No. 12-5008

IN THE UNITED STATES COURT OF APPEALS
FOR THE SECOND CIRCUIT

UNITED STATES OF AMERICA, EX REL. DR. JESSE POLANSKY,
Plaintiff-Appellant,

v.

PFIZER, INC.,
Defendant-Appellee.

On Appeal from the United States District Court
for the Eastern District of New York

BRIEF FOR APPELLANT JESSE POLANSKY
(PAGE PROOF VERSION)

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INTRODUCTION

Relator[1/] Jesse Polansky, a physician who specializes in public health and a former employee of Pfizer, Inc., filed a complaint alleging that defendant Pfizer has been marketing its extraordinarily lucrative cholesterol medication, Lipitor, in a false, misleading, and illegal off-label manner. Doc77. The complaint further alleges that, as a result of that marketing scheme, doctors have been prescribing Lipitor off-label, pharmacies have been dispensing Lipitor off-label, and, for beneficiaries of Medicare, Medicaid, and other government healthcare programs, federal and state governments have been unknowingly paying for off-label Lipitor prescriptions. Doc77,pp2-4. Federal regulations prohibit payment for such prescriptions. Doc77,p4. Accordingly, the complaint alleges that Pfizer, through its marketing, is causing millions of false claims to be made on federal and state governments in violation of the False Claims Act (ñFCAò) and corresponding state law. *Ibid.* Relator also raised employment claims against Pfizer. Doc77,p1. This case is before this Court following its dismissal by the district court pursuant to Rule 12(b)(6) of the Federal Rules of Civil Procedure. In that dismissal, the district court recognized that off-label marketing subjects a

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[1/]Dr. Polansky brought *qui tam* claims on behalf of the federal and state governments and is therefore referred to herein as Relator. Dr. Polansky also brought employment claims as a plaintiff on his own behalf. For simplicity, this brief refers to Dr. Polansky throughout as Relator.

pharmaceutical company to FCA liability (Doc108,pp1-2,10-11), but wrongly interpreted the Lipitor labeling.

STATEMENT OF SUBJECT MATTER AND APPELLATE JURISDICTION

The district court had jurisdiction over Relatorôs federal False Claims Act claims pursuant to 28 U.S.C. 1331, which relates to acts arising under the laws of the United States, and 31 U.S.C. 3732, which relates to claims pursuant to the False Claims Act. Doc77,p6.

The district court had jurisdiction over Relatorôs federal employment claims pursuant to 28 U.S.C. 1331 and 42 U.S.C. 2000e-5(f)(3), which provides for jurisdiction over Title VII claims. Doc77,p6.

The district court had jurisdiction over Relatorôs state law claims pursuant to 28 U.S.C. 1332(a)(1) because the matter in controversy exceeds $75,000 and the parties are citizens of different states, pursuant to 28 U.S.C. 1367(a), which provides supplemental jurisdiction over related state claims, and, with regard to the state false claims act claims, pursuant to 31 U.S.C. 3732(b), which provides jurisdiction over claims for recovery of funds paid by state governments. Doc77,p6.

Pursuant to 28 U.S.C. 1291, this Court has jurisdiction over Relatorôs appeal (Doc112) from the final order dismissing the complaint (Doc108), and from the final

judgment for Pfizer on all claims (Doc109). Relatorôs Notice of Appeal was timely filed in the United States District Court for the Eastern District of New York on December 14, 2012.

STATEMENT OF ISSUES

1. Whether the district court erred in dismissing Relatorôs False Claims Act and related state claims (Counts 1 and 3-19) pursuant to Rule 12(b)(6) because it incorrectly found that the National Institutes of Health National Cholesterol Education Program Guidelines are not part of the labeling and therefore are not mandatory requirements for Pfizerôs marketing of Lipitor.

2. Whether the district court erred in deciding Pfizerôs motion to dismiss by making factual determinations without the opportunity for discovery or the presentation of expert testimony.

3. Whether the district court erred in dismissing Relatorôs employment claims (Counts 2 and 20-23) pursuant to Rule 12(b)(6) because Pfizer never moved to dismiss those claims and the court never considered those claims in its dismissal order.

STATEMENT OF THE CASE

Relator brought this case against Pfizer in the District Court for the Eastern District of New York. Doc77. The United States declined to exercise its right to intervene provided by the False Claims Act. Doc. 17.

On April 28, 2008, Pfizer moved to dismiss pursuant to Rules 9(b) and 12(b)(6) of the Federal Rules of Civil Procedure. On May 22, 2009, the Court (Korman, J.) issued an order that ñassume[d] * * * that the complaint [was] sufficient to state a claim,ò granted Pfizerôs motion to dismiss under Rule 9(b), and permitted Relator to amend his complaint. Doc60,pp6,18. Separately, the court denied Pfizerôs motion to dismiss two of Relatorôs employment claims. Doc61.

On February 10, 2010, Relator filed his Fifth Amended Complaint (ñcomplaintò). Doc77. On June 18, 2010, Pfizer again moved to dismiss the False Claims Act claims pursuant to Rules 9(b) and 12(b)(6), but not the employment claims. Doc90. On November 15, 2012, the court (Cogan, J.) granted the motion to dismiss pursuant to Rule 12(b)(6), including the employment claims. Doc108; *United States ex rel. Polansky v. Pfizer, Inc.*, 2012 WL 5595933. The court did not address the Rule 9(b) or employment issues. Doc108.

On November 16, 2012, the district court issued its final judgment. Doc109. On December 14, 2012, Relator filed his notice of appeal. Doc112.

STATEMENT OF FACTS

I

LIMITATIONS ON THE MARKETING OF, AND PAYMENT FOR, PRESCRIPTION DRUGS

A. THE FOOD AND DRUG ADMINISTRATION'S LABELING AND REGULATION OF PRESCRIPTION DRUGS

Pursuant to the Food, Drug, and Cosmetic Act (21 U.S.C. 301-399), pharmaceutical manufacturers cannot market and sell pharmaceutical drugs in the United States until they have been evaluated and approved by the Food and Drug Administration (ñFDAò) as safe and effective for their intended uses. *See* 21 U.S.C. 355(a),(d); Doc77,p8. The approval process includes clinical testing by the drug manufacturer, the FDAôs review of the manufacturerôs application, and the FDAôs review of the manufacturerôs proposed labeling. *See* Doc77,pp7-9; 21 U.S.C. 352, 355; 15 U.S.C. 1451, *et seq*.

The FDA does not approve drugs for treatment of sickness in general. Doc77,p9. Instead, the FDA approves drugs as safe and effective for specific types of treatment for conditions for which the drug has been tested. *Ibid.*; *U.S. v. Caronia*, 703 F.3d 149, 153 (2d Cir. 2012). The required labeling includes, *inter alia,* the approved indications, usages, and dosages. Doc77,p8.

In addition to approving drug use, the FDA monitors and enforces restrictions

on the marketing of approved drugs. *See, e.g.,* 21 U.S.C. 352(n); Doc77,pp7-8. Pharmaceutical manufacturers are not permitted falsely to market or promote their drugs for uses not listed on the FDA-approved labeling. 21 U.S.C. 331(b),(c), 352(f); Doc77,p10; *see also Caronia*, 703 F.3d at 165, n.10, 168.

ñOff-labelò refers to the use of an approved drug for any purpose, or in any manner, other than as approved by the FDA and described in the drugôs labeling. Doc77,p9; *Caronia*, 703 F.3d at 153. Off-label use includes treatment beyond the indications and usage and treating the indicated condition at a different dose or frequency than specified in the labeling. *Ibid.*; *Association of American Physicians & Surgeons, Inc. v. United States FDA*, 226 F. Supp. 2d 204, 206 (D.D.C. 2002).

Although the FDA is responsible for ensuring that a drug is safe and effective according to the specifications on the labeling, the FDA does not regulate the practice of medicine. Doc77,p9; *Caronia*, 703 F.3d at 153. Therefore, once a drug is approved for a particular use, the FDA does not prohibit doctors from prescribing the drug for off-label uses. Doc77,p10; *Caronia*, 703 F.3d at 153. The FDA can only limit off-label marketing of the drug. While the FDA has authority to enforce compliance with its marketing restrictions for the purpose of protecting the public, it has no authority to protect federal healthcare programs against false claims. Doc77,p11.

B. MEDICARE AND MEDICAID CANNOT PAY FOR OFF-LABEL PRESCRIPTIONS

Neither Medicare, nor Medicaid, nor other federal healthcare programs (the Department of Defenseôs TRICARE (formerly CHAMPUS) program, the Veteran Administrationôs healthcare program, and the Office of Personnel Managementôs Federal Employee Benefit Program), can pay for off-label prescriptions.[2/] Doc77,pp11-16; District Court Order, dated November 15, 2012, Doc108,pp1-2 (ñMedicare and Medicaid do not reimburse off-label prescriptions * * * ò (footnote with citation omitted)).

The federal programs generally are permitted only to pay for drugs that are prescribed for ñmedically accepted indications.ò Doc77,pp11-16,22; 42 U.S.C. 1396b(i)(10), 1396r-8(k)(2),(3),(6) (Medicaid); 42 U.S.C. 1395w-102(e) (Medicare); *United States ex rel. Franklin v. Parke-Davis*, 147 F. Supp. 2d 39, 44-45 (D. Mass. 2001); *United States ex rel. Carpenter v. Abbott Laboratories*, 723 F. Supp. 2d 395, 409 (D. Mass. 2010). A ñmedically accepted indicationò is a use ñwhich is approved under the Federal Food Drug and Cosmetic Actòð that is, on-labelð or which is ñsupported byò specified drug compendia. 42 U.S.C. 1396r-8(k)(6); *United States ex rel. Franklin*, 147 F. Supp 2d at 45.

[2/]The rare exceptions to this rule (*see* 42 U.S.C. 1396r-8(a)(3)) are not relevant here.

Generally, neither the pharmacy, which submits a claim for payment for a drug to any federal healthcare program, nor the program that receives the claim, has the patientôs medical records before them and therefore has any basis to know when a drug has been prescribed off-label and therefore can not be paid. Doc77,p11.

II

SPECIFIC LIMITATIONS ON THE MARKETING OF AND PAYMENT FOR LIPITOR

A. NATIONAL CHOLESTEROL EDUCATION PROGRAM GUIDELINES FOR THE USE OF STATINS

The National Institutes of Health, National Heart, Lung, and Blood Instituteôs National Cholesterol Education Program (ñNCEPò) ñpromotes the detection and treatment of individuals whose elevated blood cholesterol places them at significantly increased risk for [coronary heart disease (ñCHDò)].ò[3/] In 2001, NCEP issued the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (the ñGuidelinesò). Doc77,p29; Doc77-15,pp1-12; Doc77-16,pp1-13.[4/] The Guidelines, which were updated in 2004, provide, *inter alia*, detailed information related to cholesterol management, including cardiac risk

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[3/]NCEP Program Description, http://www.nhlbi.nih.gov/about/ncep/ncep_pd.htm (last visited April 5, 2013).

[4/]There were two earlier versions of the Guidelines. The full version of the 2001 Guidelines is at Doc45-3.

assessment, diet and exercise, and drug therapy, such as cholesterol medications called statins. Doc77,p29. Lipitor (otherwise known as atorvastatin (*e.g.*, Doc77-11,p1)) is a statin. Doc77-15,p9.

Pursuant to the Guidelines, the need for cholesterol-lowering drug therapy is based on, *inter alia*, the patientôs risk of getting CHD and the patientôs low-density lipoprotein (ñLDLò) level (otherwise known as ñbad cholesterolò). Doc77,p29.

The Guidelines summarize the assessment and treatment of people with elevated LDL cholesterol in nine steps. Doc77-15,pp7-11.

First, do a blood test to determine whether cholesterol is elevated. Doc77-15,p7.

Second, identify the presence of disease that confers high risk for CHD events. *Ibid*.

Third, determine the presence of major risk factors for CHD. *Ibid*.

Fourth, if there are two or more risk factors, calculate the risk of having a heart attack within ten years. Doc77-15,p8.

Fifth, determine the patientôs risk category. Doc77-15,p8. The table below, entitled ñNCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categoriesò (the ñGuidelines Tableò), was included in the Indications and Usages section in all of the Lipitor labeling

from 2001 until June 2009.[5/] Docs77-7-77-14; Doc108,p4.

TABLE 6. NCEP Treatment Guidelines: LDL-C Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk Category	LDL Goal (mg/dL)	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (mg/dL)	LDL Level at Which to Consider Drug Therapy (mg/dL)
CHD [a] or CHD risk equivalents (10-year risk >20%)	<100	≥100	≥130 (100-129: drug optional) [b]
2+ Risk Factors (10-year risk ≤20%)	<130	≥130	10-year risk 10%-20%: ≥130 10-year risk <10%: ≥ 160
0-1 Risk factor [c]	<160	≥160	≥190 (160-189: LDL-lowering drug optional)

[a] CHD, coronary heart disease
[b] Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of < 100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotinic acid or fibrate. Clinical judgement also may call for deferring drug therapy in this subcategory.
[c] Almost all people with 0-1 risk factor have 10-year risk <10%; thus, 10-year risk assessment in people with 0-1 risk factor is not necessary.

The Guidelines put patients into four risk categories, as summarized in the Table (Doc77,p31; Doc77-16,p1):

(a) **Highest Risk**: patients with CHD or a CHD-risk equivalent or a greater than 20 percent risk of having a heart attack within ten years;

(b) **Moderately High Risk**: patients with two or more risk factors and a 10 to 20 percent risk of having a heart attack within ten years;

[5/]Prior labeling included a prior guidelines table that corresponded to the earlier guidelines. Docs77-5,p4; Doc77-6,p11. As described below (pp. 14-15), the Lipitor labeling was modified in 2009.

(c) **Moderate Risk**: patients with two or more risk factors and less than 10 percent risk of having a heart attack within ten years;[6/] and

(d) **Low to Moderate Risk**: patients with zero or one risk factor.

The Guidelines differentiate between (1) the LDL goal, which is the LDL level that the patient should aim to achieve, (2) the LDL level at which to initiate Therapeutic Lifestyle Changes (ñTLCò), *i.e.*, diet and exercise, and (3) the LDL level at which to consider drug therapy, otherwise known as the drug therapy cutpoints. Doc77,pp30-31; Doc77-15,p8. Thus, cholesterol medication is only recommended under the Guidelines if patients are at or above their drug therapy cutpoint, but is not indicated if they are above the goal but below their drug therapy cutpoint. Doc77,pp30-31. Each risk category includes a goal, the level to initiate TLC, and a drug therapy cutpoint. *Ibid*.

Sixth, initiate TLC if the patientôs LDL level is above the goal for his or her risk category. Doc77-15,p8.

Seventh, consider cholesterol medication if LDL is at or exceeds the drug therapy cutpoints. Doc77-15,p9. The doctor should ñconsider drug [therapy]

[6/]The Moderate Risk and the Moderately High Risk groups are displayed in the same row in the table above (ñ2+ Risk Factorsò). The difference between the two categories is in the fourth column, which recommends drug therapy at different LDL levels based on different cardiac risk. Doc77,p32.

simultaneous with TLC for CHD or CHD equivalentsòð that is, for the highest risk category. *Ibid*. For all other categories, the doctor should ñconsider adding drug [therapy] to TLC after 3 months.ò *Ibid.*[7/]

B. LIPITOR'S LABELS PRIOR TO 2009 INCORPORATE THE GUIDELINES

Pfizer manufactures Lipitor, which is one of the best selling prescription drugs in the world. Doc77,p5. According to Pfizerôs website at the time that the complaint was filed, more than 26 million Americans had been prescribed Lipitor. *Ibid.*

From 2001, when the Guidelines were issued, to June 2009, the FDA-approved Lipitor labels were materially identical with regard to the issues relevant to this case. Docs77-7ï 77-14. All of those labels state that Lipitor is indicated to treat hypercholesterolemia (high cholesterol) and include the following statement in the ñIndications and Usageò section (*ibid.*):

> Therapy with lipid-altering agents should be a component of a multiple-risk-factor intervention in individuals at increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Lipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 6[8/]).

[7/]The eighth and ninth steps are irrelevant to this appeal.

[8/]The number of the referenced table changed in some of the labels when additional (continued...)

That paragraph is followed in all of the labels up to June 2009 by the Guidelines Table copied above (p. 10). The Guidelines Table informs the physician as to the goals and cutpoints based on the patientôs risk category and explains ñwhen the response to diet and other nonpharmacological measures has been inadequate.ò Doc77-11,p12.

The labels up to June 2009 (Docs77-7ï 77-14) also included the following statement in the ñDosage and Administrationò section (*e.g.*, Doc77-11,p22):

> The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of LIPITOR is 10 to 80 mg once daily. * * * The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines*, summarized at Table 6).

The reference, ñsee *NCEP Guidelines*, summarized at Table 6,ò directs the reader back to the Guidelines Table and instructs the doctor, once a drug therapy is required, to select the dose based on the goal from the Guidelines.

The inclusion of the Guidelines Table in the Lipitor labels is not surprising. Upon review of Pfizerôs initial Lipitor application to the FDA in 1996, the FDA made the following comments related to Pfizerôs proposed labeling (Doc99-11,p131):

[8/](...continued)
tables were added to the labeling and the tables were renumbered. *See, e.g.,* Doc77-12,p14. The text quoted above is from the labeling approved on January 16, 2007. Doc77-11,p12.

> [T]he inclusion in the labels of all the lipid lowering agents of the NCEP guidelines [referring to a prior version of the Guidelines] itself provides the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goals. These guidelines, in addition to information in each label pertaining specifically to the labeled drug, provide sufficient information for the safe and effective use of each agent.

The specified drug compendia (*see* p. 7 above) also incorporate the Guidelines and have not expanded the recommended uses for Lipitor beyond the FDA labeling. Doc77,p23.

C. LIPITOR'S LABELS FOR 2009 AND LATER ALSO INCORPORATE THE GUIDELINES

Lipitorôs label was revised by Pfizer pursuant to the FDAôs Physician Labeling Rule (ñPLRò) and, in June 2009, was approved by the FDA. 21 C.F.R. 201.56(b), 201.57; Doc101-2ï 101-3. The PLR was intended to make labels more understandable, not to modify or expand FDA-approved indications. *See* 71 Fed.Reg. 3922 (the ñrevisions will make it easier for health care practitioners to access, read, and use information in prescription drug labelingò); *see also* 21 C.F.R. 201.57(a)(5) (substantive modifications required to be noticed in the labeling).

The revised labeling still states that Lipitor is indicated for hypercholesterolemia, but no longer includes the Guidelines Table or refers to the Guidelines in the Indications and Usage section. Doc101-3,p4. However, the labeling continues to

incorporate the Guidelines in the Dosage and Administration section: ñThe starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*).ò Doc101-3,p5. The labeling does not identify any major changes or any other explanation for the changes in how the Guidelines are referenced. Doc101-3,pp1-24.

D. THE FDA INTERPRETS THE GUIDELINES TO BE PART OF THE LABELS FOR STATINS

Bristol-Myers Squibb Company manufactures a competing statin called Pravachol. Doc99-13,p1. When Pravachol received FDA approval in 1998, the FDA Medical Officer, in his comments related to the Indications and Usage section of the labeling, stated (Doc99-14,p36): ñBased on current guidelines (NCEP) that are included in the labeling for this and all other cholesterol-lowering drugs, those CHD patients with LDL-C on diet of >130 mg/dL should all be treated to goal LDL-C<100 mg/dL.ò

From December 2001 to May 2011, the Pravachol labeling included the Guidelines Table and the following language in the ñIndications and Usageò section, which was materially identical to that for Lipitor labels prior to June 2009: ñLipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has

been inadequate (see NCEP Guidelines below).ò[9/]

In 2003, the FDA issued a Warning Letter to Bristol-Myers Squibb regarding its off-label marketing of Pravachol. Doc99-13. The FDA stated that Pravacholôs advertisement ñbroaden[ed] the conditions and patient populations for which Pravachol was indicatedò by, *inter alia*, falsely implying that it was ñapproved for **all** patients with borderline-high cholesterolò (emphasis in original). Doc99-13,pp2,5 (ñBroadening of Indicationð Patients with Borderline-High Cholesterolò). The FDA then applied the Guidelines, including the Guidelinesô definition of borderline-high cholesterol (LDL between 130 and 159) (Doc77-15,p2): ñPravachol has only been approved for those borderline-high cholesterol patients with clinically evident CHDò (a conclusion drawn from the Guidelines Table); ñaccording to the NCEP Guidelines, borderline-high patients with 0 to 1 risk factors are not candidates for drug therapyò; and ñthe claims

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[9/] Pravachol Label and Approval History, http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Set_Current_Drug&ApplNo=019898&DrugName=PRAVACHOL&ActiveIngred=PRAVASTATIN%20SODIUM&SponsorApplicant=BRISTOL%20MYERS%20SQUIBB&ProductMktStatus=1&goto=Search.Label_ApprovalHistory (last visited April 5, 2013).

These and other documents cited in this brief are not in the record below but the Court can take judicial notice of them. Relator does not ask this Court to find facts based on them. On the contrary, Relator has cited these documents for background or to show that, not only did the district court make inappropriate factual findings, but it found facts that are contrary to the statements in these documents.

* * * are misleading because they are not accompanied by sufficient context stating that these claims only apply to patients with CHD or risk equivalents for CHDò (a conclusion drawn from the Guidelines). Doc99-13,pp6-7. Thus, the FDA confirmed that the Guidelines are incorporated into the labeling, are the labelôs limits for safe and effective use of statins, and that marketing in violation of the Guidelines amounts to off-label promotion. Doc99-13,pp2,5-6.

In 1999 and 2005, Merck, another Pfizer competitor, applied to the FDA to market its prescription statin, Mevacor, for over-the-counter (ñOTCò) use. *See* FDA Briefing Document for the Joint Session of the Nonprescription Drugs Advisory Committee and the Endocrinology and Metabolic Drugs Advisory Committee, pdf pp. 10, 119, 229 (Dec. 13, 2007), http://www.fda.gov/ohrms/dockets/ac/07/briefing/2007-4331b1-01-FDA.pdf (last visited April 5, 2012). The FDA did not approve those applications because the treatment paradigm in the labeling was not based on the Guidelines and because OTC consumers could not comply with them. *See id.*, pdf p. 10 (ñOn October 6, 2000, FDA sent Merck a letter stating that the [New Drug Application] was deficient because óneither the rationale for treating the proposed target population with Mevacor 10 mg in the OTC setting, nor a favorable benefit/risk ratio for such treatment has been adequately established. * * * The application did not: Provide sufficient evidence that

consumers could use Mevacor 10 mg in accordance with the National Cholesterol Education Program (NCEP) guidelinesò); pdf p. 229 (ñIn the October 2000 ónot Approvedô action letter * * *, one of the specific deficiencies of the application was that the Current National Cholesterol Education Program (NCEP) Guidelines were not incorporated in the OTC treatment paradigmò); pdf p. 119 (ñAt an April 25, 2005 meeting with the Sponsor, the Agency confirmed that the treatment paradigm [for OTC statins] must be consistent with * * * [the] Guidelines * * *ò). These FDA statements confirm that the use of statins to treat elevated cholesterol is limited by the NCEP Guidelines.

III

PFIZER MARKETED LIPITOR OFF-LABEL IN VIOLATION OF THE GUIDELINES

A. PFIZER'S HISTORY OF OFF-LABEL MARKETING

Pfizer has a long history of off-label marketing. Doc77,p23.

In 2004, Pfizer settled FCA claims for off-label marketing of its drug Neurontin. Doc77,p24. In connection with that settlement, Pfizer entered into a Corporate Integrity Agreement (ñCIAò) with the Department of Health and Human Services (ñHHSò) ñto promote compliance * * * with the statutes, regulations, and written directives of Medicare, Medicaid, and all other Federal health care programs * * * and

the applicable statutes, regulations, and written directives of the Food and Drug Administration * * * .ò[10/] Doc77-3,p1. In the CIA, Pfizer agreed to take extensive steps to ensure that it complied with all applicable federal healthcare programs and FDA regulations, including those prohibiting off-label marketing. Doc77,pp24-26; Doc77-4. Pfizer also agreed to submit, for five years, annual certifications of its compliance ñwith all of the requirements of th[e] CIA.ò Doc77-3,p27; Doc77,p24-25. Pfizer submitted those certifications annually from 2005 to 2009. Doc77,p26.

Pfizer entered into a similar CIA in 2009 as part of a $2.3 billion settlement related to off-label promotion of a range of drugs. Doc77,p26. The underlying conduct involved, *inter alia*, off-label sales pitches, market research to test off-label sales materials, delivery of off-label materials to physicians and hospitals, use of advisory boards and other fora to promote off-label uses, distribution of drug samples for off-label uses, and funding of purportedly independent educational programs to disseminate messages about off-label uses.[11/] Doc77,p26.

[10/]Pfizer had also entered into a CIA in 2002, which, on information and belief, included similar provisions. Doc77,p26.

[11/]The Department of Justice press release related to that settlement states (http://www.justice.gov/opa/pr/2009/September/09-civ-900.html (last visited April 5, 2013)):

> The size and seriousness of this resolution, including the huge criminal

(continued...)

The 2009 CIA required Pfizer again to take extensive steps to ensure that it complied with all applicable federal healthcare programs and FDA regulations and to certify compliance annually through 2014. Doc77-4,pp1,47-48.

B. PFIZER MARKETED LIPITOR OFF-LABEL TO DOCTORS AND PATIENTS THROUGH A FALSE AND MISLEADING MARKETING CAMPAIGN

The complaint alleges that Pfizerôs marketing campaign for Lipitor saturated the market with false and misleading information designed to induce physicians to prescribe Lipitor outside of the Guidelines. Doc77,pp33-110.

According to the Guidelines, over 100 million Americans have elevated cholesterol requiring either lifestyle modifications alone or lifestyle modification and drug therapy. Doc77,p3. The Moderate Risk group has 17.4 million people. *Ibid.* Of

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[11/](...continued)

> fine of $1.3 billion [there were additional civil remedies], reflect the seriousness and scope of Pfizerôs crimes[.] * * * Pfizer violated the law over an extensive time period. Furthermore, at the very same time Pfizer was in our office negotiating and resolving the allegations of criminal conduct by its then newly acquired subsidiary, Warner-Lambert, Pfizer was itself in its other operations violating those very same laws. Todayôs enormous fine demonstrates that such blatant and continued disregard of the law will not be tolerated.

See also United States ex rel. Wetherholt v. Pfizer, D. Mass., No. 06-10204-DPW ($14.5 million settlement to resolve allegations of off-label promotion of Detrol, http://www.justice.gov/opa/pr/2011/October/11-civ-1389.html (last visited April 5, 2013)).

those, only 2.8 million people are indicated for drug therapyð the majority, 14.6 million, require only lifestyle changes. *Ibid.* This suit relates, *inter alia,* to Pfizerôs recognition that, by marketing off-label to those Moderate Risk individuals that need only lifestyle changes and others which are not recommended for statins under the Guidelines, Pfizer could increase its revenues by billions of dollars. *Ibid.*[12/]

The Guidelines specifically state that patients in the Moderate Risk group are not recommended for drug therapy unless the patientôs LDL level reaches 160 (the drug therapy cutpoint), even though their goal is 130. Doc77,p32. The complaint alleges that Pfizer targeted these Moderate Risk patients with false and misleading information designed to induce use of Lipitor at levels below the Guidelinesô drug therapy cutpoints. Doc77,pp40-41. Those messages included the following themes: ñif you are not at your LDL goal, you should consider drug therapyò; ñGet to Goalò with the use of Lipitor; diet and exercise will not suffice to reduce your risk of heart disease; and ñLower [cholesterol] is better,ò without limit and without regard to risk category. Doc77,pp40-41. Through those themes, Pfizer tried to, *inter alia*, remove the distinction between the goals and cutpoints for drug therapy to encourage drug therapy

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[12/]In 2003, Pfizer made a presentation to investors, which described a goal of having Lipitor prescribed to 64 million American users. Doc77,pp81-82. Pfizerôs operating plan from 2002 stated that only 36 million Americans were eligible for statin use. *Ibid.* The 28-million difference would have had to be made up of off-label users. *Ibid.*

for Moderate Risk patients at 30 points below the approved level. Doc77,pp32, 40-41.

The complaint alleges that Pfizer did not simply disregard the Guidelinesð it falsely represented them while purporting to explain them to medical professionals and the public, and amplified the off-label messages through a range of inducements for off-label use, including free software and software support (Doc77,pp50-54,74), free continuing education programs (Doc77,pp84-101), paid speakers (Doc77,pp44-45,63-64,69,92,118), and free samples intended to promote off-label Lipitor prescriptions (Doc77,pp101-107). The complaint describes how Pfizerôs false and misleading message was disseminated to medical professionals and patients through a broad array of marketing tools, including training programs and instructions to Pfizer sales representatives (Doc77,pp44-45,76-77); training programs to medical groups, physicians, and clinic staff (Doc77,pp45-48,54-56,84-101,107-110); training programs for pharmacy benefit managers who help clinicians and patients select prescription drugs (Doc77,pp48-50); computer programs for physicians to determine when Lipitor is necessary (Doc77,pp50-54,72-76,77-78); statements on the Lipitor.com website (Doc77,p54); misleading interpretations of studies regarding the safety and effectiveness of Lipitor (Doc77,pp56-62,66-67); and advertisements to the public (Doc77,pp70-72). The complaint alleges that Pfizer made all of these false and misleading representations with knowledge of the Guidelines and that the Guidelines

were incorporated into the label. Doc77,pp4,23,41,43-45,50-51,134-135.

Below are just a few examples of the numerous false and misleading statements and marketing tools described in the complaint.

False presentations to Pfizer sales representatives and consultants. A Pfizer presentation about the Guidelines that was used to train sales representatives and physician consultants stated: ñLipid-lowering drug therapy should be considered for patients not at LDL goal after 3 months of therapeutic lifestyle changes.ò Doc77,p45. This statement is false because, under the Guidelines, statins are only appropriate if patients are at or above their drug therapy cutpoint, but not if they are above the goal, but below their drug therapy cutpoint.

False statements from Pfizer sales representatives. A Pfizer district sales manager for over 15 years stated the following: ñI donôt even remember using the terminology ócut-points.ô We never used that terminology. We always used NCEP goals.ò Doc77,p77.

False presentations to doctors. Speakers hired by Pfizer to explain the Guidelines told doctors that risk assessment was not necessary for multiple-risk patients. Doc77,p47. However, risk assessment is essential under the Guidelines for multiple risk patientsð it determines whether a patientôs drug therapy cutpoint is 160 (Moderate Risk patients) or 130 (Moderately High Risk patients).

False representations to patients. On a Pfizer website aimed at what Pfizer referred to as ñlow health literacyò Spanish-speaking populations, Pfizer provided a Guidelines table showing three, rather than four risk categories, stated that the goal for all people with two or more risk factors is 130, and recommended Lipitor for people with an LDL level greater than 130. Doc77,pp70-71. The website never mentioned the cutpoint levels, but stated: ñYour LDL should not be greater than your goal but it is best to have an LDL below 100.ò Doc77,p71. Again, under the Guidelines for Moderate Risk patients, Lipitor is only appropriate at an LDL level of 160.

Pfizerôs misrepresentations regarding the Guidelines extend well beyond the Guidelinesô Moderate Risk group. For example, Pfizer promoted Lipitor use without regard to the requirement for a trial of diet and exercise. Doc77,pp40-42,70-72. Diet and exercise is required prior to initiation of statin therapy under the Guidelines, except for people that fall into the highest risk group.[13/]

[13/]On July 12, 2001, the FDA sent Pfizer a letter instructing it to cease distribution of an advertisement that ñsuggest[ed] that all patients, including those with high cholesterol who have not tried to lower cholesterol using diet and exercise, are candidates for Lipitorò and was therefore ñmisleading because it broaden[ed] the approved indication by minimizing information about the correct use of Lipitor.ò http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM166440.pdf, pp. 2-3 (last visited April 5, 2013). On August 12, 2002, the FDA sent Pfizer a warning letter regarding a Lipitor advertisement that ñmisleadingly suggests that Lipitor is safer than other statinsò and ñminimiz[es] * * * (continued...)

Pfizer also falsely marketed that chronic kidney disease is a risk equivalent to coronary heart disease, which would cause all people with chronic kidney disease to fall into the highest risk group in the Guidelines. Doc77,pp62-70. According to the Guidelines, patients in the highest risk group are treated with drug therapy at lower cholesterol levels and at higher dosages. Moreover, Pfizer falsely marketed Lipitor as a safe and effective medication to preserve kidney function. Doc77,pp64-66,83. The 26 million Americans that suffer from chronic kidney disease is a massive market for Pfizer. Doc77,p62.

Pfizer also marketed Lipitor at excessive doses across all Guideline risk levels. Doc77,pp40-41,54,56-57,60,98-100,103-105. For example, it provided high dose samples to doctors while limiting access to low dose samples to encourage prescription and continued use of Lipitor in high doses, which are more expensive and are not available in generic alternatives. Doc77,pp103-105.

The labeling identifies a range of significant risks for the use of Lipitor, including increased rates of diabetes, hemorrhagic stroke, and debilitating and irreversible muscle damage. Doc106; Doc106-1,pp1,5,6; *see also* Doc77,pp17-22,27-28,66. The risks

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[13/](...continued)
serious risks associated with Lipitor therapy.ò http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/UCM164805.pdf, pp. 1, 2.

are dose dependent, *i.e.*, the higher the dose the higher the risks. Doc77,p104; Doc45-3,pVI-19.

C. THE GOVERNMENT PAID FOR OFF-LABEL LIPITOR AS A RESULT OF PFIZER'S OFF-LABEL MARKETING

The complaint alleges that Pfizerôs marketing has had an impact on the decisions by doctors and patients to initiate drug therapy. Doc77,p4. As the district court observed, that is precisely why Pfizer invests hundreds of millions of dollars annually in that effort. Doc58,pp39,43-44.

To analyze the impact of Pfizerôs off-label marketing, Relator commissioned a leading research firm to analyze national statin use for the period from 2001 to 2006 based on data gathered by the Center for Disease Controlôs (ñCDCò) National Center for Health Statistics. Doc77,pp111-115. The study concluded that Lipitor was being prescribed off-Guidelines far more than any competing statins. Doc77,pp112-115. Over the study period, an average of 20.9% of Lipitor prescriptions were off-Guidelines, while only 12.8% of competitorsô statins were off-Guidelines. Doc77,p112. Lipitor off-Guideline use increased by over 150 percent over the study period while there was no increase in off-Guideline usage of competitorsôstatins. *Ibid*.

For Medicare, Medicaid, and other federal healthcare program beneficiaries, the false claims for off-label prescriptions are submitted by pharmacies to the government

and its contractors. Doc77,pp4,11-16; *see* p. 7-8 above.

IV

RELATOR'S EMPLOYMENT CLAIMS

Relator also raised employment claims against Pfizer, which are described below (pp. 60-61).

SUMMARY OF ARGUMENT

1. The complaint alleges that, by marketing Lipitor in a false and misleading manner in violation of the Guidelines, which are incorporated into Lipitorôs labeling, Pfizer knowingly caused doctors to prescribe Lipitor off-label, pharmacies to dispense Lipitor off-label, pharmacies to bill the government for beneficiaries of Medicare, Medicaid, or other government health benefits, and the government unknowingly to pay for millions of off-label Lipitor claims, even though it is prohibited from doing so.

The district court dismissed the complaint based on the conclusion that the Guidelines are not a mandatory part of the Lipitor labeling and therefore Pfizer did not market off-label. That conclusion is wrong.

The Lipitor labeling up to 2009 explicitly included the Guidelines as the limits of when to prescribe Lipitor and how it should be dosed. The FDA stated that the Guidelines ñprovide[] the relevant information necessary for the identification of the appropriate treatment populations for [Lipitor] and for the determination of

individualized treatment goalsò (Doc99-11,p131), stated in a warning letter to a Pfizer competitor that marketing in violation of the Guidelines is an impermissible ñbroaden[ing of] the conditions and patient populations for which [that statin] is indicatedò (Doc99-13,p2), and underscored their importance when it did not approve Merckôs applications to market Mevacor OTC because the treatment paradigm in that labeling was not based on the Guidelines and because OTC consumers could not comply with them. Judge Korman, the prior district court judge, stated that ñTable 6 [the Guidelines Table] summarizes the NCEP Guidelines * * *, which provide the basis for FDA-approved indications for the treatment of persons with elevated levels of LDL cholesterol.ò Doc60,pp2-3. The district court did not address the FDA or Judge Kormanôs statements in its opinion. Moreover, the district courtôs reasoning is internally inconsistent. In short, whether or not the Guidelines standing alone would be mandatory, they were incorporated in the Lipitor labeling, and therefore claims on the government that are beyond the explicit limits of the Guidelines and result from Pfizerôs false and misleading marketing are off-label and are false claims under the FCA.

The decision also wrongly concluded that the Guidelines are not incorporated into the 2009 and subsequent labeling because the reference to the Guidelines in the Indications and Usage section of those labels was removed pursuant to an FDA rule

regarding revisions in order to make labeling easier to understand. However, the Guidelines continue to be referenced in the Dosage section. Moreover, FDA regulations require substantive changes to labeling to be explicitly noted in a highlights section and no such changes were noted in the 2009 labeling. Since the Guidelines provide the basis for determining when cholesterol is high, and how and when it should be treated, the removal of one reference to the Guidelines from the labeling, without explanation, while retaining it in another section, did not make the Guidelines inapplicable to Lipitor marketing.

2. The district courtôs decision was also premised on prohibited factual findings about the meaning of the Lipitor labels and the FDAôs conduct and decisionmaking, which are contrary to the complaintôs allegations and the FDA documents that were presented to it. Such fact-finding is not permissible in deciding a motion to dismiss under Rule 12(b)(6). The Relator was entitled to discovery and the presentation of expert testimony on these issues.

3. The district court also wrongfully dismissed Relatorôs employment claims despite the fact that Pfizer did not move to dismiss those claims, the parties therefore did not brief them, and the district court did not consider them.

ARGUMENT

Standard of Review

Appellate courts ñreview *de novo* the dismissal of a complaint under Federal Rule of Civil Procedure 12(b)(6), accepting all factual allegations as true and drawing all reasonable inferences in favor of the plaintiff.ò *New Jersey Carpenters Health Fund v. Royal Bank of Scotland Group, PLC*, 2013 WL 765178, *7 (2d Cir. 2013) (quotation omitted).

I

THE DISTRICT COURT WRONGLY DISMISSED THE FALSE CLAIMS ACT CLAIMS

A. THE COMPLAINT'S ALLEGATIONS SHOW THAT, THROUGH ITS FALSE AND MISLEADING MARKETING CAMPAIGN, PFIZER KNOWINGLY CAUSED LIPITOR TO BE PRESCRIBED, DISPENSED, AND PAID FOR IN VIOLATION OF THE FALSE CLAIMS ACT

The FCA seeks to remedy fraud on the federal government by allowing individuals, such as Relator, to sue to recover fraudulent proceeds on behalf of the United States government. *See* 31 U.S.C. 3730(b). As the United States stated in its Statement of Interest that was filed in the district court (Doc98,p1): ñ[T]he statute should be read broadly to reach all fraudulent attempts to cause the government to pay out sums of moneyò (citing *United States v. Neifert-White*, 390 U.S. 228, 233 (1968)).

The complaint alleges two claims under the False Claims Act. Doc77,pp134-

135. First, the complaint alleges that Pfizer is liable pursuant to 31 U.S.C. 3729(a)(1), for ñknowingly * * * caus[ing] to be presented, to an officer or employee of the United States Government or a member of the Armed Forces of the United States a false or fraudulent claim for payment or approval.ò[14/] Doc77,pp134-135.

Second, Relator alleges that Pfizer is liable pursuant to 31 U.S.C. 3729(a)(1)(B), for ñknowingly mak[ing], us[ing], or caus[ing] to be made or used, a false record or statement material to a false or fraudulent claim.ò[15/] Doc77,pp134-135.

We briefly address below how these allegations satisfy the FCA elements. We then address the basis for the district courtôs dismissal.

1. 31 U.S.C. 3729(a)(1)

To state a claim pursuant to 31 U.S.C. 3729(a)(1), a plaintiff must allege that (1)

[14/]This provision was amended and renumbered in 2009 pursuant to the Fraud Enforcement and Recovery Act of 2009 (ñFERAò), but those amendments explicitly apply only to conduct on or after the date of enactment. *See* Pub. L. No. 111-21, Sec. 4(f), 123 Stat. 1617 (May 20, 2009); *United States ex rel. Kirk v. Schindler Elevator Corp.*, 601 F.3d 94, 113 (2d Cir. 2010), *rev'd on other grounds*, 131 S.Ct. 1885 (2011). Accordingly, Relator cites herein this provision pre-FERA. For violations occurring on or after May 20, 2009, the relevant statute is 31 U.S.C. 3729(a)(1)(A), which makes liable ñany person who * * * knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval.ò

[15/]This provision was also amended and renumbered pursuant to FERA. In contrast to 31 U.S.C. 3729(a)(1), the amendments to this provision explicitly affect all claims that were pending as of June 7, 2008. *See Kirk*, 601 F.3d at 113. Accordingly, Relator cites herein this provision post-FERA.

there was a false or fraudulent claim, (2) the defendant knew that it was false or fraudulent, (3) the defendant presented the claim or caused it to be presented to the United States, and (4) the defendant did so to seek payment from the federal treasury. *United States ex rel. Pervez v. Beth Israel Medical Center,* 736 F. Supp. 2d 804, 811 (S.D.N.Y. 2010); *see also Mikes v. Straus*, 274 F.3d 687, 695 (2d Cir. 2001).

The complaint satisfies these elements by alleging that, by marketing Lipitor beyond the prescribed boundaries of the Guidelines (*see* pp. 20-26 above), which are incorporated into the labeling (*see* pp. 12-18 above), Pfizer knowingly and to seek payment (*see* pp. 20-26 above) caused doctors to prescribeð and pharmacies to dispenseð Lipitor off-label, the government to be billed for such off-label Lipitor dispensed to beneficiaries of Medicare, Medicaid, and other government health programs (the false claim), and the government unknowingly to pay for that off-label Lipitor, even though it was prohibited from doing so (*see* pp. 5-8, 26-27 above).[16/]

2. 31 U.S.C. 3729(a)(1)(B)

To state a claim pursuant to 31 U.S.C. 3729(a)(1)(B), a plaintiff must allege that (1) the defendant made or caused to be made a false or fraudulent record or statement, (2) that the defendant knew to be false, and (3) that was material to a claim on the

[16/]As stated above (p. 14), the statutory compendia also incorporate the Guidelines and have not expanded the uses for Lipitor beyond the FDA labeling. They therefore provide no basis for payment of off-label Lipitor prescriptions.

government. *Pervez,* 736 F. Supp. 2d at 811.

The complaint satisfies the elements of this claim for similar reasons as it does for the claim arising under 31 U.S.C. 3729(a)(1). Pfizerôs false and misleading marketing, which Pfizer knew to be false, caused doctors to write off-label prescriptions that caused pharmacies to make false claims on the government.[17/]

B. THE DISTRICT COURT ERRED IN CONCLUDING THAT THE GUIDELINES DO NOT SET FORTH THE CONDITIONS FOR WHICH LIPITOR CAN BE MARKETED AND THEREFORE THAT PFIZER DID NOT CAUSE THE SUBMISSION OF FALSE CLAIMS

1. Claims for Reimbursement for Drugs that Are Prescribed Off-Label Are False Claims

When a pharmacy submits a claim to the government for reimbursement for a dispensed drug, the pharmacy is making an implied certification that the government can pay for the drug. *See Mikes*, 274 F.3d at 697; *United States ex rel. Carpenter*, 723 F. Supp. 2d at 408-409; *see also* U.S. Statement of Interest, Doc98,p5 (ñWhether the provider ócertifiedô on the claim for payment that the prescribed usage was on-label or otherwise reimbursable is irrelevant. Rather, the core question for ófalsityô under the

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[17/]This Court recently ñconstrue[d] the misbranding provisions of the [Food, Drug, and Cosmetic Act] as not prohibiting and criminalizing the truthful off-label promotion of FDA-approved prescription drugs.ò *Caronia*, 703 F.3d at 168. However, this Court explained that ña defendant may be prosecuted for untruthfully promoting the off-label use of an FDA-approved drug, *e.g.,* making false or misleading statements about a drug.ò *Id*. at 165, n.10.

FCA is whether the government received a bill from a healthcare provider for an item or service that was not legally reimbursableò). Medicare, Medicaid, and other federal healthcare programs are forbidden from knowingly paying for drugs that are prescribed off-label and are for uses not supported by the statutory compendia. *See* pp. 7-8 above. Therefore, when pharmacies submit claims to the government for payment for off-label and off-compendia uses, those are false claims. Accordingly, numerous courts have held that FCA liability can be based on off-label marketing of drugs that causes off-label prescriptions to be dispensed at the governmentôs expense. *See* pp. 44-45 below.

2. The Guidelines Were Incorporated into the Pre-2009 Lipitor Labels and Therefore Marketing Lipitor in Violation of the Guidelines is Off-Label

The pre-2009 Lipitor labeling stated in the Indications and Usage section that Lipitor ñshould be used in addition to a diet restricted in saturated fat and cholesterol only when the response to diet and other non-pharmacological measures has been inadequate (*see National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 6).ò *E.g.,* Doc77-11,p12. Table 6 summarized the Guidelines and appears on the labels. *Ibid.* It provides the goals and cutpoints that apply to each risk category and thereby explains when ñdiet and other nonpharmacological measures ha[ve] been inadequateò (Doc77-11,p12) and Lipitor should be prescribed. *See* pp. 12-14 above.

The Dosage section of the Lipitor labeling up to 2009 also explicitly incorporates the Guidelines. It states: ñ[t]he starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see *NCEP Guidelines*, summarized at Table 6)ò *E.g.,* Doc77-11,p22.

The FDA regulations provide that material from a scientific body, such as the National Institutes of Health, National Heart, Lung, and Blood Instituteôs National Cholesterol Education Program, which promulgated the Guidelines, can be incorporated into labeling by reference. *See* 21 C.F.R. 201.57(c)(16) (ñWhen prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the informationò (emphasis added)); 21 C.F.R. 201.80(m). Here, the label incorporated the Guidelines by reference and explicitly included the Guidelines Table itself.

Moreover, upon approval of the initial Lipitor application in 1996, the FDA made the mandatory nature of the Guidelines clear (Doc99-11,p131):

> [T]he inclusion in the labels of all the lipid lowering agents of the NCEP guidelines itself provides the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goals. These guidelines, in addition to information in each label pertaining specifically to the

> labeled drug, provide sufficient information for the safe and effective use of each agent.

Thus, the labeling states that Lipitor should be used to treat high cholesterol and the Guidelines explain what is high, and when and how it should be treated.

Moreover, FDA regulations provide that the Indications and Usage section of a labeling ñshall state,ò *inter alia*, the following (21 C.F.R. 201.80(c)(3)(i)):

> If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease * * *, the labeling shall describe the available evidence and state the limitations or usefulness of the drug. * * * If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the ñDosage and Administrationò section of the labeling and referenced in this section.

See also 21 C.F.R. 201.57(c)(2)(i). As the FDA stated, the Guidelines ñprovide[] the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goals.ò Doc99-11,p131.

Accordingly, Judge Korman, the prior district court judge, stated that the Guidelines ñprovide the basis for FDA-approved indications for the treatment of persons with elevated levels of LDL cholesterol.ò Doc60,pp2-3; *see also* Doc60,p4 (ñBecause the Guidelines are incorporated into Lipitorôs label * * * ò).

Nonetheless, the district court dismissed the FCA claims based primarily on the conclusion that ñGuidelines óguide,ôthey do not mandate,ò and therefore Pfizer cannot be liable for marketing in violation of the Guidelines. Doc108,p5. Relator does not dispute that documents called ñguidelinesò can be permissive. However, here, regardless of whether the Guidelines would be mandatory standing alone, the FDA made the Guidelines mandatory by incorporating them in Pfizerôs Lipitor labeling. The district courtôs contrary conclusion is directly inconsistent with the position taken by the FDA and is a fact-finding that is prohibited on a Rule 12(b)(6) motion to dismiss (*see* pp. 51-57 below).

The district court also said that the Guidelines must not be mandatory because the labeling does not explicitly state that they must be followed (Doc108,p10):

> [T]he FDA could have limited reimbursable prescriptions of Lipitor to patients within the Guidelines had it wanted to do so. For example, it could have easily required Pfizer to simply add to the label: ñThis drug is not approved for, and should not be prescribed to, any patient who falls outside of the NCEP Guidelines.ò [footnote omitted] If that or similar language appeared on the label, then virtually any effort by Pfizer to market to doctors for their patients outside of the Guidelines would have to be considered off-label marketing. But there is no such restriction.

That conclusion, and the district courtôs other reasons for believing that the Guidelines are not mandatory, are wrong for numerous reasons.[18/]

[18/]Before addressing those reasons, it is important to note the district courtôs apparent (continued...)

First, the district court disregarded the mandatory language of the pre-June 2009 labels. The district court did not address how its proposed language (ñThis drug is not approved for, and should not be prescribed to, any patient who falls outside of the NCEP Guidelinesò) is materially different than the language in the actual labeling (Lipitor ñshould be used * * * **only when** the response to diet and other nonpharmacological measure has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 6) (bold added)).ò Doc77-11,p12. Both labels include mandatory terms.

The same problem applies to the district courtôs discussion of the medication Kaletra (Doc108,pp10-11):

> [I]n *U.S. ex rel. Carpenter v. Abbot Laboratories. Inc.*, 723 F. Supp.2d 396,398 (D. Mass. 2010), the approved label included the admonition that ñonce-daily administration of Kaletra is not recommended in therapy-experienced patientsò (emphasis omitted), and the pharmaceutical company defendant was accused of marketing Kaletra to doctors for therapy-experienced patients. That is clearly an off-label marketing campaign, and stands in contrast to plaintiff's accusation against Pfizer in this case.

[18/](...continued)
misunderstanding of the FDAôs role. The district court wrote that ñthe FDA could have limited reimbursable prescriptions of Lipitor to patients within the Guidelines had it wanted to do so.ò Doc108,p10. While the FDA indirectly affects reimbursement by Medicare and Medicaid by approving labeling and thereby determining what is on or off-label, the FDA has no direct responsibility for regulating reimbursement by the government. *See* p. 6 above.

The district court therefore concluded that the phrase ñis not recommended,ò is mandatory, whereas the phrase ñshould be used * * * only whenò is not. The district court provided no explanation for that distinction. In fact, the Kaletra language is far less strong.

In contrast, other FDA labeling includes clearly permissive language with respect to other guidelines. For example, in March 2011, the FDA released a Guidance document regarding blood pressure medication called *Guidance for Industry, Hypertension Indication: Drug Labeling for Cardiovascular Outcome Claims* (http://www.fda.gov/downloads/ Drugs/.../Guidances/ucm075072.pdf (last visited April 5, 2013)). That document states the following (p. 4):

> The INDICATIONS AND USAGE section of the Full Prescribing Information should be modeled after the following. * * * For specific advice on goals and management, see published guidelines, such as those of the National High Blood Pressure Education Programôs Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC). [emphasis added]

Permissive language such as ñ[f]or specific advice on goals and management, see published guidelinesò (emphasis added), stands in sharp contrast to the language in the Lipitor labeling.

Second, the FDA concluded that the Guidelines in the materially identical labeling for a competitor statin, Pravachol, are mandatory and not mere advice. *See* pp.

15-17 above. The FDA wrote the manufacturer a warning letter ordering it to pull its advertisements that are inconsistent with the Guidelines because those advertisements ñbroaden[ed] the conditions and patient populations for which Pravachol is indicated.ò Doc99-13,p2. The district court should have deferred to the FDAôs interpretation of its own rules. *See Lopes v. Department of Social Services*, 696 F.3d 180, 187 (2d Cir. 2012) (ñThe interpretive guidance of an administrative agency such as HHS óconstitute[s] a body of experience and informed judgment to which courts and litigants may properly resort for guidanceôò (citation omitted)); *Biediger v. Quinnipiac University*, 691 F.3d 85, 96-97 (2d Cir. 2012) (court deferring to agency interpretation of its own regulation). However, the district court did not even address the FDA opinion.[19/]

Moreover, in 1999 and 2005, Merck applied to the FDA to market its prescription statin, Mevacor, for over-the-counter use. *See* pp. 17-18 above. The FDA did not approve those applications because the treatment paradigm in the labeling was

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[19/]The Lipitor labeling is even stronger than the Pravachol label. The relevant Pravachol labels say ñLipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol when the response to diet and other nonpharmacological measures alone has been inadequate (see NCEP Guidelines below).ò *See* pp. 15-16 above. The Lipitor label says: ñLipid-altering agents should be used in addition to a diet restricted in saturated fat and cholesterol **only** when the response to diet and other nonpharmacological measures has been inadequate (see *National Cholesterol Education Program (NCEP) Guidelines*, summarized in Table 6 (bold added)ò Doc77-11,p12.

not based on the Guidelines and because OTC consumers could not comply with them. *Ibid.* (*E.g.,* ñAt an April 25, 2005 meeting with the Sponsor, the Agency confirmed that the treatment paradigm [for OTC statins] must be consistent with * * * [the] Guidelines * * *ò). The FDA statements confirm that the use of statins to lower cholesterol is limited by the NCEP Guidelines.[20/]

Third, the district courtôs conclusion that, with the right language (ñThis drug is not approved for, and should not be prescribed to, any patient who falls outside of the NCEP Guidelinesò (Doc108,p10)), the Guidelines could have been mandatory, is inconsistent with its other suggestion that the Guidelines could never be mandatory (Doc108,p9):

> I cannot accept plaintiffôs theory that what the scientists at the National Cholesterol Education Program clearly intended to be advisory guidance is transformed into a legal restriction simply because the FDA has determined to pass along that advice through the label.

As explained above, the FDA stated that the Guidelines ñprovide[] the relevant information necessary for the identification of the appropriate treatment populations for [Lipitor] and for the determination of individualized treatment goals.ò Doc99-11,p131.

[20/]In another warning letter, the FDA concluded that other guidelines were mandatory. *See* Warning Letter to Slate Pharmaceuticals, dated March 24, 2010, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/ucm259232.htm (last visited April 5, 2013), p.8.

That is not just a recommendation.

Fourth, the district courtôs interpretation of a footnote to the Guidelines Table raises questions as to the district courtôs understanding of the Guidelines. The Guidelines Table states that, for the highest risk individuals (the first row), the LDL goal is an LDL level of less than 100, diet and exercise should be started when the LDL level is greater than or equal to 100, and Lipitor is appropriate when the LDL level is greater than or equal to 130 (the drug therapy cutpoint). *See* p. 10 above. On the same row, the table includes a parenthetical, stating ñ100-129: drug optionalò and footnote b to it states the following:

> Some authorities recommend use of LDL-lowering drugs in this category if an LDL-C level of <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL-C, e.g., nicotine acid or fibrate. Clinical judgement also may call for deferring drug therapy in this category.

Without explanation, the district court concluded that ñ[t]he advisory, rather than mandatory, application of the NCEP chart [the Guidelines Table] is made plain by [this footnote].ò Doc108,p9. Presumably the district court reached that conclusion because the footnote states that there is no firm instruction as to treatment of certain high risk patients.

However, rather than undermine Relatorôs argument, the footnote bolsters it. It makes clear that Lipitor is optional for high risk patients with LDL levels of 100-129.

In contrast, Lipitor is not optional for high risk patients with LDL levels above 130 (stated otherwise, it is recommended) and is not optional for high risk patients with LDL levels below 100 (stated otherwise, it is off-label).

Although the district court does not reference it, the Guidelines Table includes a similar comment with regard to low risk individuals. Their cutpoint is an LDL level greater than or equal to 190, but the table adds a parenthetical that says ñ160-189: LDL-lowering drug optional.ò

Noticeably absent from the table is any such ñoptionalò comment or footnote for the Moderate or Moderately High risk categories, which, as described above (pp. 20-24), represent millions of individuals that the complaint alleges to have been prescribed Lipitor as a result of Pfizerôs false and misleading marketing campaign.

This error also underscores the district courtôs misunderstanding of the Lipitor labels more broadly. The district court stated that the FDA ñhas not restricted or even recommended against its use for any particular patient population except those with active liver disease, demonstrated hypersensitivity to the drug, and pregnant women and nursing mothers.ò Doc108,pp11-12. To the contrary, the Lipitor labels restrict Lipitorôs use in accordance with the specific numerical limits in the Guidelines.

Finally, the district courtôs conclusion is undermined by its statements that as long as Pfizer marketed Lipitor for use regarding cholesterol, rather than something

entirely different, such as hair growth or cancer, it was not violating the labeling. Doc108,pp6-7,11-12. That conclusion is simply wrongð marketing of Lipitor can be off-label even if it relates to cholesterol. Thus, the FDA concluded that Bristol Myers Squibb was marketing another statin, Pravachol, off-label by marketing it as appropriate for all patients with borderline high cholesterol rather than to patients with borderline high cholesterol with CHD. *See* pp. 15-17 above.

Similarly, other courts have not required for liability such a wide disparity between off-label promotion and the FDA-approved use. *See, e.g.*, *United States ex rel. Carpenter*, 723 F. Supp. 2d at 399-404 (D. Mass. 2010) (denying motion to dismiss FCA claim for off-label marketing of antiviral drug to ñtherapy-experienced,ò rather than approved use for ñtherapy-naiveò patients, and as monotherapy, rather than for use in combination with other drugs); *United States ex rel. Kennedy v. Aventis Pharmaceuticals, Inc.*, 610 F. Supp. 2d 938, 941-945 (N.D. Ill. 2009) (denying motion to dismiss FCA claim for off-label marketing), 512 F. Supp. 2d 1158, 1161-1163 (N.D. Ill. 2007) (alleged off-label marketing was for an anticoagulant in different inpatient contexts from which it was approved); *United States ex rel. Strom v. Scios, Inc.*, 676 F. Supp. 2d 884, 885 (N.D. Cal. 2009) (denying motion to dismiss FCA claim for off-label marketing of drug to patients with ñchronicò congestive heart failure rather than for approved use by patients with ñacutely decompensatedò congestive heart failure);

United States ex rel. Franklin, 147 F. Supp. 2d at 45, 50-53 (denying motion to dismiss FCA claim for off-label marketing of drug for uses, including pain control and as a monotherapy for epilepsy, rather than for approved use as an adjunctive treatment for epilepsy), 2003 WL 22048255, *1-3 (D. Mass. 2003) (denying related motion for summary judgment).

3. The Guidelines Have Been Incorporated into the June 2009 and Subsequent Lipitor Labels and Therefore Marketing Lipitor in Violation of the Guidelines Is Off-Label

Lipitor labels in and after June 2009 were revised by Pfizer and approved by the FDA pursuant to the Physician Labeling Rule (ñPLRò). 21 C.F.R. 201.56(b), 201.57. Amendments made pursuant to the PLR are to make labels more understandable, not to modify or expand FDA-approved indications. *See* 71 Fed.Reg. 3922.

Substantive changes are required to be noticed on labeling in a section called ñRecent major changes.ò 21 C.F.R. 201.57(a)(5) (ñThe following information must appear in all prescription drug labeling: * * * (5) Recent major changes. A list of the section(s) of the full prescribing information, [including Indications and Usage and Dosage and Administration] * * * that contain(s) substantive labeling changes that have been approved by FDA * * *ò). That includes deletions from the labeling (Guidance for Industry, Labeling for Human Prescription Drug and Biological Productsï Implementing the PLR Content and Format Requirements, February 2013

(ñFinal PLR Guidanceò), p. 10, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075082.pdf (last visited April 5, 2013)):

> Although it is unusual for information to be completely deleted from labeling (e.g., removing a warning as opposed to revising it or moving the discussion to a different section), if such a situation occurs, the applicant should propose labeling that identifies the change in both Recent Major Changes in Highlights and in the [Full Prescribing Information (ñFPIò)].[21/]

The labels in and after June 2009 state the following in the ñIndications and Usageò section (*see* Doc101-3,p4):

> Therapy with lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for atherosclerotic vascular disease due to hypercholesterolemia. Drug therapy is recommended as an adjunct to diet when the response to a diet restricted in saturated fat and cholesterol and other nonpharmacologic measures alone has been inadequate. In patients with CHD or multiple risk factors for CHD, LIPITOR can be started simultaneously with diet.

Unlike the prior labeling, the June 2009 labeling does not reference the Guidelines in the Indications and Usage section or include the Guidelines Table, although it retains the Guidelinesô reference in the Dosage section. The effect of that difference is disputed. Nonetheless, the district court stated that ñit is noteworthy that the FDA did not consider the NCEP Guidelines chart to consist of sufficiently ócritical

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[21/]The Draft Guidance, which was issued in January 2006, included a similar statement. Doc99-12,pp9-10.

informationô to include in the 2009 label, which of course is an indication of its permissive nature in the 2005 label.ò Doc108,p9. The district court then concluded that, by approving this labeling modification, the FDA was stating that the Guidelines do not dictate the use and administration of Lipitor. Doc108,pp7-8. That conclusion is erroneous for several reasons.

First, there is a factual question as to the meaning of the removal of the reference to the Guidelines and Guidelines Table from the Indications and Usage section of the labeling. That removal does not appear to have been considered a substantive change under the PLR since no ñmajor changeò was identified in the revised labeling. *See* Doc101-3; 21 C.F.R. 201.57(a)(5). However, the revision also does not fit neatly into the non-substantive change category. The Guidance from the FDA states that ñChanges that must not be listed in Recent Major Changes include: * * * Changes that are not substantive (i.e., minor revisions such as correcting typographical errors or grammatical changes).ò[22/] Final PLR Guidance, p. 8. Removal of the Guidelines Table hardly amounts to the correction of a typographical or grammatical error if it is deemed to remove the requirements in the earlier labels basing usage of Lipitor on the Guidelines.

[22/]The Draft Guidance included a similar statement. Doc99-12,p8. The ñRecent Major Changesò section also need not include changes ñresulting from converting to the PLR format alone.ò Final PLR Guidance, p. 8.

As we have seen above (pp. 12-18), the FDA has repeatedly emphasized the importance of the Guidelines as incorporated in statin labeling. The Guidelines provide the basis for determining when cholesterol is high and how and when it should be treated with statins. The removal of the reference to the Guidelines from the Indications and Usage section of the labeling, while retaining it in the Dosage section, without any explanation, does not affect that fact.

The district court concluded that, by approving the removal of the reference to the Guidelines from the Indications and Usage section of the label, the FDA concluded that the Guidelines do not provide the required basis for determining when cholesterol is high and how and when it should be treated. Doc108,pp7-8. That is a factual issue that cannot be resolved on a motion to dismiss. *See* pp. 51-57 below.

Second, the continued relevance of the Guidelines is evidenced by the ñDosage and Administrationò section of the 2009 labeling. That section of the revised labeling is nearly identical to the earlier labeling. It states, in relevant part, the following (Doc101-3,p5):

> The recommended starting dose of LIPITOR is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily.[23/] The dosage range of LIPITOR is 10 to 80 mg once daily. LIPITOR can be administered as a single dose at any time

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[23/] Pfizerôs marketing of excessive starting dosage (*see* p. 25 above) violates these portions of the Lipitor labeling, regardless of the Guidelines.

> of the day, with or without food. The starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response (see current *NCEP Guidelines*).

The parenthetical ñsee current *NCEP Guidelines*ò no longer directs the reader to the Guidelines Table because that table is no longer physically part of the labeling. However, it still directs the reader to the Guidelines.

As we have seen above (p. 35), a reference to the Guidelines is alone enough. This reference instructs the physician to select the dose based on the goal from the Guidelines.[24/] Therefore, even if this Court were to conclude that the Guidelines are not incorporated in the June 2009 and later Lipitor labels regarding Indication and Usage, it should conclude that the Guidelines are incorporated regarding dosage and that, therefore, Relatorôs allegations that relate to off-label marketing regarding dosage for 2009 and later state a claim upon which relief can be granted.

Third, Pfizer drafted the revised labeling and submitted it to the FDA for review and approval. Doc101-2,p1. The labeling was drafted while this lawsuit was pending. *Ibid.* This lawsuit gave Pfizer a substantial motivation to modify its labeling to remove

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[24/]The district court stated that ñ[t]here is nothing restrictive in * * *[the following] sentenceò in the label: ñThe starting dose and maintenance doses of LIPITOR should be individualized according to patient characteristics such as goal of therapy and response [the actual label states here: (see current *NCEP Guidelines*)].ò Doc108,p7. Again, this is indistinguishable from language that the district court concluded is restrictive. *See* pp. 37-39 above.

reference to the Guidelines. As with other legal documents, the 2009 labeling should be interpreted against its author. *See Mastrobuono v. Shearson Lehman Hutton, Inc*., 514 U.S. 52, 62-63 (1995) (ñ[R]espondents cannot overcome the common-law rule of contract interpretation that a court should construe ambiguous language against the interest of the party that drafted itò); *see also Wyeth v. Levine*, 555 U.S. 555, 571 (2009) (ñWyeth suggests that the FDA, rather than the manufacturer, bears primary responsibility for drug labeling. Yet through many amendments to the Food, Drug, and Cosmetic Act and to FDA regulations, it has remained a central premise of federal drug regulation that the manufacturer bears responsibility for the content of its label at all times. It is charged both with crafting an adequate label and with ensuring that its warnings remain adequate as long as the drug is on the marketò (citing regulations)).

Finally, the district court found that the changes to the labeling in 2009 demonstrate not only that the Guidelines were not mandatory after 2009, but that they were also not mandatory prior to 2009. Doc108,p8 (ñ[P]laintiff concedes that no substantive change was effected by the 2009 label, so if plaintiffôs claim fails under the latest label, it must fail under the earlier one as wellò). However, since Relator had argued that the earlier labels incorporated the Guidelines (Doc. 99, pp.49-53,57), this so-called ñconcessionò clearly meant that the 2009 labels also encompassed the Guidelines, not the opposite.

For all of these reasons, the district court erred when it concluded that the Guidelines were not incorporated into the Lipitor labels and that therefore Pfizer did not market off-label.

Moreover, we emphasize that, if the Court concludes that Relator cannot state a claim under the June 2009 and subsequent labels, that would not affect Relatorôs claims under the earlier labels. As the United States stated in its Statement of Interest (Doc98,p8):

> If a claim was false when it was submitted in 2004, a label change five years later does not transform that false claim into a reimbursable one. To hold otherwise would be to render federal health care program restrictions on coverage meaningless. It also would undermine the gatekeeping role of the federal government in protecting public health as well as the public fisc in ensuring that, based on the information available at the time, only indications that have been FDA-approved or are sufficiently supported by scientific literature as safe and effective are reimbursed.

Accordingly, this Court should reverse and remand at least with regard to the claims that relate to the labels prior to June 2009.

C. THE DISTRICT COURT ERRONEOUSLY FAILED TO ASSUME THE TRUTH OF THE FACTS ALLEGED IN THE COMPLAINT AND INSTEAD PREMISED DISMISSAL ON ITS OWN FACTUAL FINDINGS WITHOUT DISCOVERY OR EXPERT TESTIMONY

The district court was required to assume the truth of the facts alleged in the Complaint for purposes of Pfizerôs motion to dismiss and construe all reasonable inferences in the light most favorable to the plaintiff. *Anderson News, L.L.C. v.*

American Media, Inc., 680 F.3d 162, 185 (2d Cir. 2012). ñThe choice between two plausible inferences that may be drawn from factual allegations is not a choice to be made by the court on a Rule 12(b)(6) motion.ò *Id*. at 190.

When Pfizer first moved to dismiss this case pursuant to Rules 9(b) and 12(b)(6) (Doc. 46), Judge Korman, who was then the district court judge, stated the following (Doc60,p12):

> While I do not decide the case on this ground, [Rule 12(b)(6)], because a motion for summary judgment would be a more appropriate vehicle, the tenuous nature of the cause of action provides all the more justification for a strict application of Rule 9(b), as opposed to a relaxed pleading standard of Rule 9(b). [emphasis added]

Judge Korman granted the motion to dismiss pursuant to Rule 9(b) and granted Relator leave to replead his claims. Doc60,pp6,18. Thus, he did not dismiss the case under Rule 12(b)(6), even though he had doubts regarding the caseôs merit.

After Relator amended his complaint, and Pfizer again moved to dismiss pursuant to Rules 9(b) and 12(b)(6), Judge Cogan reached the opposite conclusion and dismissed the case pursuant to Rule 12(b)(6). Doc108.

The district court based its dismissal of the complaint on numerous factual findings concerning the reading of the labels. It did so even though, before even analyzing the labels, it described the labelsô length and complexity and stated: ñAlthough a consumer (who probably never sees it) might be able to understand parts

of the label, much if not most of the document is only within the ken of a doctor, pharmacist, or biochemist.ò Doc108,p3.

The interpretation of a label, at least if not clear, is a question of fact. *See In re Fosamax Products Liability Litigation*, 2013 WL 76140, *12 (S.D.N.Y. 2013) (expert testimony appropriate to interpret FDA label warnings); *DeGidio v. Centocor Ortho Biotech, Inc.*, 2010 WL 4628903, *4 (N.D. Ohio 2010) (ñAdequacy of a drugôs warning label is generally a question of fact, though it can become a question of law where the warning is accurate, clear and unambiguousò).

The district courtôs order is replete with impermissible findings of fact.

First, the district court concluded that the Guidelines are not mandatorily incorporated into the labels based on, *inter alia,* ñthe ease with which the FDA could have limited reimbursable prescriptions of Lipitor to patients within the Guidelines had it wanted to do soò (Doc108,p10) and that ñ[e]verything about the two labels at issue in this case suggests that the NCEP Guidelines, as a matter of plain language, fall well within the usual, non-compulsory definition of the word guidelinesò (Doc108,p6). As described above (pp. 34-45), those findings disregard the incorporation of the Guidelines in the labels, the mandatory language in the labels, the FDAôs statement in the Pravachol approval letter that the Guidelines were included in the labeling for all cholesterol-lowering drugs at that time, the Pravachol warning letter for off-label

marketing beyond the Guidelines, and the FDAôs statement regarding Lipitor that the Guidelines ñprovide[] the relevant information necessary for the identification of the appropriate treatment populations for these drugs and for the determination of individualized treatment goalsò (Doc99-11,p131). However, if this Court has any doubt that the Guidelines were incorporated into the labels prior to 2009, discovery and expert analysis are appropriate.

Second, the district court concluded that the removal of the Guidelines from the Indications and Usage section of the labeling in 2009 meant that the Guidelines were not mandatory, both before and after 2009. *See* pp. 46-47 above. The district court based that conclusion on, *inter alia,* the fact that ñ[a] person reading the ólndications and Usageôsection of the 2009 label must come away with one clear meaning: the drug is to be used if a physician believes his patient should lower his cholesterolò (Doc108,p6) and that it is ñnoteworthy that the FDA did not consider the NCEP Guidelines chart to consist of sufficiently ócritical informationô to include in the 2009 labelò (Doc108,p9), which the district court concluded was ñan indication of its permissive nature in the 2005 label as wellò (*ibid.*). Those findings disregard the Guidelinesô continued presence in the dosage section of the labeling, the FDAôs statements regarding the incorporation of the Guidelines, and the ambiguity with regard to the effect of the change in the labeling. *See* pp. 45-51 above. Discovery and expert

analysis related to the meaning of the 2009 label is necessary.

Third, the district court found that ñ[n]otably the 2009 label does include a guideline range for patients between the ages of ten and seventeen ï making the absence of similar guidelines for adults more conspicuous.ò Doc108,p7. However, the pre-2009 labeling also included that pediatric guidelines range along with the Guidelines Table for adults. *See, e.g.,* Doc77-11,p12. It is not apparent what is meant by the removal of the Guidelines Table despite the continued inclusion of the pediatric guidelines range. That is a factual question that is an appropriate subject of discovery and expert testimony.

Fourth, the district court stated the following (Doc108,pp7-8):

> First, dealing with that parenthetical in the 2009 label alone, it defies reason to believe that the FDA, well aware that physicians regularly prescribe Lipitor for patients outside of the Guidelines, would relegate these important and mandatory (in plaintiffôs view) restrictions to something that a doctor must search for elsewhere-not to mention that the label does not even tell the doctor where to find the Guidelines. Itôs like a citation in a brief to a reported decision which contains no information as to where the decision is reported.
>
> It is not as though the 2009 label could not bear the weight of the deleted chart, or at least a website citation. As noted, the label is over twenty pages long, so including this crucial (in plaintiffôs view) information would not have added much to its verbosity. The fleeting reference to the NCEP Guidelines is particularly telling since obviously the FDA not only knew that doctors were widely prescribing Lipitor for patients outside the Guidelines when it approved this revised label, but it also must have known about the pendency of this lawsuit.

In these paragraphs, the district court improperly drew conclusions as to the FDAôs knowledge of off-label promotion and usage of Lipitor and its policies for approving labels. To reach these factual conclusions, the district court would need a thorough understanding of the FDAôs policies and procedures as to how labels should be drafted and its reasoning related to this labeling.

Moreover, there is good reason to doubt the district courtôs assumptions about the FDAôs decisionmaking. In 2009, the Supreme Court described the limitations on the FDAôs ability to ñmonitor the 11,000 drugs on the marketò (*Wyeth*, 555 U.S. at 578-579 & n.11):

> In 1955, * * * an FDA advisory committee issued a report finding ñconclusivelyò that ñthe budget and staff of the Food and Drug Administration are inadequate to permit the discharge of its existing responsibilities for the protection of the American public.ò * * * Three recent studies have reached similar conclusions[:] * * * ñ[T]he Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilitiesò[;] * * * ñThe [FDA] lacks the resources needed to accomplish its large and complex mission . . . . There is widespread agreement that resources for postmarketing drug safety work are especially inadequate and that resource limitations have hobbled the agencyôs ability to improve and expand this essential component of its missionò[;] * * * ñFDA lacks a clear and effective process for making decisions about, and providing management oversight of, postmarket safety issuesò; ñ[T]he Office of Chief Counsel ignored the warnings from FDA scientists and career officials that the preemption language [of the 2006 preamble] was based on erroneous assertions about the ability of the drug approval process to ensure accurate and up-to-date

drug labels.ò[25/]

Relator is also entitled to discovery and expert testimony as to these issues.

Fifth, the district court concluded by stating that, ñ[h]aving determined that the NCEP Guidelines in the 2005 label, and the passing reference to them in the 2009 label, were merely informational and advisory rather than restrictive limitations, I hold that defendant has not engaged in off-label marketing, and has therefore not violated the FCA.ò Doc108,pp12-13. This conclusion hinges on the findings described above and is impermissible in resolving a Rule 12(b)(6) motion.

This fact-finding requires reversal. *See Global Network Communications, Inc. v. City of New York,* 458 F.3d 150, 158 (2d Cir. 2006) (ñIn light of the ubiquity of the courtôs procedural error [fact-findings on a motion to dismiss], we cannot be certain that the district courtôs apparent conclusion that appellants would not pay its obligations did not color its analysis of the merits of Globalôs other claimsò (citation omitted)).

[25/]*See also* Doc58,pp69,76 (Judge Korman: ñWhy government agencies do things -- you know, thereôs a great big bureaucracy. And I donôt know why -- thereôs often no rhyme or reason for why things get done in particular waysò; ñ[T]he whole assumption is that the watchdogs arenôt enough. Otherwise, you wouldnôt need a [*qui tam*] Act.ò

D. THE DISTRICT COURT ERRED IN CONCLUDING THAT RELATOR'S CLAIMS DRASTICALLY EXTENDED THE REACH OF THE FALSE CLAIMS ACT

The district court characterized the complaint as ñdrastically elongat[ing] [the] reach of the False Claims Actò and stated that the FCA was ñnever intended to be used as a back-door regulatory regime to restrict practices that the relevant federal and state agencies have chosen not to prohibit through their regulatory authority.ò Doc108,pp5,12.

However, the FDA has no role in protecting the funds that would be paid by Medicare and Medicaid for drugs prescribed for purposes not authorized by the FDA. That role is filled here by the FCA.

Moreover, numerous courts have found that claims for FCA liability can be based on off-label marketing of drugs which causes off-label prescriptions to be dispensed at the governmentôs expense. *See* cases cited pp. 44-45 above; *see also United States ex rel. Dickson v. Bristol Myers Squibb Co.*, 2013 WL 360299, *2ï 3 (S.D. Ill. 2013) (denying motion to dismiss FCA claim for false marketing regarding the efficiency of on-label use compared to cheaper alternatives, resulting in over-payment by Medicare).

Furthermore, Pfizer and its subsidiaries have paid large settlements to resolve claims brought under this theory. *United States v. Pharmacia & Upjohn Co.* ($2.3

billion settlement by Pfizer and its subsidiary of claims, including FCA claims, related to off-label marketing for uses and dosages that the FDA declined to approve, http://www.justice.gov/opa/pr/2009/September/09-civ-900.html (last visited April 5, 2013)); *United States ex rel. Wetherholt* ($14.5 million settlement by Pfizer to resolve allegations of off-label promotion of Detrol, http://www.justice.gov/opa/pr/2011/October/11-civ-1389.html (last visited April 5, 2013)).

The district court also suggested that these claims will interfere with the physician-patient relationship. Doc108,p12. However, nothing about these claims prevents a doctor from prescribing Lipitor to a patient. These claims are about a pharmaceutical companyôs false off-label marketing that has caused the government to pay for drugs in violation of federal law.

E. THE DISTRICT COURT'S ERROR WITH REGARD TO THE FEDERAL FALSE CLAIMS ACT ALSO APPLIES TO THE STATE LAW CLAIMS

Relator raised 17 counts for violations of state false claims acts (Counts 3-19). The district court dismissed those claims without any reference to them. The dismissal of those claims should be reversed for the reasons stated above with regard to the federal claims.

II

THE DISTRICT COURT WRONGLY DISMISSED RELATOR'S EMPLOYMENT CLAIMS DESPITE THE FACT THAT PFIZER DID NOT MOVE TO DISMISS THEM AND THE DISTRICT COURT DID NOT CONSIDER THEM

The complaint alleges that, while he was employed by Pfizer, Relator investigated and repeatedly informed Pfizer about its false and misleading marketing materials as well as its harassing and discriminatory treatment toward women and that, as a result of his protected activity, he was fired in violation of federal and state law. Doc 77,pp121-134,135-136,153-155.

In 2008, Pfizer moved to dismiss two of Relatorôs employment claims as they were pled in an earlier version of the complaint. Doc44. That motion was denied as to those claims. Doc61.

Relator then filed the Fifth Amended Complaint, which includes five employment claims (Counts 2, 20-23). Doc77,pp135-136,153-155. Pfizerôs motion to dismiss, which is the subject of the decision on appeal, did not move to dismiss any of the employment claims. That motion was titled ñMotion to Dismiss Counts I and III Through XIX of the Fifth Amended Complaint.ò Doc90. Counts 1 and 3 through 19 are the federal and state false claims act claims discussed above, not the employment claims. Doc77,pp134-153. Relatorôs opposition to the motion to dismiss also did not

deal with the employment claims. Doc. 99. Accordingly, the district court did not consider any of the employment claims in its decision on that motion. *See* Doc108.

Nonetheless, upon granting the motion to dismiss, the district court directed the clerk ñto enter judgment in favor of defendant, dismissing the complaint.ò Doc108,p13. The clerk entered judgment for Pfizer (Doc109) and this appeal followed (Doc112).

It appears that the district court simply overlooked the employment claims when it dismissed the complaint. That was clear error. The district courtôs decision must therefore be reversed and at least the employment claims must be remanded so that Relator can have an opportunity to be heard on those claims. *See Acosta v. Artuz*, 221 F.3d 117, 124 (2d Cir. 2000) (ñThe long-standing general rule is that a court may not dismiss an action without providing the adversely affected party with notice and an opportunity to be heardò (citations omitted)); *Square D Co. v. Niagara Frontier Tariff Bureau, Inc.*, 760 F.2d 1347, 1365 (2d Cir. 1985) (ñThe district court has no authority to dismiss a complaint for failure to state a claim upon which relief can be granted without giving the plaintiff an opportunity to be heardò (citation omitted); reversed and remanded where court dismissed the entire complaint, although a claim for injunctive relief was not the basis for the motion to dismiss and the court gave no explanation as to why that claim was dismissed).

CONCLUSION

For all of these reasons, the district courtôs decision should be reversed and the case should be remanded to the district court.

REQUEST FOR ORAL ARGUMENT

Relator requests oral argument and oral argument is justified by the complexity and importance of this case.

Respectfully submitted,
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April 9, 2013

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CERTIFICATE OF COMPLIANCE WITH RULE 32(a)

I hereby certify that on this 9th day of April, 2013:

(1) this brief complies with the type-volume limitation of Fed. R. App. P. 32(a)(7)(B) because this brief contains 13,948 words, excluding the parts of the brief exempted by Fed. R. App. P. 32(a)(7)(B)(iii); and

(2) this brief complies with the typeface requirements of Fed. R. App. P. 32(a)(5) and the typestyle requirements of Fed. R. App. P. 32(a)(6) because the brief has been prepared in a proportionally spaced typeface using WordPerfect X3 in 14 point Times New Roman font.

/s/ Bruce J. Terris
BRUCE J. TERRIS

CERTIFICATE OF SERVICE

I hereby certify that on April 9, 2012, I had the foregoing brief electronically filed with the United States Court of Appeals for the Second Circuit by using the appellate CM/ECF system. I further certify that I will have six paper copies of this brief delivered to the Court.

The participants in the case are registered CM/ECF users and service will be accomplished by the appellate CM/ECF system.

/s/ Bruce J. Terris
BRUCE J. TERRIS

ADDENDUM

TABLE OF CONTENTS

Federal Statutes:

Federal Rules:

Federal Regulations:

21 U.S.C. 331(a),(b),(c),(d)

§ 331. Prohibited acts

The following acts and the causing thereof are prohibited:

(a) The introduction or delivery for introduction into interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded.

(b) The adulteration or misbranding of any food, drug, device, tobacco product, or cosmetic in interstate commerce.

(c) The receipt in interstate commerce of any food, drug, device, tobacco product, or cosmetic that is adulterated or misbranded, and the delivery or proffered delivery thereof for pay or otherwise.

(d) The introduction or delivery for introduction into interstate commerce of any article in violation of section 344, 350d, 355, or 360bbb-3 of this title.

21 U.S.C. 352

§ 352. Misbranded drugs and devices

A drug or device shall be deemed to be misbrandedð

(a) False or misleading label

If its labeling is false or misleading in any particular. * * *

* * *

(c) Prominence of information on label

If any word, statement, or other information required by or under authority of this chapter to appear on the label or labeling is not prominently placed thereon with such conspicuousness (as compared with other words, statements, designs, or devices, in the labeling) and in such terms as to render it likely to be read and understood by the ordinary individual under customary conditions of purchase and use.

* * *

(f) Directions for use and warnings on label

Unless its labeling bears (1) adequate directions for use; and (2) such adequate warnings against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application, in such manner and form, as are necessary for the protection of users, except that where any requirement of clause (1) of this paragraph, as applied to any drug or device, is not necessary for the protection of the public health, the Secretary shall promulgate regulations exempting such drug or device from such requirement.

* * *

(n) Prescription drug advertisements: established name; quantitative formula; side effects, contraindications, and effectiveness; prior approval; false

advertising; labeling; construction of the Convention on Psychotropic Substances

In the case of any prescription drug distributed or offered for sale in any State, unless the manufacturer, packer, or distributor thereof includes in all advertisements and other descriptive printed matter issued or caused to be issued by the manufacturer, packer, or distributor with respect to that drug a true statement of (1) the established name as defined in paragraph (e) of this section, printed prominently and in type at least half as large as that used for any trade or brand name thereof, (2) the formula showing quantitatively each ingredient of such drug to the extent required for labels under paragraph (e) of this section, and (3) such other information in brief summary relating to side effects, contraindications, and effectiveness as shall be required in regulations which shall be issued by the Secretary in accordance with section 371(a) of this title * * *.

31 U.S.C. 3729(a) (pre-FERA)

§3729. False claims

(a) Liability for Certain Acts.ð Any person whoð

> (1) knowingly presents, or causes to be presented, to an officer or employee of the United States Government or a member of the Armed Forces of the United States a false or fraudulent claim for payment or approval;
>
> (2) knowingly makes, uses, or causes to be made or used, a false record or statement to get a false or fraudulent claim paid or approved by the Government;
>
> * * *

is liable to the United States Government for a civil penalty of not less than $5,000 and not more than $10,000, plus 3 times the amount of damages which the Government sustains because of the act of that person * * *.

31 U.S.C. 3729(a)(1) (post-FERA)

§ 3729. False claims

(a) Liability for certain acts.--

(1) In general.--Subject to paragraph (2), any person who--

(A) knowingly presents, or causes to be presented, a false or fraudulent claim for payment or approval;

(B) knowingly makes, uses, or causes to be made or used, a false record or statement material to a false or fraudulent claim;

* * *

is liable to the United States Government for a civil penalty of not less than $5,000 and not more than $10,000 * * * plus 3 times the amount of damages which the Government sustains because of the act of that person.

31 U.S.C. 3730(b)

§ 3730. Civil Actions for false claims

(b) Actions by private persons.--(1) A person may bring a civil action for a violation of section 3729 for the person and for the United States Government. The action shall be brought in the name of the Government. The action may be dismissed only if the court and the Attorney General give written consent to the dismissal and their reasons for consenting.

(2) A copy of the complaint and written disclosure of substantially all material evidence and information the person possesses shall be served on the Government pursuant to Rule 4(d)(4) of the Federal Rules of Civil Procedure. The complaint shall be filed in camera, shall remain under seal for at least 60 days, and shall not be served on the defendant until the court so orders. The Government may elect to intervene and proceed with the action within 60 days after it receives both the complaint and the material evidence and information.

(3) The Government may, for good cause shown, move the court for extensions of the time during which the complaint remains under seal under paragraph (2). Any such motions may be supported by affidavits or other submissions in camera. The defendant shall not be required to respond to any complaint filed under this section until 20 days after the complaint is unsealed and served upon the defendant pursuant to Rule 4 of the Federal Rules of Civil Procedure.

(4) Before the expiration of the 60-day period or any extensions obtained under paragraph (3), the Government shall--

> (A) proceed with the action, in which case the action shall be conducted by the Government; or
>
> (B) notify the court that it declines to take over the action, in which case the person bringing the action shall have the right to conduct the action.

(5) When a person brings an action under this subsection, no person other than the Government may intervene or bring a related action based on the facts underlying the pending action.

31 U.S.C. 3732

§ 3732. False claims jurisdiction

(a) Actions under section 3730.--Any action under section 3730 may be brought in any judicial district in which the defendant or, in the case of multiple defendants, any one defendant can be found, resides, transacts business, or in which any act proscribed by section 3729 occurred. A summons as required by the Federal Rules of Civil Procedure shall be issued by the appropriate district court and served at any place within or outside the United States.

(b) Claims under state law.--The district courts shall have jurisdiction over any action brought under the laws of any State for the recovery of funds paid by a State or local government if the action arises from the same transaction or occurrence as an action brought under section 3730.

(c) Service on State or local authorities.--With respect to any State or local government that is named as a co-plaintiff with the United States in an action brought under subsection (b), a seal on the action ordered by the court under section 3730(b) shall not preclude the Government or the person bringing the action from serving the complaint, any other pleadings, or the written disclosure of substantially all material evidence and information possessed by the person bringing the action on the law enforcement authorities that are authorized under the law of that State or local government to investigate and prosecute such actions on behalf of such governments, except that such seal applies to the law enforcement authorities so served to the same extent as the seal applies to other parties in the action.

42 U.S.C. 1395w-102(e)

§ 1395w-102. Prescription drug benefits

(e) Covered part D drug defined

(1) In general

Except as provided in this subsection, for purposes of this part, the term ñcovered part D drugò means--

(A) a drug that may be dispensed only upon a prescription and that is described in subparagraph (A)(i), (A)(ii), or (A)(iii) of section 1396r-8(k)(2) of this title; or

* * *

(2) Exclusions

(A) In general

Such term does not include drugs or classes of drugs, or their medical uses, which may be excluded from coverage or otherwise restricted under section 1396r-8(d)(2) of this title * * *.

(B) Medicare covered drugs

A drug prescribed for a part D eligible individual that would otherwise be a covered part D drug under this part shall not be so considered if payment for such drug as so prescribed and dispensed or administered with respect to that individual is available (or would be available but for the application of a deductible) under part A or B of this subchapter for that individual.

* * *

(4) Medically accepted indication defined

(A) In general

For purposes of paragraph (1), the term ñmedically accepted

indicationò has the meaning given that termï

(i) in the case of a covered part D drug used in an anticancer chemotherapeutic regimen, in section 1395x(t)(2)(B) of this title, except that in applying such section--

(I) ñprescription drug plan or MA-PD planò shall be substituted for ñcarrierò each place it appears; and

(II) subject to subparagraph (B), the compendia described in section 1396r-8(g)(1)(B)(i)(III) of this title shall be included in the list of compendia described in clause (ii)(I) section 1395x(t)(2)(B) of this title; and

(ii) in the case of any other covered part D drug, in section 1396r-8(k)(6) of this title.

42 U.S.C. 1396b(i)(10)

§ 1396b. Payment to States

(i) Payment for organ transplants; item or service furnished by excluded individual, entity, or physician; other restrictions

Payment under the preceding provisions of this section shall not be made--

* * *

(10)(A) with respect to covered outpatient drugs unless there is a rebate agreement in effect under section 1396r-8 of this title with respect to such drugs or unless section 1396r-8(a)(3) of this title applies,

(B) with respect to any amount expended for an innovator multiple source drug (as defined in section 1396r-8(k) of this title) dispensed on or after July 1, 1991, if, under applicable State law, a less expensive multiple source drug could have been dispensed, but only to the extent that such amount exceeds the upper payment limit for such multiple source drug;

(C) with respect to covered outpatient drugs described in section 1396r-8(a)(7) of this title, unless information respecting utilization data and coding on such drugs that is required to be submitted under such section is submitted in accordance with such section, and

(D) with respect to any amount expended for reimbursement to a pharmacy under this subchapter for the ingredient cost of a covered outpatient drug for which the pharmacy has already received payment under this subchapter (other than with respect to a reasonable restocking fee for such drug)[.] * * *

42 U.S.C. 1396r-8(k)(2),(3),(6)

§ 1396r-8. Payment for covered outpatient drugs

(k) Definitions

In this sectionï

* * *

(2) Covered outpatient drug

Subject to the exceptions in paragraph (3), the term ñcovered outpatient drugò means--

(A) of those drugs which are treated as prescribed drugs for purposes of section 1396d(a)(12) of this title, a drug which may be dispensed only upon prescription (except as provided in paragraph (5)), andï

(i) which is approved for safety and effectiveness as a prescription drug under section 505 or 507 of the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. § 355 or 357] or which is approved under section 505(j) of such Act [21 U.S.C.A. § 355(j)];

* * *

(3) Limiting definition

The term ñcovered outpatient drugò does not include any drug, biological product, or insulin provided as part of, or as incident to and in the same setting as, any of the following (and for which payment may be made under this subchapter as part of payment for the following and not as direct reimbursement for the drug):

(A) Inpatient hospital services.

(B) Hospice services.

(C) Dental services, except that drugs for which the State plan authorizes direct reimbursement to the dispensing dentist are covered outpatient drugs.

(D) Physiciansô services.

(E) Outpatient hospital services.

(F) Nursing facility services and services provided by an intermediate care facility for the mentally retarded.

(G) Other laboratory and x-ray services.

(H) Renal dialysis.

Such term also does not include any such drug or product for which a National Drug Code number is not required by the Food and Drug Administration or a drug or biological used for a medical indication which is not a medically accepted indication. Any drug, biological product, or insulin excluded from the definition of such term as a result of this paragraph shall be treated as a covered outpatient drug for purposes of determining the best price (as defined in subsection (c)(1)(C) of this section) for such drug, biological product, or insulin.

* * *

(6) Medically accepted indication

The term ñmedically accepted indicationò means any use for a covered outpatient drug which is approved under the Federal Food, Drug, and Cosmetic Act [21 U.S.C.A. § 301 et seq.] or the use of which is supported by one or more citations included or approved for inclusion in any of the compendia described in subsection (g)(1)(B)(i) of this section.

42 U.S.C. 2000e-5(f)(3)

§ 2000e-5. Enforcement provisions

(f) Civil action by Commission, Attorney General, or person aggrieved; preconditions; procedure; appointment of attorney; payment of fees, costs, or security; intervention; stay of Federal proceedings; action for appropriate temporary or preliminary relief pending final disposition of charge; jurisdiction and venue of United States courts; designation of judge to hear and determine case; assignment of case for hearing; expedition of case; appointment of master

* * *

(3) Each United States district court and each United States court of a place subject to the jurisdiction of the United States shall have jurisdiction of actions brought under this subchapter. Such an action may be brought in any judicial district in the State in which the unlawful employment practice is alleged to have been committed, in the judicial district in which the employment records relevant to such practice are maintained and administered, or in the judicial district in which the aggrieved person would have worked but for the alleged unlawful employment practice, but if the respondent is not found within any such district, such an action may be brought within the judicial district in which the respondent has his principal office. For purposes of sections 1404 and 1406 of Title 28, the judicial district in which the respondent has his principal office shall in all cases be considered a district in which the action might have been brought.

Fraud Enforcement and Recovery Act of 2009 ("FERA"), Pub. L. No. 111-21, Sec. 4(f), 123 Stat. 1617 (May 20, 2009)

SEC. 4. CLARIFICATIONS TO THE FALSE CLAIMS ACT TO REFLECT THE ORIGINAL INTENT OF THE LAW.

* * *

(f) EFFECTIVE DATE AND APPLICATION.--The amendments made by this section shall take effect on the date of enactment of this Act and shall apply to conduct on or after the date of enactment, except that--

(1) subparagraph (B) of section 3729(a)(1) of title 31, United States Code, as added by subsection (a)(1), shall take effect as if enacted on June 7, 2008, and apply to all claims under the False Claims Act (31 U.S.C. 3729 et seq.) that are pending on or after that date; and

(2) section 3731(b) of title 31, as amended by subsection (b); section 3733, of title 31, as amended by subsection (c); and section 3732 of title 31, as amended by subsection (e); shall apply to cases pending on the date of enactment.

Fed. R. Civ. P. 12(b)(6)

Rule 12. Defenses and Objections: When and How Presented; Motion for Judgment on the Pleadings; Consolidating Motions; Waiving Defenses; Pretrial Hearing

(b) How to Present Defenses. Every defense to a claim for relief in any pleading must be asserted in the responsive pleading if one is required. But a party may assert the following defenses by motion:

* * *

(6) failure to state a claim upon which relief can be granted; and

* * *

A motion asserting any of these defenses must be made before pleading if a responsive pleading is allowed. If a pleading sets out a claim for relief that does not require a responsive pleading, an opposing party may assert at trial any defense to that claim. No defense or objection is waived by joining it with one or more other defenses or objections in a responsive pleading or in a motion.

21 C.F.R. 201.56(b)

§ 201.56 Requirements on content and format of labeling for human prescription drug and biological products.

* * *

(b) Categories of prescription drugs subject to the labeling content and format requirements in §§ 201.56(d) and 201.57.

(1) The following categories of prescription drug products are subject to the labeling requirements in paragraph (d) of this section and § 201.57 in accordance with the implementation schedule in paragraph (c) of this section:

(i) Prescription drug products for which a new drug application (NDA), biologics license application (BLA), or efficacy supplement was approved by the Food and Drug Administration (FDA) between June 30, 2001 and June 30, 2006;

(ii) Prescription drug products for which an NDA, BLA, or efficacy supplement is pending on June 30, 2006; or

(iii) Prescription drug products for which an NDA, BLA, or efficacy supplement is submitted anytime on or after June 30, 2006.

(2) Prescription drug products not described in paragraph (b)(1) of this section are subject to the labeling requirements in paragraph (e) of this section and § 201.80.

21 C.F.R. 201.57

§ 201.57 Specific requirements on content and format of labeling for human prescription drug and biological products described in § 201.56(b)(1).

The requirements in this section apply only to prescription drug products described in § 201.56(b)(1) and must be implemented according to the schedule specified in § 201.56(c), except for the requirement in paragraph (c)(18) of this section to reprint any FDAï approved patient labeling at the end of prescription drug labeling or accompany the prescription drug labeling, which must be implemented no later than June 30, 2007.

(a) Highlights of prescribing information. The following information must appear in all prescription drug labeling:

* * *

(5) Recent major changes. A list of the section(s) of the full prescribing information, limited to the labeling sections described in paragraphs (c)(1), (c)(2), (c)(3), (c)(5), and (c)(6) of this section, that contain(s) substantive labeling changes that have been approved by FDA or authorized under § 314.70(c)(6) or (d)(2), or § 601.12(f)(1) through (f)(3) of this chapter. The heading(s) and, if appropriate, the subheading(s) of the labeling section(s) affected by the change must be listed together with each section's identifying number and the date (month/year) on which the change was incorporated in labeling. These labeling sections must be listed in the order in which they appear in the full prescribing information. A changed section must be listed under this heading in Highlights for at least 1 year after the date of the labeling change and must be removed at the first printing subsequent to the 1 year period.

(6) Indications and usage. A concise statement of each of the product's indications, as required under paragraph (c)(2) of this section, with any appropriate subheadings. Major limitations of use (e.g., lack of effect in particular subsets of the population, or second line therapy status) must be briefly noted. If the product is a member of an established pharmacologic class, the concise statement under this heading in Highlights must identify the class in the following manner: ñ(Drug) is a (name of class) indicated for (indication(s)).ò

(7) Dosage and administration. A concise summary of the information required under paragraph (c)(3) of this section, with any appropriate subheadings, including the recommended dosage regimen, starting dose, dose range, critical differences among population subsets, monitoring recommendations, and other clinically significant clinical pharmacologic information.

* * *

(b) Full prescribing information: Contents. Contents must contain a list of each heading and subheading required in the full prescribing information under § 201.56(d)(1), if not omitted under § 201.56(d)(4), preceded by the identifying number required under § 201.56(d)(1). Contents must also contain any additional subheading(s) included in the full prescribing information preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(c) Full prescribing information. The full prescribing information must contain the information in the order required under paragraphs (c)(1) through (c)(18) of this section, together with the headings, subheadings, and identifying numbers required under § 201.56(d)(1), unless omitted under § 201.56(d)(4). If additional subheadings are used within a labeling section, they must be preceded by the identifying number assigned in accordance with § 201.56(d)(2).

(1) Boxed warning. Certain contraindications or serious warnings, particularly those that may lead to death or serious injury, may be required by the FDA to be presented in a box. The boxed warning ordinarily must be based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data. The box must contain, in uppercase letters, a heading inside the box that includes the word ñWARNINGò and conveys the general focus of the information in the box. The box must briefly explain the risk and refer to more detailed information in the ñContraindicationsò or ñWarnings and Precautionsò section, accompanied by the identifying number for the section or subsection containing the detailed information.

(2) 1 Indications and usage. This section must state that the drug is indicated for the treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition.

(i) This section must include the following information when the conditions listed are applicable:

(A) If the drug is used for an indication only in conjunction with a primary mode of therapy (e.g., diet, surgery, behavior changes, or some other drug), a statement that the drug is indicated as an adjunct to that mode of therapy.

(B) If evidence is available to support the safety and effectiveness of the drug or biological product only in selected subgroups of the larger population (e.g., patients with mild disease or patients in a special age group), or if the indication is approved based on a surrogate endpoint under § 314.510 or § 601.41 of this chapter, a succinct description of the limitations of usefulness of the drug and any uncertainty about anticipated clinical benefits, with reference to the ñClinical Studiesò section for a discussion of the available evidence.

(C) If specific tests are necessary for selection or monitoring of the patients who need the drug (e.g., microbe susceptibility tests), the identity of such tests.

(D) If information on limitations of use or uncertainty about anticipated clinical benefits is relevant to the recommended intervals between doses, to the appropriate duration of treatment when such treatment should be limited, or to any modification of dosage, a concise description of the information with reference to the more detailed information in the ñDosage and Administrationò section.

(E) If safety considerations are such that the drug should be reserved for specific situations (e.g., cases refractory to other drugs), a statement of the information.

(F) If there are specific conditions that should be met before the drug is used on a long term basis (e.g., demonstration of responsiveness to the drug in a short term trial in a given patient), a statement of the conditions; or, if the indications for long term use are different from those for short term use, a statement of the specific indications for each use.

(ii) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective or that the therapeutic benefits of the product do not generally outweigh its risks, FDA may require that this section state that there is a lack of evidence that the drug is effective or safe for that use or condition.

(iii) Any statements comparing the safety or effectiveness of the drug with other agents for the same indication must, except for biological products, be supported by substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter. For biological products, such statements must be supported by substantial evidence.

(iv) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(v) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of the labeling if not included in this section.

(3) 2 Dosage and administration.

(i) This section must state the recommended dose and, as appropriate:

(A) The dosage range,

(B) An upper limit beyond which safety and effectiveness have not been established, or beyond which increasing the dose does not result in increasing effectiveness,

(C) Dosages for each indication and subpopulation,

(D) The intervals recommended between doses,

(E) The optimal method of titrating dosage,

(F) The usual duration of treatment when treatment duration should be limited,

(G) Dosing recommendations based on clinical pharmacologic data (e.g., clinically significant food effects),

(H) Modification of dosage needed because of drug interactions or in special patient populations (e.g., in children, in geriatric age groups, in groups defined by genetic characteristics, or in patients with renal or hepatic disease),

(I) Important considerations concerning compliance with the dosage regimen,

(J) Efficacious or toxic concentration ranges and therapeutic concentration windows of the drug or its metabolites, if established and clinically significant. Information on therapeutic drug concentration monitoring (TDM) must also be included in this section when TDM is necessary.

(ii) Dosing regimens must not be implied or suggested in other sections of the labeling if not included in this section.

* * *

(4) 3 Dosage forms and strengths. This section must contain information on the available dosage forms to which the labeling applies and for which the manufacturer or distributor is responsible, including:

(i) The strength or potency of the dosage form in metric system (e.g., 10 milligram tablets), and, if the apothecary system is used, a statement of the strength in parentheses after the metric designation; and

(ii) A description of the identifying characteristics of the dosage forms, including

shape, color, coating, scoring, and imprinting, when applicable. The National Drug Code number(s) for the drug product must not be included in this section.

(5) 4 Contraindications. This section must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication). If no contraindications are known, this section must state ñNone.ò

* * *

(16) 15 References. When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

* * *

21 C.F.R. 201.80

§ 201.80 Specific requirements on content and format of labeling for human prescription drug and biological products; older drugs not described in § 201.56(b)(1).

Each section heading listed in § 201.56(d), if not omitted under § 201.56(d)(3), shall contain the following information in the following order:

* * *

(c) Indications and Usage.

(1) Under this section heading, the labeling shall state that:

(i) The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or

(ii) The drug is indicated for the treatment, prevention, or diagnosis of an important manifestation of a disease or condition, e.g., chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or

(iii) The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g., chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or

(iv) The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g., diet, surgery, or some other drug, is an adjunct to the mode of therapy.

(2)(i) For drug products other than biological products, all indications listed in this section must be supported by substantial evidence of effectiveness based on adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. Indications or uses must not be implied or suggested in other sections of labeling

if not included in this section.

(ii) For biological products, all indications listed in this section must be supported by substantial evidence of effectiveness. Indications or uses must not be implied or suggested in other sections of labeling if not included in this section.

(3) This section of the labeling shall also contain the following additional information:

(i) If evidence is available to support the safety and effectiveness of the drug only in selected subgroups of the larger population with a disease, syndrome, or symptom under consideration, e.g., patients with mild disease or patients in a special age group, the labeling shall describe the available evidence and state the limitations of usefulness of the drug. The labeling shall also identify specific tests needed for selection or monitoring of the patients who need the drug, e.g., microbe susceptibility tests. Information on the approximate kind, degree, and duration of improvement to be anticipated shall be stated if available and shall be based on substantial evidence derived from adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless the requirement is waived under § 201.58 or § 314.126(c) of this chapter. If the information is relevant to the recommended intervals between doses, the usual duration of treatment, or any modification of dosage, it shall be stated in the ñDosage and Administrationò section of the labeling and referenced in this section.

(ii) If safety considerations are such that the drug should be reserved for certain situations, e.g., cases refractory to other drugs, this information shall be stated in this section.

(iii) If there are specific conditions that should be met before the drug is used on a long-term basis, e.g., demonstration of responsiveness to the drug in a short-term trial, the labeling shall identify the conditions; or, if the indications for long-term use are different from those for short-term use, the labeling shall identify the specific indications for each use.

(iv) If there is a common belief that the drug may be effective for a certain use or if there is a common use of the drug for a condition, but the preponderance of evidence related to the use or condition shows that the drug is ineffective, the Food and Drug Administration may require that the labeling state that there is a lack of evidence that the drug is effective for that use or condition.

(v) Any statements comparing the safety or effectiveness, either greater or less, of the drug with other agents for the same indication shall be supported by adequate and well-controlled studies as defined in § 314.126(b) of this chapter unless this requirement is waived under § 201.58 or § 314.126(c) of this chapter.

(d) Contraindications. Under this section heading, the labeling shall describe those situations in which the drug should not be used because the risk of use clearly outweighs any possible benefit. These situations include administration of the drug to patients known to have a hypersensitivity to it; use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by it; or continued use of the drug in the face of an unacceptably hazardous adverse reaction. Known hazards and not theoretical possibilities shall be listed, e.g., if hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication. If no contraindications are known, this section of the labeling shall state ñNone known.ò

* * *

(j) Dosage and Administration. This section of the labeling shall state the recommended usual dose, the usual dosage range, and, if appropriate, an upper limit beyond which safety and effectiveness have not been established; dosages shall be stated for each indication when appropriate. Dosing regimens must not be implied or suggested in other sections of labeling if not included in this section. This section shall also state the intervals recommended between doses, the optimal method of titrating dosage, the usual duration of treatment, and any modification of dosage needed in special patient populations, e.g., in children, in geriatric age groups, or in patients with renal or hepatic disease. Specific tables or monographs may be included to clarify dosage schedules.
* * *

* * *

(m) ñClinical Studiesò and ñReferencesò. These sections may appear in labeling in the place of a detailed discussion of a subject that is of limited interest but nonetheless important. A reference to a specific important clinical study may be made in any section of the format required under §§ 201.56 and 201.57 if the study is essential to an understandable presentation of the available information. References may appear in sections of the labeling format, other than the ñClinical Studiesò or ñReferencesò section, in rare circumstances only. A clinical study or reference may be cited in prescription drug labeling only under the following conditions:

(1)(i) If the clinical study is cited in the labeling in place of a detailed discussion of data and information concerning an indication for use of the drug, the clinical study must constitute an adequate and well-controlled study as described in § 314.126(b) of this chapter, except for biological products, and must not imply or suggest indications or uses or dosing regimens not stated in the ñIndications and Usageò or ñDosage and Administrationò section.

(ii) When prescription drug labeling must summarize or otherwise rely on a recommendation by an authoritative scientific body, or on a standardized methodology, scale, or technique, because the information is important to prescribing decisions, the labeling may include a reference to the source of the information.

(2) If the clinical study or reference is cited in the labeling in the place of a detailed discussion of data and information concerning a risk or risks from the use of the drug, the risk or risks shall also be identified or discussed in the appropriate section of the labeling for the drug.