March 2012, Pfizer and ODOJ entered into an Assurance of Voluntary Compliance ("the March 2012 AVC") regarding sponsored internet links. Paragraph 7 of the AVC provides that "Pfizer shall ensure that it complies with 21 U.S.C. 352(a) & (n), and 21 C.F.R. 202.1(e)(1)-(5), including future amendments to those statutes and rules." A copy of the March AVC is attached as Exhibit 1.

3. In May 2012, FDA's Office of Prescription Drug Promotion issued a Warning Letter to Pfizer regarding a television direct-to-consumer advertisement for the prescription drugs EpiPen® and EpiPen Jr® Auto-Inject. These Pfizer products are promoted and distributed by Mylan Specialty, L.P. per its agreement with Pfizer. In this Warning Letter, FDA alleged that "The TV ad is false and misleading because it overstates the efficacy of the drug product. Thus, the TV ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(n), and FDA implementing regulations. 21 CFR 202.1(e)(6)(i). This violation is particularly alarming from a public health perspective because the misleading presentation of the use of EpiPen may result in serious consequences, including death." A copy of this Warning Letter is attached as Exhibit 2.

4. In June 2012, FDA's Office of Prescription Drug Promotion issued an untitled letter to Pfizer relating to a direct-to-consumer brochure for the prescription drug Zmax®. The letter alleged that the "brochure is false or misleading because it omits and minimizes important risk information, makes unsubstantiated superiority claims, omits material facts, broadens the indication for the drug product, makes misleading efficacy claims, and makes unsubstantiated claims for Zmax. Therefore, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C), 21 U.S.C. 352(a); 321(n). *Cf.* 21 CFR 202.1(e)(5)(i)&(iii);(e)(6)(i)&(ii);(e)(7)(i) & (viii)." A copy of this letter is attached as Exhibit 3.

5. This AVC resolves the ODOJ's allegations that the Zmax brochure that was the subject of the untitled letter described in Paragraph 4 above violated the October 2008 Stipulated General Judgment resolving prior litigation between Pfizer and the State of Oregon regarding Bextra ("2008 Judgment"). A copy of the 2008 Judgment is attached as Exhibit 4. This AVC also resolves ODOJ's concern's that the advertisement that was the subject of the Warning Letter described in Paragraph 3 above (the EpiPen advertisement") violated the March 2012

AVC and the 2008 Bextra Judgment. Effective immediately upon execution of this AVC, Pfizer agrees to adhere to each of the following requirements:

a. To resolve concerns that Pfizer violated the March 2012 AVC, Pfizer shall pay ODOJ one million dollars ($1,000,000) within seven days of the execution of this agreement for deposit to the Department of Justice Account established pursuant to ORS 180.095 to be used by ODOJ as provided by law.

b. Comply with Paragraph 8 of the 2008 Judgment. Paragraph 8 provides that "Pfizer agrees to submit all new DTC television advertising campaigns for an Pfizer Product to FDA for Pre-review, to wait a reasonable time (not less than 45 days) until Pfizer receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any written comments from FDA, whenever received. Simultaneous with running any new DTC television advertisement for which FDA has not provided Pfizer with a pre-review response addressing the substance of the advertisement with the 45-day waiting period described herein, Pfizer shall provide written notice to the Oregon Attorney General and other members of the Multistate Executive Committee that Pfizer is running the advertisement and that the FDA has not provided Pfizer with a pre-review response addressing the substance of the advertising within the 45-day waiting period, and also provide a copy of all material submitted to FDA for the review of the subject advertisement." To ensure future compliance with Paragraph 8 of the Stipulated General Judgment, Pfizer shall also be required to pay ODOJ an additional civil penalty of $1,000,000 to the Department of Justice Account established pursuant to ORS 180.095, provided, however, that this payment is not due at the time of the execution of this agreement and shall be suspended so long as Pfizer complies with the obligations of Paragraph 8 of the Stipulated General Judgment. At such time that Pfizer's obligations under Paragraph 8 expire, pursuant to Paragraph 5(c) of this agreement, suspended penalty shall also expire.

c. The seven year time period which Paragraph 9 of the 2008 General Judgment provides as the time period for Pfizer's obligations under Paragraph 8 of the 2008 Judgment shall be extended for an additional 18 months.

d. Pfizer shall disseminate corrective advertising that addresses the issues identified in the Warning Letter described in Paragraph 3. The corrective advertising program shall consist of a television advertisement that has been approved by FDA and that was reviewed by the Attorney General prior to submission of this AVC. The television advertisement shall be broadcast on national and network television; its dissemination shall be equal to or greater than the advertisement that was the subject of the Warning Letter. The specific content and timing of this corrective advertising campaign shall be as specified and approved by FDA and reviewed by the Attorney General.

e. All Zmax direct-to-consumer advertising in any medium shall clearly and conspicuously disclose: "Zmax does not work against infections caused by viruses or the flu. Only your doctor can determine whether an antibiotic is indicated."

f. Zmax direct-to-consumer advertisements shall not cite patient survey data that are not permitted under the FD&C Act, 21 U.S.C.§ 301 *et seq*, accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA or by Oregon state or federal courts interpreting these provisions.

g. For all Pfizer prescription drug products, Pfizer shall not make claims about patient preferences that are not permitted under the FD&C Act, 21 U.S.C.§ 301 *et seq*, accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA or by Oregon state or federal courts interpreting these provisions.

6. This AVC is a settlement of a disputed matter. Pfizer is entering into this AVC solely for the purpose of settlement, and nothing contained herein may be taken as or construed to be an admission or concession of any violation of law, rule, or regulation, or of any other matter of fact or law, or of any liability or wrongdoing, all of which Pfizer expressly denies. . However, while not admitting a violation or any other matter of fact or law, Pfizer expresses regret for any confusion that may have been caused by the dissemination of the advertisements that are the subject of this AVC. Pfizer and ODOJ agree that no provision of this AVC operates as a penalty, forfeiture, or punishment under the laws of the United States, the laws of Oregon, or any other laws or regulations.

APPROVAL BY COURT

APPROVED FOR FILING and SO ORDERED this 20th day of December, 2012.

Circuit Court Judge

REVIEW BY PFIZER'S ATTORNEY

Approved as to form.

Michael (Sam) Sandmire
Attorney for Pfizer

PFIZER'S SIGNATURE AND ACKNOWLEDGMENTS

Corporate Pfizer

I, _____ being first duly sworn on oath depose and say that I am the _____ of Pfizer Inc. and am fully authorized and empowered to sign this Assurance of Voluntary Compliance on behalf of Pfizer Inc. and bind the same to the terms hereof.

Gary F. Giampetruzzi

Print Name

Vice President + Ass't General Counsel

Title

Address 235 East 42nd Street
New York, N.Y. 10017

SUBSCRIBED AND SWORN to before me this 18 day of December, 2012.

JOHN J BLAKEY NOTARY PUBLIC STATE OF NEW YORK NO. 01BL6152271 QUALIFIED IN KINGS COUNTY COMM. EXP. 09/05/2014

Notary Public for New York

ACCEPTANCE OF DOJ

Accepted this 18 day of December, 2012.

ELLEN ROSENBLUM
Attorney General

David A. Hart OSB #002750
Assistant Attorney-in-Charge
Oregon Department of Justice
Financial Fraud/Consumer Protection Section
Of Attorneys for Plaintiff
1515 SW Fifth Ave, Suite 410
Portland, OR 97201

Phone: (971) 673-1880
Fax: (971) 673-1882
Email: david.hart@doj.state.or.us

CIRCUIT COURT OF OREGON

~~MULTNOMAH~~ Marion COUNTY

IN THE MATTER OF:	Case No. 12C13402
PFIZER INC	ASSURANCE OF VOLUNTARY COMPLIANCE

1. This Assurance of Voluntary Compliance ("AVC") is an agreement between Pfizer Inc ("Pfizer") and the Oregon Department of Justice ("ODOJ") acting pursuant to ORS 646.632.

2. In October 2008, Pfizer and the ODOJ entered into a Stipulated General Judgment resolving prior litigation between Pfizer and the State of Oregon regarding the medication Bextra (the "Stipulated General Judgment"). Paragraph 5 of the Stipulated General Judgment provides: "Pfizer shall not make any written or oral promotional claims of safety or effectiveness for any FDA-approved Pfizer Product in a manner that violates the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. ("FDCA"), accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA."

3. On March 26, 2009, FDA's Division of Drug Marketing, Advertising and Communications ("DDMAC") (DDMAC has been renamed Office of Prescription Drug Promotion) issued untitled letters to 14 pharmaceutical companies, including Pfizer, pertaining to the use of sponsored links on internet search engines. In these letters, DDMAC alleged that the companies' sponsored links at issue did not adequately communicate information regarding the drugs' indications and risks.

4. On August 31, 2011, DDMAC issued an untitled letter to Pfizer which cited a Lipitor "Online Resources" webpage (hereinafter "Online Resources Webpage") accessible from the Lipitor.com website that included three internet links referencing Caduet, Chantix and Norvasc. DDMAC alleged that the references in the three internet links did not adequately communicate information regarding the drugs' risks. Any visitor to the Online Resources Webpage who clicked on the internet links was directed to either Pfizer branded websites or approved labeling, all of which are fully compliant with the FDCA and FDA regulations.

5. This AVC resolves the ODOJ's concerns that Pfizer's use of sponsored links and internet links as described in the two untitled letters discussed in Paragraphs 3 and 4 above violated Paragraph 5 of the Stipulated General Judgment.

DEPARTMENT OF JUSTICE
1515 SW Fifth Ave, Suite 410
Portland, OR 97201
(971) 673-1880 / FAX: (971) 673-1884

6. Effective immediately upon execution of this AVC, Pfizer agrees to adhere to each of the following requirements:

   a. Pfizer shall ensure that it complies with 21 U.S.C. 352(a) & (n), and 21 C.F.R. 202.1(e)(1)-(5), including future amendments to those statutes and rules.

   b. When promoting online in any format, including in sponsored links and internet links as described in Paragraphs 3 and 4 above, Pfizer shall comply with the FDCA and all applicable FDA regulations.

   c. Pfizer shall refrain from internet promotion that is inconsistent with DDMAC's position set forth in the two untitled letters described in Paragraphs 3 and 4 above, unless and until FDA's Office of Prescription Drug Promotion (formerly DDMAC) changes its position.

7. The AVC is a settlement of a disputed matter. It shall not be considered an admission of a violation for any purpose. Pfizer and ODOJ agree that no provision of this AVC operates as a penalty, forfeiture, or punishment under the laws of the United States, the laws of Oregon, or any other laws or regulations.

APPROVAL BY COURT

APPROVED FOR FILING and SO ORDERED this ___ day of _____, 2012.

_____
Circuit Court Judge

REVIEW BY PFIZER'S ATTORNEY

Approved as to form.

_____
Michael J. (Sam) Sandmire
Ater Wynne LLP
Attorney for Pfizer Inc

DEPARTMENT OF JUSTICE
1515 SW Fifth Ave, Suite 410
Portland, OR 97201
(971) 673-1880 / FAX: (971) 673-1884

PFIZER'S SIGNATURE AND ACKNOWLEDGMENT

Corporate Pfizer

I, Bradley E. Lerman, being first duly sworn on oath depose and say that I am the a Senior Vice President and Associate General Counsel of Pfizer Inc. and am fully authorized and empowered to sign this Assurance of Voluntary Compliance on behalf of Pfizer Inc. and bind the same to the terms hereof.

Bradley E. Lerman
Senior Vice President and
Associate General Counsel
Pfizer Inc
235 East 42nd Street
New York, NY 10017

SUBSCRIBED AND SWORN to before me this 14th day of March, 2012.

Katia Conte
Notary Public for New York

KATIA CONTE
Notary Public, State of New York
No. 01CO6041281
Qualified in Suffolk County
Commission Expires July 25, 2014

ACCEPTANCE OF DOJ

Accepted this 16th day of March, 2012.

JOHN R. KROGER
Attorney General

David A. Hart OSB #002750
Assistant Attorney-in-Charge
Oregon Department of Justice
Financial Fraud/Consumer Protection Section
Of Attorneys for Plaintiff
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Ian C. Reed
Chairman and Chief Executive Officer
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

RE: **NDA # 019430**
EpiPen® and EpiPen® Jr. (epinephrine) Auto-Injectors
MA # 388

WARNING LETTER

Dear Mr. Reed:

The Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP) of the U.S. Food and Drug Administration (FDA) has reviewed a 60-second Direct-to-Consumer broadcast television advertisement (TV ad) distributed by Mylan Specialty, L.P. (Mylan) on behalf of Pfizer, Inc. (Pfizer)[1] entitled "Max's Birthday Party" (EPI12-1003) for EpiPen® and EpiPen® Jr. (epinephrine) Auto-Injectors (EpiPen). The TV ad was submitted as a complaint to the OPDP Bad Ad Program. The TV ad is false and misleading because it overstates the efficacy of the drug product. Thus, the TV ad misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(n), and FDA implementing regulations. 21 CFR 202.1(e)(6)(i). This violation is particularly alarming from a public health perspective because the misleading presentation of the use of EpiPen may result in serious consequences, including death.

Background[2]

Below is the indication and summary of the most serious and most common risks associated with the use of EpiPen. According to the FDA-approved EpiPen product labeling (PI) (in pertinent part):

> EpiPen® and EpiPen® Jr Auto-Injectors are indicated in the emergency treatment of allergic reactions (Type I) including anaphylaxis to stinging insects...and biting insects...allergen immunotherapy, foods, drugs, diagnostic testing

[1] Mylan Specialty, L.P. (f/k/a Dey Pharma, L.C.) holds the exclusive license from Meridian Medical Technologies, Inc, a subsidiary of Pfizer, to market, sell, and distribute EpiPen in the United States.
[2] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.

> substances...and other allergens, as well as idiopathic anaphylaxis or exercise-induced anaphylaxis. EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate administration in patients, who are determined to be at increased risk for anaphylaxis, including individuals with a history of anaphylactic reactions.
> ...
>
> EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy only and are not a substitute for immediate medical care.

EpiPen is associated with a number of serious risks. According to the PI, EpiPen has Warnings pertaining to the administration, accidental injection, sulfite allergy, and cardiovascular disease, and proper use and storage conditions. In addition, there are Precautions regarding the need for immediate medical care after using EpiPen; caution in patients who have cardiac arrhythmia, coronary artery or organic heart disease; greater risk of developing adverse reactions after epinephrine administration in patients who have hyperthyroidism, cardiovascular disease, hypertension, or diabetes, in elderly, pregnant women, or pediatric patients who require epinephrine doses greater than 0.01 mg/kg; caution with concomitant administration of cardiac glycosides, diuretics, anti-arryhythmics, alpha-and beta-adrenergic blocking agents, tricyclic antidepressants, monoamine oxidase inhibitors, levothyroxine sodium, and certain antihistamines.

Adverse reactions observed with EpiPen are anxiety, apprehensiveness, restlessness, tremor, weakness, dizziness, sweating, palpitations, pallor, nausea and vomiting, headache, respiratory difficulties, arrhythmias, hypertension, and angina.

Overstatement of Efficacy

Promotional materials are misleading if they contain representations or suggestions that a drug is better or more effective than has been demonstrated by substantial evidence or substantial clinical experience. The TV ad includes the following presentation (bolded emphasis original):

- Mother: "Excited for Max's birthday party? Should be pretty awesome."
- Son: "Yeah!"
- Mother: "Even with your peanut allergy and a cake made of who-knows-what."

  SUPER (over visual): EpiPen® (epinephrine) Auto-Injector can't eliminate the risk of anaphylaxis. [frames 1 to 2]

- Mother: "Because we're prepared, right Jake?"
- Son: "Yup!"
- Mother: "With EpiPen."

SUPER (over visual): Be prepared. With EpiPen®. EpiPen® (epinephrine) Auto-Injector can't eliminate the risk of anaphylaxis. [frame 3]

The overwhelming impression conveyed by this presentation in the TV ad is that EpiPen *alone* can provide assurance that a child who has a history of life-threatening allergic reactions does not need to worry or take precautionary measures to avoid exposure to allergens. Specifically, the TV ad misleadingly suggests that a child who has a peanut allergy can take a chance eating a piece of birthday cake with unknown ingredients and feel completely free from worry about any potential risk of anaphylaxis if prepared with EpiPen. This claim is misleading because it implies that EpiPen *alone* obviates the need for taking precautionary measures and provides protection against any potential risks due to exposure to an allergen, when this has not been demonstrated by substantial evidence or substantial clinical experience. According to the INDICATIONS and USAGE section of the PI (emphasis added), "EpiPen® and EpiPen® Jr Auto-Injectors are intended for immediate self-administration as emergency supportive therapy . . . ." In addition, the **What is the most important information I should know about EpiPen® and EpiPen® Jr Auto-Injector** section of the FDA-approved Patient Labeling states (bolded emphasis original, underlined emphasis added), "**When you have an allergic reaction (anaphylaxis) use the EpiPen® or EpiPen® Jr Auto-Injector right away and immediately go to your doctor or emergency room for more medical treatment.**" We note the SUPER, "EpiPen® (epinephrine) Auto-Injector can't eliminate the risk of anaphylaxis." However, this does not mitigate the overall misleading impression. The standard of care to prevent a potentially life-threatening anaphylactic reaction is to take precautionary measures to avoid the allergen.

Conclusion and Requested Action

For the reasons described above, the TV ad misbrands EpiPen in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(n), and FDA implementing regulations. 21 CFR 202.1(e)(6)(i).

OPDP acknowledges that, following a teleconference with OPDP and Pfizer on April 20, 2012, during which OPDP outlined its serious concerns with the piece discussed above, Pfizer committed to comply with OPDP's request to immediately cease the dissemination of this material and any materials with the same or similar claims for EpiPen. We appreciate this commitment and the steps that Pfizer has taken thus far to address some of the issues outlined in this letter.

OPDP requests that Pfizer submit a written response to this letter on or before June 7, 2012, listing all promotional materials (with the 2253 submission date) for EpiPen that contain the same or similar claims for EpiPen described above and discussed during the April 20, 2012, teleconference, and explaining your plan for discontinuing use of such violative materials. Because the violation described above is serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. In order to clearly identify the violative promotional

piece(s) and/or activity and focus on the corrective message(s), OPDP recommends that corrective piece(s) include a description of the violative promotional piece(s) and/or activity, include a summary of the violative message(s), provide information to correct each of the violative message(s), and be free of promotional claims and presentations. To the extent possible, corrective messaging should be distributed using the same media, and generally for the same duration of time and with the same frequency that the violative promotional material was disseminated.

Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Direct-to-Consumer Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and the Division of Consumer Drug Promotion (DCDP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to MA # 388 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for EpiPen comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

{See appended electronic signature page}

Robert Dean, MBA
Division Director
Division Consumer Drug Promotion
Office of Prescription Drug Promotion

cc: John Thievon
President
Mylan Specialty L.P.
110 Allen Road, 4th Floor
Basking Ridge, NJ 07920

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT T DEAN
05/24/2012

Reference ID: 3135644

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Brian E. Harvey, M.D., Ph.D.
Vice President, U.S. Regulatory Strategy
Pfizer Inc.
235 East 42nd Street
New York, NY 10017

RE: **NDA # 050797**
Zmax® (azithromycin extended release) for oral suspension
MA #175

Dear Dr. Harvey:

As part of its routine monitoring and surveillance program, the Office of Prescription Drug Promotion (OPDP), Division of Consumer Drug Promotion (DCDP) of the U.S. Food and Drug Administration (FDA) has reviewed a "1 Day. 1 Dose" Brochure (ZMU00162APDF/282549-01) (brochure) for Zmax® (azithromycin extended release) for oral suspension (Zmax) submitted by Pfizer Inc. (Pfizer) under cover of Form FDA-2253. The brochure is false or misleading because it omits and minimizes important risk information, makes unsubstantiated superiority claims, omits material facts, broadens the indication for the drug product, makes misleading efficacy claims, and makes unsubstantiated claims for Zmax. Therefore, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a); 321(n). *Cf.* 21 CFR 202.1(e)(5)(i) & (iii); (e)(6)(i) & (ii); (e)(7)(i) & (viii).

Background

Below are the indication (in pertinent part), and summary of the most serious and most common risks associated with the use of Zmax.[1,2]

Zmax is indicated for the treatment of mild to moderate infections caused by susceptible isolates of the designated microorganisms in the specific conditions listed below:

- **Acute bacterial sinusitis** in adults due to *Haemophilus influenzae, Moraxella catarrhalis* or *Streptococcus pneumoniae.*

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional piece cited in this letter.
[2] The version of the approved product labeling for Zmax (PI) that was approved when the piece cited in this letter was disseminated and the version referred to in this letter is dated 06/2009. However the most recent version of the PI, which includes additional risks and contraindications, was approved on 03/01/2012.

- **Community-acquired pneumonia** in adults and pediatric patients six months of age or older due to *Chlamydophila pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae* or *Streptococcus pneumoniae*, in patients appropriate for oral therapy. Pediatric use in this indication is based on extrapolation of adult efficacy.

Zmax is contraindicated in patients with known hypersensitivity to azithromycin, erythromycin or any macrolide or ketolide antibiotic. The FDA-approved product labeling (PI) for Zmax includes Warnings and Precautions for severe (including fatal) allergic and skin reactions, *Clostridium difficile*-associated diarrhea, exacerbation of myasthenia gravis, gastrointestinal disturbances, prolongation of QT interval, and development of drug resistant bacteria. The most common adverse reactions associated with Zmax include diarrhea/loose stools, nausea, abdominal pain, headache, and vomiting.

Omission and Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts in light of representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Although the brochure contains information regarding the most commonly reported adverse events, it fails to include information regarding a serious warning and precaution associated with the use of Zmax. Specifically, the brochure omits the important risk of QT prolongation associated with Zmax use. The WARNINGS AND PRECAUTIONS section of the PI states, "[p]rolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with other macrolides. A similar effect with azithromycin cannot be completely ruled out in patients at increased risk for prolonged cardiac repolarization" (emphasis in original). By omitting this serious risk associated with Zmax, the brochure misleadingly suggests that the drug is safer than has been demonstrated.

In addition, the brochure minimizes the risks associated with Zmax by failing to disclose that severe and fatal allergic and skin reactions have been observed with azithromycin. Specifically, the WARNINGS AND PRECAUTIONS section of the PI states (emphasis in original):

> "Serious allergic reactions, including angioedema, anaphylaxis, Stevens Johnson syndrome and toxic epidermal necrolysis have been reported rarely in patients on azithromycin therapy using other formulations. Although rare, fatalities have been reported. Despite initially successful symptomatic treatment of the allergic symptoms, when symptomatic therapy was discontinued, the allergic symptoms **recurred soon thereafter in some patients without further azithromycin exposure.**"

We acknowledge that page seven of the brochure states, "Seek emergency help right away if you develop hives, skin rash, sores in your mouth, trouble swallowing, swelling of your face, tongue, or throat or have wheezing or trouble breathing after Zmax"; however, failure to disclose the severity of the potentially fatal allergic reactions, including recurrence of the allergic symptoms even when the drug was discontinued, that have been observed with azithromycin misleadingly minimizes the risks associated with Zmax.

Promotional materials are misleading if they fail to present information about risks associated with a drug with a prominence and readability reasonably comparable with the presentation of information related to the effectiveness of the drug. The brochure prominently presents efficacy claims in large bolded font size and in colorful text and graphics surrounded by a significant amount of white space; in contrast, the risk information is placed in obscure locations, in block paragraph format, without the use of headers or other signals to alert readers to its significance. The overall effect of this presentation undermines the communication of important risk information, minimizing the risks associated with Zmax, and misleadingly suggests that Zmax is safer than has been demonstrated. We note that the statement "*Please see Zmax full Patient and Prescribing Information, attached*" (emphasis original) is included in the brochure. However, this does not mitigate the misleading risk presentation.

Unsubstantiated Safety Superiority Claim/Minimization of Risk Information

Promotional materials are misleading if they contain representations or suggestions that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The brochure includes the following claims (emphasis original):

- **"Will my child be able to handle a medicine with just one strong dose?**

  Zmax is different from other drugs, because it's not released in the stomach. *Zmax* goes to work in the small intestine so it's easier on the stomach. Unlike many other drugs, you should take Zmax on an empty stomach."

The above claims are misleading because they imply that Zmax demonstrates a superior safety profile when compared to other antibiotics, due to the supposed superior tolerability of the drug. FDA is not aware of adequate and well-controlled head-to-head studies to support this implication. Furthermore, the suggestion that pediatric patients will necessarily tolerate Zmax minimizes the risk of gastrointestinal adverse events that may occur while using this drug product. The ADVERSE REACTIONS section of the PI states, "[t]he most common treatment-related adverse reactions in pediatric subjects were gastrointestinal in nature." Moreover, the PI states that vomiting, diarrhea, loose stools, and abdominal pain were the most common adverse events reported in the pediatric studies; therefore, claims that minimize the gastrointestinal adverse events associated with Zmax are misleading. The above claims are particularly concerning considering that the PI for Zmax includes a Warning and Precaution regarding gastrointestinal disturbances.

Omission of Material Facts

Promotional materials are false or misleading if they fail to reveal facts that are material in light of the representations made or with respect to consequences that may result from the use of the drug as recommended or suggested in the materials. The brochure omits important information regarding the dosage and administration of Zmax. Specifically, the brochure fails to include information regarding the required course of action in the event that a patient vomits after administration of the drug. The PATIENT COUNSELING INFORMATION section of the PI states, "Patients who vomit within the first hour should contact their health care provider about further treatment." Additionally, the DOSAGE AND ADMINISTRATION section of the PI states that ". . . if a patient vomits between 5 and 60 minutes following administration, alternative therapy should be considered." The omission of this important information, coupled with claims such as "1 dose and you're done" diminishes the significance of the consequences that may result from the use of Zmax as recommended in the brochure, and is therefore misleading.

The brochure also includes the following claims (emphasis in original):

- **"Will a 1-day, 1-dose antibiotic work?**

  In clinical trials, *Zmax* worked just as well as other antibiotics that needed to be dosed for 7 days."

The above presentation misleadingly suggests that Zmax demonstrates similar efficacy when compared to a wide array of antibiotics when this is not supported by substantial evidence or substantial clinical experience. According to the CLINICAL STUDIES section of the PI, the pivotal studies for Zmax included comparator arms where patients received either clarithromycin or levofloxacin. Failure to disclose this information, coupled with the claim that Zmax "worked just as well as other antibiotics," implies that Zmax demonstrates similar efficacy compared to an extensive group of antibiotics, when this is not the case, and is therefore misleading.

Broadening of Indication

Promotional materials are misleading if they suggest that a drug is useful in a broader range of patients or conditions than has been demonstrated by substantial evidence or substantial clinical experience. The brochure includes the following claim (bolded emphasis in original, underlined emphasis added):

- **"Zmax fights bacteria that cause certain infections, <u>including</u> bacterial sinusitis in adults, and pneumonia in adults and children 6 months and older."**

The above presentation of the indication for Zmax is misleading because it implies that Zmax is indicated to treat additional types of infections, other than acute bacterial sinusitis and community-acquired pneumonia, when this is not the case. Specifically, the use of the word "including," following the words "certain infections," implies that Zmax is used to treat infections **in addition** to those for which the drug is indicated to treat. According to the PI, Zmax is approved to treat "mild to moderate infections caused by susceptible isolates of the

designated microorganisms" in the following **specific** conditions: acute bacterial sinusitis in adults, and community-acquired pneumonia in adults and pediatric patients six months of age and older. Therefore, any suggestion that Zmax may be used to treat conditions other than, or in addition to, those for which Zmax has been FDA-approved is misleading.

The brochure also includes the following presentation: (emphasis original)

> "**Do you or your child have any of these symptoms?**
> - Fever
> - Cough
> - Chills
> - Chest pain
> - Low in energy
> - Tired
>
> If so, talk to your doctor, as it may be germs in the body that need to be treated with an antibiotic."

The totality of this presentation misleadingly suggests that Zmax is approved to treat any conditions associated with the listed symptoms, including viral infections that cause influenza or the common cold, when this has not been demonstrated by substantial evidence or substantial clinical experience. The FDA-approved patient labeling (PPI) states, "Zmax only works against bacteria. It does not work against viruses, like the common cold or flu." Thus, failure to disclose this material information misleadingly broadens the indication for Zmax.

Unsubstantiated Superiority Claims

Promotional materials are misleading if they represent or suggest that a drug is safer or more effective than another drug, when this has not been demonstrated by substantial evidence or substantial clinical experience. The brochure includes the following claims: (emphasis original)

- "**What are the benefits of an antibiotic that is given as a 1 day, 1 dose?**

  For Adults: . . .

  - Your body gets more medicine on Day 1 when it needs it most"

The totality of these claims misleadingly suggests that Zmax is clinically superior to other antibiotics because of its "1 day, 1 dose" dosage regimen. However, the clinical studies for Zmax only demonstrated that Zmax was **non-inferior** to a ten day dosage regimen of levofloxacin for the treatment of acute bacterial sinusitis and a seven day dosage regimen of both levofloxacin and clarithromycin for the treatment of community acquired pneumonia. In general, claims of superiority must be supported by adequate and well-controlled head-to-head clinical trials comparing appropriate doses and dose regimens of your drug and the comparator drug or drugs. FDA is not aware of any substantial evidence or substantial clinical experience that supports the implication that Zmax is clinically superior to other antibiotic treatments due to its dosage regimen. If you have data to support these claims,

please submit them to FDA for review.

Misleading Efficacy Claims

The brochure includes the following presentations (bolded emphasis in original; underlined emphasis added):

- "**1 DAY. 1 DOSE.**

  And your treatment is done.*

  . . . *Dosing of treatment is complete; however, *Zmax* will continue to work in your system for 10 days."
- "**Is 1 dose enough?**

  With just 1 dose, the medicine in *Zmax* goes on to work in you or your child for 10 days."
- "**1 dose and you're done, but *Zmax* keeps on working for 10 days**," accompanied by an image of an arrow with a highlighted panel which fades progressively from day 1 to day 10.

These presentations misleadingly suggest that Zmax demonstrates clinically significant efficacy for a period of time (i.e., for 10 days following administration) not demonstrated in the clinical trials that evaluated Zmax for the treatment of acute bacterial sinusitis and community-acquired pneumonia. We acknowledge that in the clinical trials for Zmax, clinical and microbiologic evaluations for both approved indications were conducted at the Test of Cure visit, 7 to 14 days post treatment. However, since Zmax is only administered one time as a single dose, it is unclear exactly how long the extent of the therapeutic benefit would be maintained. Therefore, any suggestion that the clinical effect of Zmax for the treatment of acute bacterial sinusitis and community-acquired pneumonia lasts for 10 days following administration is misleading. FDA is not aware of any substantial evidence or substantial clinical experience supporting any claim that Zmax demonstrates clinical efficacy for the treatment of either acute bacterial sinusitis or community-acquired pneumonia for 10 days following administration. If you have data to support these claims, please submit them to FDA for review.

Unsubstantiated Claims

The brochure includes the following claims (emphasis in original):

- "**84% of adult patients said they would most likely take *Zmax* again for the same infection**"

- "**78% of parents said they would most likely use *Zmax* to treat their kids again**"

These claims misleadingly suggest that adult patients and parents of pediatric patients (caretakers) would take Zmax again if they were to have the same infection, when these outcomes are not supported by substantial evidence or substantial clinical experience. Specifically, the support for these claims is based on patient and caretaker responses to the

following telephone survey questions approximately 5-10 days after taking Zmax: "Would you take Zmax again?" and "How likely are you to give your child Zmax again?," respectively. The use of responses to these survey questions is not sufficient to support the outcomes claimed because these survey questions cannot adequately assess all of the various factors (e.g., all aspects of efficacy, adverse events, and cost) which may influence patients' or caretakers' decisions to take any particular treatment again. If you have substantial evidence or substantial clinical evidence to support these claims, please submit them to FDA for review.

Additionally, the brochure includes the following claim (emphasis in original):

- **"80% also agreed *Zmax* made it much easier to complete treatment as directed by their physician"**

This claim misleadingly suggests that treatment with Zmax is "much easier" to complete as compared to other antibiotic products, when this is not supported by substantial evidence or substantial clinical experience. Specifically, in support of this claim, the brochure references patient responses to the following survey question: "Was Zmax easier or harder to take than other medicines?" The use of responses to this single question is not sufficient to support the outcomes claimed because it does not assess whether the effects of the drug, combined with its risks, translate into an overall "easier" treatment to complete as compared to other antibiotic treatment options. As described in the Background section above, Zmax is associated with numerous risks, including several warnings and precautions, and common adverse reactions, which are all factors that may negatively impact a patient's perception of the "eas[e]" of completing treatment with a given drug therapy. If you have substantial evidence or substantial clinical evidence to support this claim, please submit them to FDA for review.

Conclusion and Requested Action

The brochure is false or misleading because it omits and minimizes important risk information, makes unsubstantiated superiority claims, omits material facts, broadens the indication for the drug product, makes misleading efficacy claims, and makes unsubstantiated claims for Zmax. Therefore, the brochure misbrands the drug in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(a); 321(n). *Cf.* 21 CFR 202.1(e)(5)(i) & (iii); (e)(6)(i) & (ii); (e)(7)(i) & (viii).

OPDP requests that Pfizer immediately cease the dissemination of violative promotional materials for Zmax such as those described above. Please submit a written response to this letter on or before July 3, 2012, stating whether you intend to comply with this request, listing all promotional materials (with the 2253 submission date) for Zmax that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to the undersigned by facsimile at (301) 847-8444, or at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Consumer Drug Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266**. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been

reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Drug Promotion (DPDP) and DCDP. To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP. In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA # in addition to the NDA number in all future correspondence relating to this particular matter. DCDP/OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Zmax comply with each applicable requirement of the FD&C Act.

Sincerely,

{See appended electronic signature page}

Adora Ndu, Pharm.D.
LCDR, USPHS
Regulatory Review Officer
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

Amy Toscano, Pharm.D., CPA
Team Leader
Division of Consumer Drug Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ADORA NDU
06/19/2012

AMY TOSCANO
06/19/2012

STATE OF OREGON } ss
County of Marion
The foregoing copy has been compared and is certified by me as a full, true and correct copy of the original on file in my office and in my custody.
In Testimony Whereof, I have hereunto set my hand and affixed the seal of the Court on: 10/22/08
TRIAL COURT ADMINISTRATOR
By

STATE OF OREGON
Marion County Circuit Courts
OCT 22 2008
FILED

IN THE CIRCUIT COURT OF THE STATE OF OREGON

FOR THE COUNTY OF MARION

STATE OF OREGON ex rel HARDY MYERS, Attorney General for the STATE OF OREGON, Plaintiff, v. PFIZER INC, Defendant.	Case No. 08C23533 STIPULATED GENERAL JUDGMENT

The parties voluntarily enter in this Stipulated General Judgment on the terms and conditions set forth below:

1.

Definitions:

a. "Covered Conduct" shall mean Pfizer's promotional and marketing practices regarding the prescription drugs Celebrex® and Bextra®, that were the subject of an investigation by the Signatory Attorneys General under the State Consumer Protection Laws.

b. "Effective Date" shall mean the date by which Pfizer and ninety percent (90%) of the States that comprise the Multistate Working Group have executed the Consent Judgment

c. "FDA Amendments Act of 2007" (or "FDA Amendments Act" or "the Act") shall mean Public Law No. 110-85, which among other things, creates a federal clinical trial registry and results data bank.

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d. "FDA's Guidance for Industry" shall mean documents published by the United States Department of Health and Human Services, Food and Drug Administration (FDA), that represent the FDA's current recommendations on a topic.

e. "Individual States" and "State" shall mean each Signatory Attorney General who is participating in the Multistate Working Group.

f. "Pfizer" shall mean Pfizer Inc and its United States-based affiliates, subsidiaries, predecessors, successors, and assigns.

g. "Multistate Executive Committee" shall mean the Attorneys General and their staffs representing Arizona, California, Florida, Illinois, Massachusetts, New York, Ohio, Oregon, Texas, and Vermont

h. "Multistate Working Group" ("MSWG") shall mean the Attorneys General and their staffs representing Alaska, Arizona, Arkansas, California, Connecticut, Florida, District of Columbia, Idaho, Illinois, Iowa, Kansas, Kentucky, Maine, Maryland, Massachusetts, Michigan, Montana, Nebraska, Nevada, New Jersey, New Mexico, New York, North Carolina, North Dakota, Ohio, Oregon, Pennsylvania, South Carolina, South Dakota, Tennessee, Texas, Vermont, Washington, and Wisconsin.

i. "Off-Label" shall mean related to an indication that was not approved by the FDA at the time of dissemination or relating to information that was not contained in the FDA label.

j. "Prescriber" shall mean any physician, dentist, physician assistant, nurse practitioners, and all others with legal authority to prescribe any Pfizer product, as well as pharmacists, members of Pharmacy &Therapeutics committees and others who potentially have an impact on the prescribing of any Pfizer product.

k. "Parties" shall mean Pfizer and the Individual States.

l. "Product" shall mean any prescription drug or biological product manufactured, distributed, sold, marketed or promoted in the United States in any way.

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m. "Signatory Attorney(s) General" shall mean the Attorney General, or his or her designee, of each state in the Multistate Working Group

n. "State Consumer Protection Laws" shall mean the consumer protection laws under which the Signatory Attorneys General have conducted their investigation.[1]

o. "Celebrex" shall mean celecoxib

p. "Bextra" shall mean valdecoxib

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[1] The States' consumer protection statutes are: ALASKA - *Unfair Trade Practices and Consumer Protection Act*, AS 45.50.471 *et seq.*; ARIZONA - *Consumer Fraud Act*, A.R.S. § 44-1521 *et seq.*; ARKANSAS - Ark. Code Ann § 4-88-101 *et seq.*; CALIFORNIA - Bus. & Prof. Code §§ 17200 *et seq.* and 17500 *et seq.*; CONNECTICUT - Conn. Gen. Stat. §§ 42-110a *et seq.*; DISTRICT OF COLUMBIA - *Consumer Protection Procedures Act*, D.C. Code § 28-3901 *et seq.*; FLORIDA - *Deceptive and Unfair Trade Practices Act*, Fla. Stat. Ch 501.201 *et seq.*; IDAHO - *Consumer Protection Act*, Idaho Code Section § 48-601 *et seq* ; ILLINOIS - *Consumer Fraud and Deceptive Business Practices Act*, 815 ILCS § 505/1 *et seq.* (2006 State Bar Edition); IOWA - *Iowa Consumer Fraud Act*, Iowa Code Section 714.16; KANSAS - *Consumer Protection Act*, K.S.A. 50-623 *et seq* ; KENTUCKY - *Consumer Protection Statute*, KRS 367.110 *et seq* ; MAINE - *Unfair Trade Practices Act*, 5 M.R.S.A. § 207 *et seq.*; MARYLAND - *Consumer Protection Act*, Md. Code Ann., Com. Law § 13-101 *et seq.*; MASSACHUSETTS - *Consumer Protection Act*, M.G.L. c. 93A *et seq.*; MICHIGAN - *Michigan Consumer Protection Act*, MCL 445.901 *et seq.*; MONTANA - Mont. Code Ann. § 30-14-101 *et seq.*; NEBRASKA - *Uniform Deceptive Trade Practices Act*, NRS § 87-301 *et seq.*; NEW JERSEY - *New Jersey Consumer Fraud Act*, 56:8-1 *et seq.*; NEW YORK - General Business Law Article 22-A Sections 349, 350 and Executive Law Section 63 (12); NEW MEXICO - *Unfair Practices Act*, NMSA 1978, § 57-12-1 *et seq.*; NEVADA - *Deceptive Trade Practices Act*, Nevada Revised Statutes 598.0903 *et seq.*; NORTH CAROLINA - *Unfair and Deceptive Trade Practices Act*, N.C. Gen. Stat. § 75-1.1 *et seq.*; NORTH DAKOTA - *Unlawful Sales or Advertising Practices*, N.D. Cent. Code. § 51-15-02 *et seq.*; OHIO - *Consumer Sales Practices Act*, R.C. 1345.01 *et seq.*; OREGON - *Unlawful Trade Practices Act*, ORS 646.605 to 646.656; PENNSYLVANIA - *Unfair Trade Practices and Consumer Protection Law*, 73 P.S. § 201-1 *et seq.*; SOUTH CAROLINA - *Unfair Trade Practices Act*, S.C. CODE. ANN Sections 39-5-10 *et seq.*; SOUTH DAKOTA - *Deceptive Trade Practices Act*, S.D. Codified Laws § 37-24 *et seq.*; TENNESSEE - *Consumer Protection Act*, Tenn. Code Ann. §§ 47-18-101 *et seq.*; TEXAS - *Deceptive Trade Practices - Consumer Protection Act*, Tex. Bus. and Com. Code § 17.47 *et seq.*; VERMONT - *Consumer Fraud Act*, 9 V.S.A. § 2451 *et seq.*; WASHINGTON - *Unfair Business Practices/Consumer Protection Act*, R.C.W. 19.86 *et seq.*; WISCONSIN - Wis. Stat. § 100.18 *et seq.* (Fraudulent Representations) and Wis. Stat. § 100.182 *et seq* (Fraudulent Drug Advertising).

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2.

The parties have agreed to resolve the issues raised by the Covered Conduct by entering into this Consent Judgment (hereinafter "Judgment").

(a) Pfizer is entering into this Judgment solely for the purpose of settlement, and nothing contained herein may be taken as or construed to be an admission or concession of any violation of law, rule, or regulation, or of any other matter of fact or law, or of any liability or wrongdoing, all of which Pfizer expressly denies. Pfizer does not admit any violation of the State Consumer Protection Laws set forth in footnote 1, and does not admit any wrongdoing that was or could have been alleged by any Attorney General before the date of the Judgment under those laws. No part of this Judgment, including its statements and commitments, shall constitute evidence of any liability, fault, or wrongdoing by Pfizer. This document and its contents are not intended for use by any third party for any purpose, including submission to any court for any purpose.

(b) This Judgment shall not be construed or used as a waiver or limitation of any defense otherwise available to Pfizer in any action, or of Pfizer's right to defend itself from, or make any arguments in, any private individual, regulatory, governmental, or class claims or suits relating to the subject matter or terms of this Judgment. This Judgment is made without trial or adjudication of any issue of fact or law or finding of liability of any kind. Notwithstanding the foregoing, a State may file an action to enforce the terms of this Judgment.

(c) It is the intent of the Parties that this Judgment not be admissible in other cases or binding on Pfizer in any respect other than in connection with the enforcement of this Judgment.

(d) No part of this Judgment shall create a private cause of action or confer any right to any third party for violation of any federal or state statute except that a State may file an action to enforce the terms of this Judgment.

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(e) All obligations undertaken by Pfizer in this Judgment shall apply prospectively, except to the extent permitted by the National Library of Medicine, Pfizer shall submit, as soon as practicable, clinical trial results to the clinical trial registry and results data bank created by the FDA Amendments Act for all "applicable clinical trials" (as that term is defined by the Act) of FDA-approved Pfizer Products that were initiated after July 1, 2005.

3.

Pfizer shall register clinical trials and submit results to the registry and results data bank as required by the FDA Amendments Act and any accompanying regulations that may be promulgated pursuant to that Act.

4.

Pfizer shall not make any written or oral claim that is false, misleading or deceptive regarding any FDA-approved Pfizer Product.

5.

Pfizer shall not make any written or oral promotional claims of safety or effectiveness for any FDA-approved Pfizer Product in a manner that violates the Food, Drug and Cosmetic Act, 21 U.S.C. § 301 et seq. ("FDCA"), accompanying regulations, or voluntary agreements with FDA, as interpreted by the FDA in a writing by the Director of the Center for Drug Evaluation at the FDA.

6.

Nothing in this Judgment shall require Pfizer to:

(a) take an action that is prohibited by the FDCA or any regulation promulgated thereunder, or by FDA; or

(b) fail to take an action that is required by the FDCA or any regulation promulgated thereunder, or by FDA. Any written or oral promotional claim subject to this Judgment which is the same, or materially the same, as the language required or agreed to by the Director of Division of Drug Marketing, Advertising and Communication or the Director of the

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Center for Drug Evaluation and Research or their authorized designees in writing shall not constitute a violation of this Judgment.

7.

Following the initial approval of any Pfizer Product indicated for pain relief, Pfizer shall delay direct to consumer ("DTC") television advertising that relates to such indication, if the Director of the Center for Drug Evaluation and Research at FDA recommends such a delay in writing to Pfizer. Pfizer's delay shall be for the same period as recommended by the Director of the Center for Drug Evaluation and Research at FDA, but in no event shall the period of delay required by this provision of this Judgment exceed 18 months from approval. Should Pfizer run television DTC advertising contrary to a recommendation from the Director of the Center for Drug Evaluation and Research after the expiration of this 18 month period, Pfizer shall provide written notice to the Multistate Executive Committee 30 days prior to running the subject advertisement and shall also provide a copy of all correspondence with FDA relating to the subject advertisement.

8.

Pfizer agrees to submit all new DTC television advertising campaigns for any Pfizer Product to FDA for pre-review, to wait a reasonable time (not less than 45 days) until Pfizer receives a response from FDA prior to running the advertising campaign, and to modify such advertising consistent with any written comments from FDA, whenever received. Simultaneous with running any new DTC television advertisement for which FDA has not provided Pfizer with a pre-review response addressing the substance of the advertisement within the 45-day waiting period prescribed herein, Pfizer shall provide written notice to the Multistate Executive Committee that Pfizer is running the advertisement and that the FDA has not provided Pfizer with a pre-review response addressing the substance of the advertising within the 45-day waiting period, and also provide a copy of all material submitted to FDA for the review of the subject advertisement.

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9

Pfizer's obligations with respect to Paragraph 7 shall remain in effect for eight years following the Effective Date. Pfizer's obligations with respect to Paragraph 8 shall remain in effect for seven years following the Effective Date. With respect to Paragraph 7, Pfizer shall abide by any such written recommendation so long as the submission of the TV advertising campaign is made within eight years following the Effective Date With respect to Paragraph 8, Pfizer shall abide by any such written recommendation so long as the submission of the TV advertising campaign is made within seven years of the Effective Date.

10

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study that relates to an FDA-approved Pfizer Product, Pfizer shall: (a) accurately reflect the methodology used to conduct the Clinical Study; (b) not present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; and (c) not use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluations.

11.

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study or analysis of Clinical Studies as evidence of an FDA-approved Pfizer Product's safety, Pfizer shall not: (a) present information from a study in a way that implies that the study represents larger or more general experience with the drug than it actually does; or (b) use

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statistics on numbers of patients, or counts of favorable results or side effects derived from pooling data from various insignificant or dissimilar studies in a way that suggests either that such statistics are valid if they are not or that they are derived from large or significant studies supporting favorable conclusions when such is not the case.

12.

When presenting information in detailing pieces, brochures, booklets, mailing pieces, published journals, magazines, other periodicals and newspapers, and broadcast through media such as radio, television, the Internet, and telephone communications systems, about a Clinical Study or analysis of Clinical Studies as evidence of an FDA-approved Pfizer Product's safety, Pfizer shall not: (a) present favorable information or conclusions from a study that is inadequate in design, scope, or conduct to furnish significant support for such information or conclusions; (b) use the concept of statistical significance to support a claim that has not been demonstrated to have clinical significance or validity, or fails to reveal the range of variations around the quoted average results; or (c) use statistical analyses and techniques on a retrospective basis to discover and cite findings not soundly supported by the study, or to suggest scientific validity and rigor for data from studies the design or protocol of which are not amenable to formal statistical evaluation

13.

(a) Pfizer shall comply with the ACCME Standards for Commercial Support (a copy of the current version is attached hereto as Appendix 1).

(b) Any person who acts in a promotional capacity for Pfizer with respect to an FDA approved Pfizer Product shall be obligated under his or her contract with Pfizer, as a condition for any future promotional relationship with Pfizer, to disclose to Continuing Medical Education ("CME") participants orally and to the CME provider for inclusion in the written materials the existence, nature and purpose of his or her arrangement with Pfizer when a member of the faculty at a CME program if: (i) the Product the faculty member promoted for Pfizer is in

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the same therapeutic category as the subject of the CME program, and (ii) the CME program occurs within 12 months of the faculty member performing work for or receiving compensation from Pfizer. Such disclosure shall set forth the type of promotional work engaged in by the faculty member and the name of the therapeutic category with respect to such promotion.

(c) Pfizer shall not provide funding for CME when Pfizer has knowledge at the time the decision to fund the CME is made that a speaker at the CME has also been a promotional speaker in the past 12 months at a Pfizer-sponsored promotional event related to the class of drugs to be discussed in the CME.

14.

Pfizer's obligations with respect to CME shall remain in effect for 9 years following the Effective Date. Pfizer's obligations with respect to Paragraph 13(b) shall only apply to speakers' contracts entered into, amended to extend the contract period, or renewed after the date of this Judgment.

15.

Pfizer shall require all individuals who are named as authors on a Pfizer-sponsored manuscript reporting the results of a Pfizer-sponsored study to fulfill the following conditions: (a) the individual shall have made a substantial contribution to the conception and design, or acquisition of data, or analysis and interpretation of data; (b) the individual shall have been involved in drafting the article or revising it critically for important intellectual content; and (c) the individual shall have final approval rights of the version to be published. When a large, multi-center group has conducted the research, the manuscript shall identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship as set forth in (a), (b), and (c) above.

16.

Pfizer shall not disseminate in a promotional context any patient testimonial relating to a Product that does not clearly and conspicuously disclose what the generally expected

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performance would be in the depicted circumstances or clearly and conspicuously disclose the limited applicability of the experience described by the patient testimonial to what consumers may generally expect to achieve.

17.

Pfizer shall not market two or more Products in a manner that falsely or misleadingly conflates the various properties of the respective Products.

18.

Pfizer shall not compensate physicians for conducting individual, observational teaching sessions in their offices or in the hospital ("mentorships") in which sales representatives who detail a Product participate.

19.

Pfizer shall instruct investigators of Pfizer sponsored clinical trials regarding a Product to obtain a legally effective informed consent from all study subjects or from the subject's legally authorized representative. If Pfizer provides the investigator (or the investigator's Institutional Review Board) with a model informed consent, Pfizer shall not fail to include (a) a statement that the study involves research, an explanation of the purposes of the research and the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental; (b) a description of any reasonably foreseeable risks or discomforts to the subject; and (c) for research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

20.

Pfizer shall not affirmatively seek the inclusion of a Product in hospital protocols or standing orders unless the Product at issue has been approved by the FDA for the indication for which it is to be included in the protocol or standing order. Notwithstanding the foregoing,

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Pfizer may disclose to insurance companies and other third party payors any information regarding the inclusion of a Product in hospital protocols or standing orders even if the Product at issue has not been approved by the FDA for the indication for which it is to be included in the protocol or standing order.

21.

Pfizer shall not award prizes or other incentives to its sales force as rewards for specifically increasing the Off-Label use of a Product.

22.

Pfizer shall not disseminate any information describing any Off-Label use of a Product if such use has been submitted to the FDA for approval and the FDA has either advised Pfizer that it refuses to approve such application or that FDA-identified deficiencies must be resolved before approval can be granted unless Pfizer has first clearly and conspicuously disclosed to the information recipient that FDA had issued such advice regarding such Off-Label use. Pfizer may disclose to any recipient of such information whether the information was presented to the FDA prior to the FDA's issuance of such advice regarding the Off-Label use.

23.

Pfizer shall not disseminate a Medical Information Letter, an unabridged reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication, or written information through a Regional Medical Research Specialist ("RMRS") describing any Off-Label use of a Product in response to an unsolicited request by a prescriber or other health care professional unless (a) the information is about a clinical investigation with respect to the Product and experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product would consider the subject of the clinical investigation to be scientifically sound or the information is an unabridged reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication; (b) the information is accompanied by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical

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journal or medical or scientific text that have been previously published about the use of the Product covered by the information (unless the information is a Peer Reviewed Journal or Reference Publication which already includes such a bibliography); and (c) in cases in which experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product would consider the conclusion of the information to have been specifically called into question by another article(s) or text(s) that experts qualified by scientific training or experience to evaluate the safety or effectiveness of the Product would consider to be scientifically sound, the information must be disseminated with a representative publication that reaches contrary or different conclusions regarding the Off-Label use.

24.

Pfizer shall not disseminate any reprint or copy of an article from a Peer Reviewed Journal or a Reference Publication describing any Off-Label use of the Product to physician specialties that do not customarily prescribe the Product if these materials combined with detailing, advertising, sampling, or other promotional activities promote Off-Label use of the Product.

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In the event that FDA issues a final "Guidance For Industry: Good Reprint Practices For The Distribution Of Medical Journal Articles And Medical Or Scientific Reference Publications On Unapproved New Uses Of Approved Drugs And Approved Or Cleared Medical Devices," and a provision of said Guidance materially conflicts with any of the provisions of Paragraphs 22 through 24 of this Judgment, Pfizer may petition the Court for modification of those paragraphs, after providing thirty (30) days' notice to the Attorney General. The parties by stipulation may agree to such a modification, which agreement shall be presented to this Court for consideration provided that the parties may jointly agree to a modification only by a written instrument signed by or on behalf of both Pfizer and the Attorney General. If Pfizer wishes to seek a stipulation for a modification from the State, it shall send a written request for agreement to such modification

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to the Attorney General at least 30 days prior to filing a motion with the Court for such modification. Within 30 days of receipt from Pfizer of a written request for agreement to modify, the Attorney General shall notify Pfizer in writing if the Attorney General agrees to the requested modification. The Attorney General shall not unreasonably withhold his/her consent to the modification. The parties agree it would be unreasonable to withhold consent to the terms provided in the draft "Guidance For Industry: Good Reprint Practices For The Distribution Of Medical Journal Articles And Medical Or Scientific Reference Publications On Unapproved New Uses Of Approved Drugs And Approved Or Cleared Medical Devices," dated February 15, 2008, and attached hereto as Appendix 2, in the event that all such terms are included in the final Guidance For Industry. In the event that all such terms are not included in the final Guidance for Industry, the parties agree to consider whether any such terms that are included in the final Guidance for Industry should form the basis of a modification of Paragraphs 22 through 24 of this Judgment.

26.

Pfizer shall not disseminate any Medical Information Letter describing any Off-Label use of a Product that makes any false or misleading representation regarding a Product.

27.

Pfizer shall not disseminate samples of a Product with the intent of increasing Off-label prescribing of the Product.

28.

When submitting clinical trials relating to Off-label indications to journals for publication, Pfizer shall disclose to the journal that the FDA has not approved the drug for the indication that was the subject of the clinical trial.

29.

The Pfizer Medical Education Grants Office shall manage all requests for funding related to CME regarding Products. Approval decisions shall be made by the Pfizer Medical Education

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Grants Office alone, and shall be kept separate from the Sales and Marketing function. Notwithstanding the foregoing, decisions to approve a request for funding made by the Pfizer Medical Education Grants Office may be subject to actual funding approval by Pfizer's Chief Financial Officer or other designated officials.

30

Pfizer shall not use grants to advantage or promote Products. This provision includes, but is not limited to, the following prohibitions:

(a) Sales and Marketing personnel shall not initiate, coordinate or implement grant applications on behalf of any customer or Prescriber;

(b) Sales and Marketing personnel shall not be involved in selecting grantees or CME-funded speakers; and

(c) Sales and Marketing personnel shall not measure or attempt to track in any way the impact of grants or speaking fees on the participating Prescribers' subsequent prescribing habits, practices or patterns.

31.

Pfizer Sales and Marketing personnel shall not approve grant requests regarding Products, nor attempt to influence the Pfizer Medical Education Grants Office to reward any customers or Prescribers with grants for their prescribing habits, practices or patterns.

32.

By its execution of this Judgment, State of Oregon releases Pfizer and all of its past and present subsidiaries, affiliates, predecessors and successors (collectively, the "Released Parties") from the following: all civil claims, causes of action, damages, restitution, fines, costs, and penalties on behalf of the State of Oregon under the above-cited consumer protection statutes arising from the Covered Conduct that is the subject of this Judgment.

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33.

Notwithstanding any term of this Judgment, specifically reserved and excluded from the Release in Paragraph 32 as to any entity or person, including Released Parties, are any and all of the following:

(a) Any criminal liability that any person or entity, including Released Parties, has or may have to the State of Oregon

(b) Any civil or administrative liability that any person or entity, including Released Parties, has or may have to the State of Oregon not expressly covered by the release in Paragraph 32 above, including but not limited to any and all of the following claims:

i) State or federal antitrust violations;

ii) Reporting practices, including "best price", "average wholesale price" or "wholesale acquisition cost;"

iii) Medicaid violations, including federal Medicaid drug rebate statute violations, Medicaid fraud or abuse, and/or kickback violations related to any State's Medicaid program; and,

iv) State false claims violations.

(c) Any liability under the State of Oregon's above-cited consumer protection laws which any person or entity, including Released Parties, has or may have to individual consumers or State program payors of said State, and which have not been specifically enumerated as included herein.

34.

Within ten (10) days of the Effective Date of this Judgment, Pfizer shall pay a total amount of sixty million dollars ($60,000,000) to be divided and paid by Pfizer directly to each Signatory Attorney General in an amount to be designated by and in the sole discretion of the Multistate Executive Committee. Said payment shall be used by the States for attorneys' fees and other costs of investigation and litigation, or to be placed in, or applied to, the consumer

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protection enforcement fund, consumer education, litigation or local consumer aid fund or revolving fund, used to defray the costs of the inquiry leading hereto, or for other uses permitted by state law, at the sole discretion of each Signatory Attorney General.

35.

For the purposes of resolving disputes with respect to compliance with this Judgment, should any of the Signatory Attorneys General have a reasonable basis to believe that Pfizer has engaged in a practice that violates a provision of this Judgment subsequent to the Effective Date of this Judgment, then such Attorney General shall notify Pfizer in writing of the specific objection, identify with particularity the provisions of this Judgment that the practice appears to violate, and give Pfizer thirty (30) days to respond to the notification; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

Upon receipt of written notice, Pfizer shall provide a good-faith written response to the Attorney General notification, containing either a statement explaining why Pfizer believes it is in compliance with the Judgment, or a detailed explanation of how the alleged violation occurred and a statement explaining how Pfizer intends to cure the alleged breach. Nothing in this paragraph shall be interpreted to limit the state's Civil Investigative Demand ("CID") or subpoena authority, to the extent such authority exists under applicable state law, and Pfizer reserves all of its rights with respect to a CID or subpoena issued pursuant to such authority.

36

Upon giving Pfizer thirty (30) days to respond to the notification described above, the Signatory Attorney General shall also be permitted reasonable access to inspect and copy relevant, non-privileged, non-work product records and documents in the possession, custody or control of Pfizer that relate to Pfizer's compliance with each provision of this Judgment as to which cause that is legally sufficient in the State has been shown. If the Signatory Attorney

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General makes or requests copies of any documents during the course of that inspection, the Signatory Attorney General will provide a list of those documents to Pfizer.

37.

The State may assert any claim that Pfizer has violated this Judgment in a separate civil action solely to enforce compliance with this Judgment, or to seek any other relief afforded by law, but only after providing Pfizer an opportunity to respond to the notification described in Paragraph 35 above; provided, however, that a Signatory Attorney General may take any action if the Signatory Attorney General concludes that, because of the specific practice, a threat to the health or safety of the public requires immediate action.

38.

This Judgment represents the full and complete terms of the settlement entered into by the parties hereto. In any action undertaken by either the Attorneys General, or any of them, or Pfizer, no prior versions of this Judgment, and no prior versions of any of its terms, that were not entered by the Court in this Judgment, may be introduced for any purpose whatsoever.

IT IS SO STIPULATED

Department of Justice
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Accepted this 17th day of October, 2008

FOR PFIZER INC

Michael J. Sandmire, OSB No. 904410
Ater Wynne LLP
222 S.W. Columbia, Suite 1800
Portland, OR 97201
Phone: (503) 226-1191
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Attorney for Pfizer Inc

Markus Green
Corporate Counsel
Pfizer Inc

ACCEPTANCE OF DOJ

Accepted this 21st day of October, 2008.

HARDY MYERS
Attorney General

David Hart #00275
Senior Assistant Attorney General
1162 Court Street, N.E.
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Email: david.hart@state.or.us

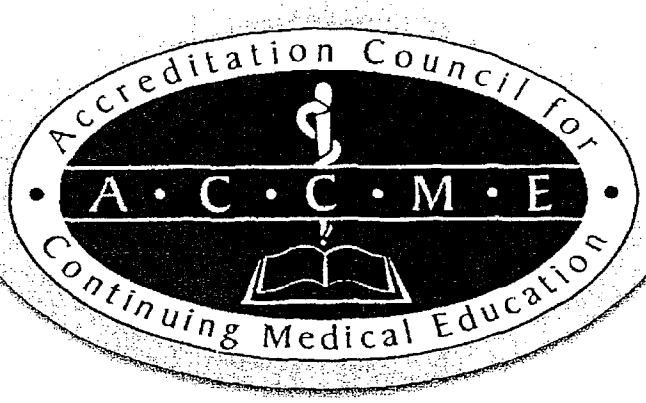
This STIPULATED GENERAL JUDGMENT is hereby accepted for entry of JUDGMENT for all purposes as set forth herein.

IT IS SO ADJUDGED AND ORDERED:

DATED this 22 day of October, 2008

CIRCUIT COURT JUDGE for Marion County

APPENDIX 1



ACCME STANDARDS FOR COMMERCIAL SUPPORT[SM]

Standards to Ensure the Independence of CME Activities

The ACCME Standards for Commercial Support℠

Standards to Ensure Independence in CME Activities

STANDARD 1: Independence

1.1 A CME provider must ensure that the following decisions were made free of the control of a commercial interest. (See www.accme.org for a definition of a 'commercial interest' and some exemptions.)

(a) Identification of CME needs;
(b) Determination of educational objectives;
(c) Selection and presentation of content;
(d) Selection of all persons and organizations that will be in a position to control the content of the CME;
(e) Selection of educational methods;
(f) Evaluation of the activity

1.2 A commercial interest cannot take the role of non-accredited partner in a joint sponsorship relationship ⌘

STANDARD 2: Resolution of Personal Conflicts of Interest

2.1 The provider must be able to show that everyone who is in a position to control the content of an education activity has disclosed all relevant financial relationships with any commercial interest to the provider. The ACCME defines "'relevant' financial relationships" as financial relationships in any amount occurring within the past 12 months that create a conflict of interest.

2.2 An individual who refuses to disclose relevant financial relationships will be disqualified from being a planning committee member, a teacher, or an author of CME, and cannot have control of, or responsibility for, the development, management, presentation or evaluation of the CME activity.

2.3 The provider must have implemented a mechanism to identify and resolve all conflicts of interest prior to the education activity being delivered to learners ⌘

STANDARD 3: Appropriate Use of Commercial Support

3.1 The provider must make all decisions regarding the disposition and disbursement of commercial support.

3.2 A provider cannot be required by a commercial interest to accept advice or services concerning teachers, authors, or participants or other education matters, including content, from a commercial interest as conditions of contributing funds or services.

3.3 All commercial support associated with a CME activity must be given with the full knowledge and approval of the provider.

Written agreement documenting terms of support

3.4 The terms, conditions, and purposes of the commercial support must be documented in a written agreement between the commercial supporter that includes the provider and its educational partner(s). The agreement must include the provider, even if the support is given directly to the provider's educational partner or a joint sponsor.

3.5 The written agreement must specify the commercial interest that is the source of commercial support.

3.6 Both the commercial supporter and the provider must sign the written agreement between the commercial supporter and the provider.

Expenditures for an individual providing CME

3.7 The provider must have written policies and procedures governing honoraria and reimbursement of out-of-pocket expenses for planners, teachers and authors.

3.8 The provider, the joint sponsor, or designated educational partner must pay directly any teacher or author honoraria or reimbursement of out-of-pocket expenses in compliance with the provider's written policies and procedures.

3.9 No other payment shall be given to the director of the activity, planning committee members, teachers or authors, joint sponsor, or any others involved with the supported activity.

3.10 If teachers or authors are listed on the agenda as facilitating or conducting a presentation or session, but participate in the remainder of an educational event as a learner, their expenses can be reimbursed and honoraria can be paid for their teacher or author role only.

Expenditures for learners

3.11 Social events or meals at CME activities cannot compete with or take precedence over the educational events.

3.12 The provider may not use commercial support to pay for travel, lodging, honoraria, or personal expenses for non-teacher or non-author participants of a CME activity The provider may use commercial support to pay for travel, lodging, honoraria, or personal expenses for bona fide employees and volunteers of the provider, joint sponsor or educational partner.

Accountability

3.13 The provider must be able to produce accurate documentation detailing the receipt and expenditure of the commercial support ⌘

STANDARD 4. Appropriate Management of Associated Commercial Promotion

4.1 Arrangements for commercial exhibits or advertisements cannot influence planning or interfere with the presentation, nor can they be a condition of the provision of commercial support for CME activities.

4.2 Product-promotion material or product-specific advertisement of any type is prohibited in or during CME activities The juxtaposition of editorial and advertising material on the same products or subjects must be avoided. Live (staffed exhibits, presentations) or enduring (printed or electronic advertisements) promotional activities must be kept separate from CME

- For *print*, advertisements and promotional materials will not be interleafed within the pages of the CME content Advertisements and promotional materials may face the first or last pages of printed CME content as long as these materials are not related to the CME content they face and are not paid for by the commercial supporters of the CME activity
- For *computer based*, advertisements and promotional materials will not be visible on the screen at the same time as the CME content and not interleafed between computer 'windows' or screens of the CME content
- For *audio and video recording*, advertisements and promotional materials will not be included within the CME There will be no commercial breaks
- For *live, face-to-face CME*, advertisements and promotional materials cannot be displayed or distributed in the educational space immediately before, during, or after a CME activity Providers cannot allow representatives of Commercial Interests to engage in sales or promotional activities while in the space or place of the CME activity

4.3 Educational materials that are part of a CME activity, such as slides, abstracts and handouts, cannot contain any advertising, trade name or a product-group message

4.4 Print or electronic information distributed about the non-CME elements of a CME activity that are not directly related to the transfer of education to the learner, such as schedules and content descriptions, may include product-promotion material or product-specific advertisement

4.5 A provider cannot use a commercial interest as the agent providing a CME activity to learners, e.g , distribution of self-study CME activities or arranging for electronic access to CME activities ⌘

STANDARD 5. Content and Format without Commercial Bias

5.1 The content or format of a CME activity or its related materials must promote improvements or quality in healthcare and not a specific proprietary business interest of a commercial interest

5.2 Presentations must give a balanced view of therapeutic options Use of generic names will contribute to this impartiality If the CME educational material or content includes trade names, where available trade names from several companies should be used, not just trade names from a single company ⌘

STANDARD 6. Disclosures Relevant to Potential Commercial Bias

Relevant financial relationships of those with control over CME content

6.1 An individual must disclose to learners any relevant financial relationship(s), to include the following information:

- The name of the individual;
- The name of the commercial interest(s);
- The nature of the relationship the person has with each commercial interest

6.2 For an individual with no relevant financial relationship(s) the learners must be informed that no relevant financial relationship(s) exist

Commercial support for the CME activity

6.3 The source of all support from commercial interests must be disclosed to learners When commercial support is in-kind' the nature of the support must be disclosed to learners

6.4 'Disclosure' must never include the use of a trade name or a product-group message

Timing of disclosure

6.5 A provider must disclose the above information to learners prior to the beginning of the educational activity ⌘

APPENDIX 2

Guidance for Industry:

Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance Submit comments to Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061 Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*

For single copies of this draft guidance, please contact: Office of Policy Food and Drug Administration 5600 Fishers Lane rm 14-101 HF-11, Rockville, MD 20857. (301) 827-3360

For questions regarding this draft document, contact Jarilyn Dupont Office of Policy, Food and Drug Administration, (301) 827-3360.

U.S. Department of Health and Human Services
Food and Drug Administration

February 2008

Contains Nonbinding Recommendations
Draft – Not for Implementation

Table of Contents

Contains Nonbinding Recommendations
Draft – Not for Implementation

Guidance for Industry: Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices

This draft guidance document represents the Food and Drug Administration's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public You may use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations If you want to discuss an alternative approach, please contact the appropriate FDA staff.

I. Introduction

This draft guidance is intended to describe the Food and Drug Administration s (FDA or Agency) current thinking regarding "Good Reprint Practices" with regard to the distribution of medical journal articles and scientific or medical reference publications (referred to generally as medical and scientific information) that discuss unapproved new uses for approved drugs[1] or approved or cleared medical devices marketed in the United States to healthcare professionals and healthcare entities

FDA's guidance documents, including this draft guidance, do not establish legally enforceable rights or responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidances means that something is suggested or recommended but not required

II. Background

Section 401 of the Food and Drug Administration Modernization Act (FDAMA (21 U S.C. § 360aaa, § 551, Federal Food. Drug, and Cosmetic Act (FD&C Act))), described certain conditions under which a drug or medical device manufacturer[2] could choose to disseminate medical and scientific information discussing unapproved uses of approved drugs and cleared or approved medical devices to healthcare professionals and certain entities (including pharmacy benefits managers, health insurance issuers, group health plans, and Federal or State governmental agencies). FDAMA section 401 provided that, if these conditions were met, dissemination of such journal articles or reference publications would not be considered as evidence of the manufacturer's intent that the product be used for an unapproved new use. FDA implementing regulations were codified at 21 C F R. Part 99

In 2000, subsequent to a decision by the United States Court of Appeals for the District of Columbia Circuit FDA published a Notice (65 Fed. Reg. 14286, March 16, 2000) clarifying the applicability of the FDAMA section 401 provision and the FDA implementing regulations. In that Notice, FDA stated that the statute and implementing regulations constituted a "safe harbor" for a manufacturer that complies with them before and while disseminating journal articles and reference publications about "new uses" of approved or cleared products. If a manufacturer complied with the FDAMA provision, the distribution of such journal articles or reference publications would not be used as evidence of an intent that the product distributed by the manufacturer be used for an unapproved use. The Notice stated that if a manufacturer chose to disseminate materials but not proceed under FDAMA section 401, that failure would not constitute an independent violation of law.

FDAMA section 401 ceased to be effective on September 30, 2006, and the implementing regulations are no longer applicable In light of the statute's sunset, FDA is providing its current views on the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities

III. Purpose

As explained in FDA's March 16, 2000 Notice, the FD&C Act and FDA s implementing regulations generally prohibit manufacturers of new drugs or medical devices from distributing products in interstate commerce for any intended use that FDA has not approved as safe and effective or cleared through a substantial equivalence determination. (E.g., FD&C Act §§ 505(a), 502(o), 501(f)(1)(B), 301(a) and (d); 21 U S.C. §§ 355, 352(o), 351(f)(1)(B) 331(a) and (d)) An approved new drug that is marketed for an unapproved use becomes misbranded and an unapproved new drug with respect to that use. Similarly, a medical device that is promoted for a use that has not been approved or cleared by FDA is adulterated and misbranded

FDA does, however, recognize the important public policy reasons for allowing manufacturers to disseminate truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs and approved or cleared medical devices to healthcare professionals and healthcare entities. Once a drug or medical device has been approved or cleared by FDA, generally healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling (or, in the case of a medical device cleared under the 510(k) process, in the product's statement of intended uses). These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care. Accordingly, the public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved or new uses of approved or cleared medical products that are truthful and not misleading

FDA s legal authority to determine whether distribution of medical or scientific information constitutes promotion of an unapproved "new use," or whether such activities cause a product to be misbranded or adulterated has not changed In recognition of the public health value to healthcare professionals of receiving truthful and non-misleading scientific and medical information, FDA is providing recommendations concerning "Good Reprint Practices" for the dissemination of medical journal articles and medical or scientific reference publications on unapproved uses of drugs and medical devices [3]

IV. Agency Recommendations for Good Reprint Practices

Scientific and medical information that concerns the safety or effectiveness of an approved drug or approved or cleared medical device for a new use that is not included in the product's approved labeling or statement of intended uses (including unapproved or new uses of approved drugs and approved or cleared devices) is often published in journal articles or reference publications These publications are often distributed by manufacturers to healthcare professionals or healthcare entities. When a manufacturer disseminates such medical and scientific information, FDA recommends that the following principles of "Good Reprint Practices be followed.

A. Types of Reprints/Articles/Reference Publications

A scientific or medical journal article that is distributed should:

- be published by an organization that has an editorial board that uses experts who have demonstrated expertise in the subject of the article under review by the organization and who are independent of the organization to review and objectively select, reject, or provide comments about proposed articles, and that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors, contributors or editors associated with the journal or organization;
- be peer-reviewed and published in accordance with the peer-review procedures of the organization; and
- not be in the form of a special supplement or publication that has been funded in whole or in part by one or more of the manufacturers of the product that is the subject of the article

A scientific or medical reference publication that is distributed should not be:

- primarily distributed by a drug or device manufacturer, but should be generally available in bookstores or other independent distribution channels where medical textbooks are sold;
- written, edited excerpted, or published specifically for, or at the request of, a drug or device manufacturer; or
- edited or significantly influenced by a drug or device manufacturer or any individuals having a financial relationship with the manufacturer

The information contained in the above scientific or medical journal article or reference publications should address adequate and well-controlled clinical investigations that are considered scientifically sound by experts with scientific training and experience to evaluate the safety or effectiveness of the drug or device[4] The information must not:

- be false or misleading, such as a journal article or reference text that is inconsistent with the weight of credible evidence derived from adequate and well-controlled clinical investigations (e.g , where a significant number of other studies contradict the article or reference text's conclusions), that has been withdrawn by the journal or disclaimed by the author, or that discusses a clinical investigation where FDA has previously informed the company that the clinical investigation is not adequate and well-controlled; or
- pose a significant risk to the public health

The following publications are examples of publications that would not be considered consistent with the Good Reprint Practices outlined in this draft guidance:

- letters to the editor;
- abstracts of a publication;
- reports of Phase 1 trials in healthy subjects; or
- reference publications that contain little or no substantive discussion of the relevant investigation or data

B. Manner in which to Disseminate Scientific and Medical Information

Scientific or medical information that is distributed should:

- be in the form of an unabridged reprint, copy of an article, or reference publication;
- not be marked, highlighted, summarized, or characterized by the manufacturer in any way;
- be accompanied by the approved labeling for the drug or medical device;
- be accompanied by a comprehensive bibliography of publications discussing adequate and well-controlled clinical studies published in a medical journal or medical or scientific text that have been previously published about the use of the drug or medical device covered by the information disseminated (unless the information already includes such a bibliography);
- in cases where the conclusions of article or text to be disseminated have been specifically called into question by another article(s) or text(s), be disseminated with a representative publication that reaches contrary or different conclusions regarding the unapproved use; and

- be distributed separately from information that is promotional in nature For example, if a sales representative delivers a reprint to a physician in his office, the reprint should not be physically attached to any promotional material the sales representative uses or delivers during the office visit and should not be the subject of discussion between the sales representative and the physician during the sales visit.[5] Similarly, while reprints may be distributed at medical or scientific conferences in settings appropriate for scientific exchange, reprints should not be distributed in promotional exhibit halls or during promotional speakers' programs

The journal reprint or reference publication should be accompanied by a prominently displayed and permanently affixed statement disclosing:

- that the uses described in the information have not been approved or cleared by FDA, as applicable to the described drug or medical device;
- the manufacturer s interest in the drug or medical device that is the subject of the journal reprint or reference text;
- any author known to the manufacturer as having a financial interest in the product or manufacturer or receiving compensation from the manufacturer if applicable;
- any person known to the manufacturer who has provided funding for the study if applicable; and
- any significant risks or safety concerns known to the manufacturer concerning the unapproved use that are not discussed in the journal article or reference text

V. Summary

FDA recognizes that the public health can be served when health care professionals receive truthful and non-misleading scientific and medical information on unapproved uses of approved or cleared medical products Accordingly, if a manufacturer follows the recommendations described in Section IV of this draft guidance and there is no unlawful promotion of the product. FDA does not intend to use the distribution of such medical and scientific information as evidence of an intent by the manufacturer that the product be used for an unapproved use [6]

Footnotes

[1] As used in this draft guidance, the term drug includes biological products licensed under Section 351(a) of the Public Health Service Act See 42 U S C § 262(j)

[2] As used in this draft guidance, the term "manufacturer" means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device The term may also include the sponsor of the approved, licensed or cleared drug or device

[3] This draft guidance does not apply to scientific or medical information distributed in response to unsolicited requests for scientific or medical information from health care professionals See 59 Fed Reg 59820 59823 (November 18, 1994)

[4] In the case of medical devices, journal articles or reference publications discussing significant non-clinical research may be consistent with this draft guidance

[5] To the extent that the recipients of such information have questions, the Agency recommends that the sales representative refer such questions to a medical/scientific officer or department, and that the officer or department to which the referral is made be separate from the sales and/or marketing departments

[6] Given the sunset of FDAMA § 401, the other elements that comprised § 401 which are not specifically described in this draft guidance are no longer applicable

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For More Information

Press Release *(February 15, 2008)*
Federal Register (Docket No FDA-2008-D-0053, OC 2007268)

STATE OF OREGON } ss
County of Marion }

The foregoing copy has been compared and is certified by me as a full, true and correct copy of the original on file in my office and in my custody.

In Testimony Whereof, I have hereunto set my hand and affixed the seal of the

Court on: 12/20/12

TRIAL COURT ADMINISTRATOR

By KK