DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 16 2013

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Re: Docket No. FDA-2011-P-0297

Dear Ms. Kahn and Drs. Barbehenn, Carome, and Wolfe:

This letter responds to your citizen petition dated April 14, 2011 (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency) immediately withdraw from marketing the prescription drug Xenical (orlistat) and the nonprescription or over-the-counter (OTC) drug alli (orlistat). You contend that these drugs pose serious risks that greatly outweigh their clinical benefits.

We have carefully reviewed your Petition, as well as the comments on the Petition submitted by Genentech, a Member of the Roche Group (Genentech) and GlaxoSmithKline Consumer Healthcare (GSK) each dated October 21, 2011. For the reasons set forth in this response, we deny your request that FDA immediately remove Xenical and alli from the market. However, as with all FDA-approved products, FDA will continue to monitor and review available safety information related to orlistat throughout the drug products' life cycles.

I. BACKGROUND

A. Orlistat Drug Products

Orlistat is a reversible lipase inhibitor that acts by inhibiting the absorption of dietary fats. Orlistat has low bioavailability, as less than 1% of the drug reaches the systemic circulation following oral ingestion. The drug exerts its therapeutic activity in the lumen of the stomach and small intestine by forming a covalent bond with the active serine residue site of gastric and pancreatic lipases. The inactivated enzymes are unavailable to hydrolyze dietary fat in the form of triglycerides into absorbable free fatty acids and monoglycerides, and the unabsorbed dietary fat is excreted in the stool. This wasting of calories has been shown to promote weight loss and weight maintenance under certain circumstances.

On April 23, 1999, FDA approved new drug application (NDA) 20-766, submitted by Hoffman La Roche, for Xenical (orlistat) 120-milligram (mg) capsules for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet.

Xenical is indicated for long-term weight loss in patients with a body mass index (BMI) ≥ 30 kilograms (kg)/square meter (m^2) or ≥ 27 kg/m^2 if accompanied by co-morbid conditions.

Orlistat was the subject of a previous citizen petition from Public Citizen in April 2006 (2006 Petition) requesting that FDA not approve an OTC formulation of the drug and immediately remove orlistat from prescription marketing. In the 2006 Petition, you asserted a causal link between orlistat and colorectal cancer based on findings of aberrant crypt foci. You also asserted that the drug did not have a favorable benefit-risk profile based on what you described as a "still unresolved potential" to cause breast cancer and "minimal efficacy" for weight loss. FDA denied the 2006 Petition. The Agency concluded that the available evidence concerning orlistat's safety did not support a causal relationship between orlistat and colorectal carcinoma or breast cancer, did not otherwise meet the statutory criteria for market withdrawal, and did not alter our favorable assessment of the risk-benefit profile of a 60-mg, nonprescription dose strength of orlistat.[1]

On February 7, 2007, FDA approved GSK's NDA (21-887) for alli (orlistat) 60-mg capsules for OTC use as a weight loss aid in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet.[2]

B. Legal Standard

Your Petition states that you seek withdrawal of Xenical (orlistat) and alli (orlistat) (Petition at 1). The Federal Food, Drug, and Cosmetic Act (FD&C Act) establishes the standard upon which the Agency will, after due notice and opportunity for a hearing, withdraw approval of an NDA. Specifically, the Agency will withdraw approval of an NDA based upon safety concerns if it finds that:

- clinical or other experience, tests, or other scientific data show that such drug is unsafe for use under the conditions of use upon the basis of which the application was approved, or,

- new evidence of clinical experience, not contained in such application or not available to the [Agency] until after such application was approved, or tests by new methods, or tests by methods not deemed reasonably applicable when such application was approved, evaluated together with the evidence available to the [Agency] when the application was approved, shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved.[3]

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[1] 2006 Petition and FDA's response are available at http://www.regulations.gov/#!searchResults;rpp=25;po=0;s=FDA-2006-P-0326.

[2] For purposes of this response, all references to "orlistat" are intended to refer to the active pharmaceutical ingredient in both Xenical (orlistat) and alli (orlistat) unless otherwise specified.

[3] Section 505(e)(1) and (2) of the FD&C Act (21 U.S.C. 355(e)(1) and (2)); see also 21 CFR 314.150. In addition, section 505(e) of the FD&C Act provides that if the Secretary of Health and Human Services "finds that there is an imminent hazard to the public health, he may suspend the approval of such application immediately."

The Agency also will withdraw approval of an NDA based upon efficacy concerns if:

> on the basis of new information before [the Agency] with respect to such drug, evaluated together with the evidence available to [the Agency] when the application was approved, . . . there is a lack of substantial evidence that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling thereof).

(Section 505(e) of the FD&C Act)

As discussed below, the information provided in your Petition and the comments on the Petition, as well as our review of available data related to the safety and efficacy of orlistat, does not meet the above-referenced statutory standard for withdrawing approval of an NDA.

II. DISCUSSION

You request that Xenical and alli (orlistat) be withdrawn from marketing because of safety concerns related to hepatotoxicity, acute pancreatitis, acute oxalate nephropathy and kidney stones, gastrointestinal (GI) pain that masks pain due to more serious conditions, and interference with the absorption of fat-soluble vitamins and lipophilic drugs. As discussed in section II.A. of this response, we have carefully considered each of these safety risks, the information provided in the Petition and comments, and other relevant information identified by the Agency, and we have determined that orlistat continues to be safe for its approved indications.

You also suggest that orlistat does not have a favorable risk-benefit profile for long-term use based on the presumed risks described in your Petition and listed above, and its "minimal efficacy" for weight loss (Petition at 1 and 3-6). As discussed in section II.B. of this response, the data in the Xenical NDA satisfied a recommended approach for demonstrating efficacy as described in the Agency's 1996 draft guidance *Clinical Evaluation of Weight-Control Drugs* (the 1996 Guidance),[4] and the Agency concluded, consistent with the recommendation of the Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee (Joint Committee), that the data from the alli NDA demonstrated efficacy for use as a nonprescription drug. You have not provided any new information that changes our conclusions that Xenical and alli are effective for their approved indications. As discussed below, based on these data, we have determined that orlistat continues to be safe and effective, that the benefits of orlistat outweigh its risks, and that the available evidence concerning orlistat's safety and efficacy do not meet the criteria for market withdrawal as set forth in section 505(e) of the FD&C Act.

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[4] The 1996 Guidance is no longer available on FDA's Web site, but the clinical endpoints described in the 1996 Guidance are described in FDA's Briefing Package, available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_02_03-FDA-Clinical-Review.pdf at 3. In February 2007, FDA published a draft guidance, *Developing Products for Weight Management,* which is discussed in section II.B.1 (the draft guidance is available on FDA's Web site at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071612.pdf).

A. Safety of Orlistat

In your Petition you state that Xenical and alli expose patients to the following five specific risks:[5]

- Severe liver injury
- Acute pancreatitis
- Acute oxalate nephropathy and kidney stones
- GI pain that masks pain due to more serious conditions
- Interference with the absorption of fat soluble vitamins and lipophilic drugs

(Petition at 1 and 15.)

We discuss each risk separately in this section of the response.

1. Risk of Severe Liver Injury

You state that orlistat may cause severe liver injury, which you maintain can lead to liver failure, the need for liver transplantation, and death (Petition at 1). To support this, you first note that early animal studies using intravenous (i.v.) orlistat revealed evidence of hepatic lipid accumulation and hepatocellular injury. You argue that it is biologically plausible that significant hepatic accumulation of orlistat could occur in patients who take Xenical or alli over a period of months or years, causing hepatic toxicity similar to that seen in animal i.v. studies (Petition at 6-8). Second, you state that FDA's clinical review of alli noted reports of liver injuries for which an association with orlistat could not be ruled out (Petition at 8). Finally, you quote the liver injury warning that was added to the labeling of Xenical and alli in 2010 (Petition at 8 and 19). We discuss each of these points in turn below.

a. Biological Plausibility of Hepatotoxicity

Based on certain nonclinical studies from the Xenical NDA, you argue that GI absorption and systemic exposure to orlistat occurs in humans at levels that can cause hepatic toxicity (Petition at 6-8). You cite 2-week studies in rats and dogs using i.v. dosing in which liver toxicity was noted in the Xenical pharmacology review as support for the biological plausibility of orlistat's causing hepatotoxicity. You also state that the data from these animal studies contradict the statement in Xenical labeling that "[s]ystemic exposure to orlistat is minimal" [6] (Petition at 6-7).

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[5] In the Petition, you also allude to the safety concerns you raised in the 2006 Petition without providing any new information or analysis. Your arguments regarding these safety concerns were addressed in our response to the 2006 Petition and will not be repeated in this response. See footnote 1, supra.

[6] See approved labeling for Xenical at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf (this link is to labeling approved after the Petition was submitted to FDA, but the labeling continues to include the language quoted in the Petition).

We agree that in these early, short-term animal studies, i.v. orlistat caused adverse effects in the livers of rats and dogs. Both Xenical and alli are, however, oral rather than i.v. drug products, and the results from these short-term i.v. studies do not reflect the entirety of the nonclinical data from the Xenical NDA, which demonstrates the low systemic absorption of oral orlistat.

Systemic absorption of orlistat is not required for effectiveness. Orlistat acts locally in the GI tract. When taken orally, orlistat prevents gastric and pancreatic lipases in the GI tract from breaking down dietary triglycerides into absorbable free fatty acids and monoglycerides. The intact triglycerides are then excreted. Local action in the intestinal epithelium is sufficient for pharmacodynamic activity, and systemic absorption is not required for efficacy.

In addition to the i.v. studies you cite, the NDA for Xenical included an abundance of sub-chronic and chronic nonclinical data gathered using oral dosing. Among studies conducted for up to 2 years duration in rodents and 1 year in dogs, only one study using oral dosing (a 13-week rat study using high doses) reported adverse liver pathology at necropsy. The animals in the adversely affected group received a dose providing a maximum plasma orlistat concentration approximately 70 times higher than the highest seen clinically. The 2-year rat carcinogenicity study also showed some evidence of liver toxicity in the clinical chemistry assessment at a dose providing maximum plasma orlistat concentrations approximately 292 times higher than the highest concentration seen clinically, but even at that dose there was no evidence of fat accumulation or other adverse effects in the liver at necropsy.[7]

The bioavailability of intact orlistat was 0.12% in rats and 0.7% in dogs.[8] In both the oral and i.v. dosing experiments, high plasma levels of intact orlistat appear to be required to cause adverse effects in the liver. In the i.v. rat studies, concentrations ≥ 5 micrograms (µg)/milliliter (mL) caused minimal effects that could be attributed to pharmacodynamic effects of orlistat in the liver and concentrations ≥ 20 µg/mL resulted in clearly adverse liver histology. In dogs, there were no adverse liver effects at peak plasma concentration (C_{max}) values up to 19 µg/mL, but concentrations ≥ 100 µg/mL caused adverse liver effects. In rats, the most sensitive species, the required C_{max} value for minimal hepatotoxicity was approximately 500 times higher than the highest C_{max} measured clinically (10 nanograms (ng)/mL) using the 120-mg, three-times-daily (TID) dose.

In the longer duration studies in rats using oral doses, much higher nominal doses were needed to approach similar plasma concentrations. Even though concentrations of orlistat appear to have been higher at the lowest observed adverse effect level (LOAEL) in the 2-year study compared to the 13-week study, the animals treated for 2 years did not have the observable liver changes at necropsy seen in the 13-week study, suggesting that there may be accommodation to the change in liver lipid handling with chronic dosing.

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[7] See the pharmacology NDA review for Xenical at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P2.pdf (p. 16-17).

[8] See the clinical pharmacology NDA review for Xenical at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_clinphrmr_P1.pdf (p. 3).

These toxicology studies show that orlistat can injure the liver when high concentrations of active drug substance are present in the organ. The biological plausibility of an orlistat-related hepatotoxicity being observed after oral dosing depends not only on the direct toxicity of orlistat, but also on the bioavailability of the drug. Systemic bioavailability and tissue levels of the intact drug, therefore, are critical factors in determining whether hepatotoxicity is a plausible occurrence with clinical use of prescription or OTC orlistat at the approved oral dosage.

Your statements in the Petition regarding absorption of orlistat rely on data from measuring levels of radioactivity observed in the urine of rats after oral ingestion of radiolabeled orlistat, which you present as evidence of absorption of presumably "active" drug (Petition at 7). Measuring the total radioactivity in the urine after an oral dose of radio-labeled drug can provide a crude estimate of drug-related material that is systemically absorbed, but it is an imperfect, and sometimes misleading, method. Absorbed drug can be eliminated through the bile (as happens to a small percentage of orlistat) rather than the urine. Moreover, measuring total radioactivity in the urine includes inactive metabolites. In a highly metabolized drug like orlistat, measurement of total radioactivity in urinary excretion leads to an overestimate of absorption of the active drug.

You also express concern about the tissue penetration of the drug and possible accumulation in sensitive organs, including the liver (Petition at 7). In a tissue distribution study in rats, less than 5% of the dosed radioactivity was measured in the tissues after oral dosing, with ~1% of the dosed radioactivity being found in the liver.[9] These radioactivity levels represent a combination of metabolites and unmetabolized drug. In rats that were given the radioactive drug for 30 days, less than 5% of the radioactivity was absorbed. Mild (three-fold) accumulation in the liver was seen by the end of the study when compared to the 24-hour time point (not compared to plasma levels as implied by the Petition). It is important to highlight that the absolute effect of this accumulation would be expected to be minimal because the amount absorbed is so small.

As with the measurement of radioactivity in urine described above, measuring plasma and tissue levels of total radioactivity, as suggested by the Petition, provides an inadequate and incomplete basis for estimating the potential for orlistat-related pharmacodynamic activity. Orlistat undergoes significant metabolism as it crosses into the systemic circulation. It is further metabolized in the plasma and to some extent in the liver. There is some evidence that orlistat partitions preferentially into the liver in both humans and rats, but we have no reason to believe that accumulation is very different between clinical and nonclinical species. Consequently, the safety margins provided by the rat studies are more than adequate to provide an assurance of safety from a nonclinical perspective. It is also worth noting that hepatic adverse effects were always preceded by increases in plasma triglycerides in animals that were given oral orlistat, but clinical subjects with the highest orlistat plasma concentrations had no evidence of this indicator for hepatic adverse effects (increased triglycerides).

[9] See Xenical Pharmacology Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf at 48-49.

In a relevant clinical study reported in the medical literature[10] in which orlistat and metabolites M1 and M3 were measured in bile samples after 4 weeks of 120-mg, TID dosing, concentrations were 19.6, 21.5, and 73 ng/mL respectively. Orlistat levels were higher in the bile (and presumably the liver) than in plasma (where the maximum observed concentration during development was < 10 ng/mL). The authors estimate that 0.02 mg/day (or 0.0056% of the daily dose) is eliminated via the bile. Thus, even with time for orlistat to accumulate in the liver in these clinical subjects, concentrations only reached relatively low levels in the bile, which we can expect to be indicative of similarly low levels in the liver.

One group of researchers has suggested that orlistat inhibits the metabolic enzyme carboxylesterase-2 (CES-2)[11] and interprets the in vitro results to speculate that the inhibition of CES-2 may provide "an alternative explanation to the organ-based toxicity" that they ascribe to orlistat, presumably by preventing the detoxification of various endogenous or exogenous compounds in the GI tract and liver. We reviewed the published manuscript, as well as related scientific literature, and found that the current data do not support the authors' suggestion that inhibition of CES-2 is associated with organ, specifically liver, toxicity.

In summary, although systemic exposure to orlistat at high plasma concentrations can cause adverse effects in the liver in animals, such high plasma concentrations are not found in humans when the dosage level is closer to the amount intended for use clinically. You highlight in the Petition certain specific aspects of the nonclinical data, but the totality of the clinical and nonclinical data suggests that very little unmetabolized orlistat reaches systemic circulation at relevant dose levels. The data for orlistat does not support your conclusion that significant hepatic accumulation of orlistat can occur in patients taking Xenical or alli and cause hepatic toxicity similar to that seen in the animal studies you reference in the Petition.

b. FDA's Clinical Review of alli and FDA's Analysis of Reports Involving Liver Injury

You refer to the 2006 NDA clinical review for alli, and you state that the FDA medical officer discussed nine cases of hepatic failure or cholestatic hepatitis (two resulting in death and one in liver transplantation) and noted that an association with orlistat could not be ruled out (Petition at 8). You also note the reviewer's conclusion that none of the reports demonstrated a definitive association between orlistat and hepatic injury.[12] This information was included in FDA's background package presented to the Joint Meeting of the Joint Committee on January 23,

[10] Trouillot, TE, DG Pace, C McKinley, et al., 2001, Orlistat maintains biliary lipid composition and hepatobiliary function in obese subjects undergoing moderate weight loss, The American Journal of Gastroenterology, 96(6): 1888-1894.

[11] Xiao D, D Shi, D Yang, et al., 2013, Carboxylesterase-2 is a highly sensitive target of the antiobesity agent orlistat with profound implications in the activation of anticancer drugs, Biochemical Pharmacology, 85:439-447.

[12] See alli Clinical Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf (p. 110).

2006.[13] The Joint Committee found by a vote of 12 to 3 that the safety and tolerability characteristics of orlistat were acceptable for a nonprescription drug.[14]

After additional safety information became available, in 2009, FDA conducted a comprehensive review of safety information for orlistat-associated severe liver injury. After reviewing the cases of serious liver injury, FDA ultimately concluded that the risk of hepatic injury with orlistat is considered "rare." FDA approved changes to the labeling for Xenical and alli regarding the risk of liver injury, and the sponsors implemented these changes for both drug products in 2010. The current labeling concerning the risk of liver injury is described in section II.A.1.c. of this response. In addition, the sponsor of Xenical was required to submit to the Agency all serious suspected cases of liver injury as expedited, 15-day reports for a period of 3 years.[15]

Following receipt of your Petition, we reviewed the safety information available for orlistat since 2009. As part of our review, we conducted a search of the Adverse Event Reporting System (AERS)[16] database and published literature focusing on serious liver injuries that resulted in death, liver transplant, or hospitalization.

Our review identified a total of 17 reports of severe liver injury associated with orlistat from approval in 1999 through April 21, 2011. Of these, 13 were associated with Xenical and the remaining four were associated with alli. Among the 13 reports associated with Xenical, there were two deaths and four liver transplants. The four alli reports included one liver transplant and one death. Most of the cases (15/17, 88%) were reported from outside the United States.

The background incidence rate of idiopathic acute liver failure in the general population is estimated at about 1 per million person-years.[17] Although utilization data does not provide person-years of exposure or the distribution of duration of exposure, based on cumulative utilization sales data from manufacturers for years 2005-2010, it is estimated that over 900 million orlistat capsules have been purchased by various retail and nonretail channels.[18] In 2010 it was estimated that over 40 million people worldwide had used Xenical or alli.[19] Considering

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[13] FDA's Briefing Document and other materials related to the January 23, 2006, meeting can be found on FDA's Web site at http://www.fda.gov/ohrms/dockets/ac/cder06.html#EndocrinologicMetabolic.

[14] See Joint Committee meeting minutes at http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4201M.pdf.

[15] See letter from FDA regarding NDA 20766/S-028 dated May 25, 2010, at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/020766s028ltr.pdf.

[16] When the review was conducted, the postmarket adverse event reporting system was AERS. On September 10, 2012, AERS was replaced by the FDA Adverse Event Reporting System (FAERS).

[17] Graham, DJ and L Green, Final Report, Office of Postmarketing Drug Risk Assessment, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, MD (2000).

[18] Manufacturer information provided to FDA.

[19] See FDA Drug Safety Communication: Completed safety review of Xenical/Alli (orlistat) and severe liver injury, available at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm.

the level of exposure, the rate of observed orlistat-induced severe liver injury appears closer in magnitude to the background idiopathic rate than to the rate of well-described hepatotoxins such as isoniazid (INH), troglitazone, and bromfenac. The frequency of severe liver injury/failure associated with these drugs is between 1/1,000 and 1/10,000.[20]

Consequently, we have determined that the information in your Petition and the results of our analysis of the risk of liver toxicity do not change our previous conclusion that the risk of hepatic injury with orlistat is "rare."

c. Current Labeling Adequately Addresses the Risk of Hepatotoxicity

Labeling for Xenical describes the potential risk for liver injury in WARNINGS AND PRECAUTIONS (Section 5.2) and in ADVERSE REACTIONS (Section 6.2):

> **5.2 Liver Injury**
> There have been rare postmarketing reports of severe liver injury with hepatocellular necrosis or acute hepatic failure in patients treated with XENICAL, with some of these cases resulting in liver transplant or death. Patients should be instructed to report any symptoms of hepatic dysfunction (anorexia, pruritus, jaundice, dark urine, light-colored stools, or right upper quadrant pain) while taking XENICAL. When these symptoms occur, XENICAL and other suspect medications should be discontinued immediately and liver function tests and ALT and AST levels obtained.
>
> **6.2 Postmarketing Surveillance**
> Rare cases of increase in transaminases and in alkaline phosphatase and hepatitis that may be serious have been reported. There have been reports of hepatic failure observed with the use of XENICAL in postmarketing surveillance, with some of these cases resulting in liver transplant or death *[see Warnings and Precautions (5.2)]*.
>
> (Emphasis in the original.)[21]

The Patient Information labeling for Xenical includes the following:

> **What are the possible risks of XENICAL?**
>
> **XENICAL may cause serious side effects, including**:
>
> **Severe liver problems.** Stop taking XENICAL and call your doctor right away if you have the following symptoms of liver problems:
>
> - loss of appetite

[20] Saukkonen, JJ, DL Cohn, RM Jasmer, et al., 2006, An Official ATS statement: Hepatotoxicity of Antituberculosis Therapy. American Thoracic Society Document; Graham, DJ, L Green, JR Senior, et al., 2003, Troglitazone-induced liver failure: a case study, Am J Med, 114(4):299-306; Goldkind, L and L Laine, 2006, A systematic review of NSAIDs withdrawn from the market due to hepatotoxicity: lessons learned from the bromfenac experience, Pharmacoepidemiol Drug Saf, 15(4):213-220.

[21] See Xenical labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf.

- itchy skin
- yellowing of your skin or the white part of your eyes
- amber-colored urine
- light-colored bowel movements (stools)
- pain in the upper right portion of your stomach.

(Emphasis in the original.)[22]

The alli Drug Facts label includes the warning: "Stop use and ask a doctor if [bullet] you develop itching, yellow eyes or skin, dark urine or loss of appetite. There have been rare reports of liver injury in people taking orlistat."[23]

In sum, the data associated with orlistat and liver injury have been evaluated extensively and repeatedly by the Agency. We conclude that the frequency of orlistat-induced serious liver injury is low and may not differ from the background rate of idiopathic liver failure. The risk of orlistat-associated liver injury is appropriately and adequately managed by current labeling and continued monitoring.

2. Risk of Acute Pancreatitis

You state that orlistat can cause acute pancreatitis, which frequently results in hospitalization and can lead to death (Petition at 1). As with your description of the risk of liver toxicity, you cite selected nonclinical studies regarding absorption of orlistat as the basis for a theory of biological plausibility, as well as cite excerpts from the Joint Committee meeting transcript (Petition at 8-9). You list case reports of pancreatitis from the medical literature and provide your analysis of cases found in AERS (Petition at 10-11). You also state that the pancreatitis warning in the Xenical labeling is "not helpful" (Petition at 21). Each of your points is discussed below.

a. Biological Plausibility

Your theory is that it is biologically plausible that orlistat accumulates in the pancreas and can cause pancreatic toxicity in humans similar to what is seen in animals. Your theory is based on results from nonclinical studies conducted for the Xenical NDA. In general, findings related to orlistat's systemic effects from any of the nonclinical studies may not be applicable to humans, given that orlistat has been shown to have low systemic exposure in humans. In addition, as described above in section II.A.1.a., bioavailability for orlistat is minimal in oral studies of nonclinical species.

In support of your theory of biological plausibility, you reference a 30-day rat study using orlistat with a radioactive marker in which radioactivity was measured in the pancreas and many other tissues after multiple doses (Petition at 8). However, as described in section II.A.1.a., measuring total radioactivity is not a reliable substitute for measuring unmetabolized orlistat because it does not allow for identification of the parent versus metabolite chemicals. Like intact orlistat, some

[22] Id.

[23] See letter from FDA to GSK at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/021887s002ltr.pdf.

of the drug's inactive metabolites are also lipophilic and would also partition into tissues. It is possible that some of the radioactivity in the pancreas reflects the presence of unmetabolized orlistat; however, the radioactivity level in the pancreas in this study was among the lowest in all the tissues measured.[24] Notably, there were no changes in the pancreas in any of the toxicity studies.

You also point to increased α-amylase in a 2-week study in dogs cited in the pharmacology review for Xenical[25] (Petition at 8-9). In this study, dogs that were treated with oral orlistat for 2 weeks while on a high-fat diet were noted to have increases in serum α-amylase and lipase. You state that serum α-amylase and lipase are key indicators of pancreatic injury (Petition at 8-9). The study referenced was a dose-range-finding study that used nominal doses of 0, 0.3, 1, 3, and 9 mg/kg/day of orlistat along with a diet high in lipids. The increase in α-amylase was attributable to the high-fat diet and occurred in all groups. Xenical and alli are intended to be used only with a reduced-calorie diet that contains approximately 30% of calories from fat. In addition to being attributable to the high-fat diet, the effect seen in the study was not dose-dependent. There were no treatment-related effects in similarly designed follow-up studies, including a 20-day study using 250 and 1000 mg/kg and the pivotal 1-year study using doses of 0, 10, 100, and 1000 mg/kg.[26] There were no histopathology findings suggesting a treatment-related effect on the pancreas in any of the dog studies.[27] We conclude again, therefore, that the data from dog studies do not support pancreatic toxicity in the wide dose ranges tested.

Although FDA's Xenical pharmacology review of the rat study you cite noted that "for rats, at doses ≥ 450 mg/kg/day, plasma amylase activity was increased" (Petition at 9), we have determined that the statement is incorrect. After examining the original review documents for the rat studies in question, it appears the word "increased" was mistakenly substituted for the word "decreased." The same NDA review concludes that doses of 125-150 mg/kg/day (rather than ≥ 450mg/kg/day) cause increased plasma amylase activity.[28]

The medical officer's review correctly describes the outcome on page 7 of the review.[29] Alpha-amylase actually decreased significantly at the high dose (450 mg/kg) in the referenced study. This is consistent with the observation in the 1-year rat study, where both amylase and lipase levels decreased in animals given a high dose (125 mg/kg).

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[24] See Xenical Pharmacology Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf at 48-49.

[25] See Xenical Pharmacology Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P3.pdf at 34-35.

[26] Id. at 36-39.

[27] Id. at 36.

[28] Id. at 59.

[29] Xenical Medical Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P6.pdf at 7.

In conclusion, you have not presented (and the Agency has not identified) a biologically plausible basis to conclude that there is pancreatic toxicity based on the available nonclinical data. Decreased α-amylase was seen in rats in this and other studies. The increased plasma α-amylase in dogs occurred in all groups and is attributed to the high-fat diet.

b. Pancreatitis in FDA's Clinical Safety Review of alli and Discussion by the alli Joint Committee

You cite portions of the alli clinical review and the Joint Committee discussion about the safety of alli to support your position that orlistat poses an unacceptable risk of acute pancreatitis. Specifically, you note that the clinical review stated that 99 "raw" cases of pancreatitis associated with orlistat were found in the AERS database and that 68 of those were confounded by other factors. You note that the remaining 31 cases contrasted with 8 cases found associated with sibutramine (trade name Meridia), another FDA-approved drug for the chronic treatment of obesity[30] (Petition at 9).

FDA had been monitoring AERS reports of Xenical and pancreatitis before the alli review. As noted in the alli clinical review, reports of pancreatitis associated with orlistat were discussed at the Joint Committee meeting in 2006 at which alli was considered.[31]

In the Petition, you quote advisory committee members expressing concerns about pancreatitis in the discussion on the safety of alli (Petition at 9). The Joint Committee was asked to specifically comment on safety concerns related to pancreatitis (among other safety concerns) and on the ability of labeling to convey these risks to the OTC consumer. The specific comments you quote all appear to reflect the committee members' concerns about use of orlistat without physician oversight, and it was noted that pancreatitis was a post-marketing adverse event of interest that FDA was looking into further. FDA's review looked at pancreatitis-related adverse events through May 2006, and the results are described in the alli Medical Review.[32] After a full discussion of this and other safety and efficacy issues, the Joint Committee voted 12 to 3 that the safety profile of orlistat was acceptable for a nonprescription product.[33] FDA completed its review of post-marketing information on pancreatitis prior to approval of alli and the medical reviewer concluded that the number of pancreatitis-related adverse events from the current period (through 2006) appeared relatively comparable to previous time periods.[34]

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[30] The manufacture of sibutramine has been discontinued; see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails.

[31] See Joint Committee meeting minutes at http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4201M.pdf.

[32] See alli Medical Review at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P1.pdf at 98.

[33] See Joint Committee meeting minutes at http://www.fda.gov/ohrms/dockets/ac/06/minutes/2006-4201M.pdf.

[34] See alli Medical Review at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P1.pdf at 9.

In conclusion, the Petition accurately points out that concerns were raised about pancreatitis associated with the nonprescription use of orlistat. These concerns were adequately evaluated and addressed in the clinical reviews and by the Joint Committee.

c. Pancreatitis Cases Cited in the Literature and Reported in AERS

In your Petition, you noted four case reports of orlistat-associated pancreatitis in the medical literature (in fact, the four referenced publications include a total of 5 case reports)[35] (Petition at 10). In two[36] of these five cases, no obvious alternative etiology was identified, but other causes for the events cannot be ruled out because we do not have the full medical history of these patients. The clinical information available to us for one of the three remaining cases was limited, because it was obtained from an abstract from a paper from Spain and we are not able to draw any conclusions about the likelihood of orlistat causation.[37] In each of the last two cases, our review identified at least one alternative explanation that was as likely a cause as orlistat.

In one of these two cases, the patient[38] had a medical history of known alcohol excess, and one previous episode of known alcohol-induced pancreatitis 1 year earlier. Although there is a temporal association with orlistat in this case, excess alcohol consumption may be an alternative explanation for the acute pancreatitis experienced by the patient, particularly because the patient had had an episode of alcohol-related acute pancreatitis in the recent past.

In the second case,[39] the patient had previously taken orlistat for 8 months "without any adverse event," although it had been discontinued in the previous course of treatment because of "intolerance." Eight weeks before the reported adverse event, she had begun taking sitagliptin as part of her treatment for diabetes. Four weeks before the event, she began taking orlistat again. The authors of this case report stated that no case of sitagliptin-induced pancreatitis had been reported previously. However, FDA issued a safety alert in 2009 noting revisions to the prescribing information for sitagliptin products to include information on reported cases of acute pancreatitis, and the sitagliptin label includes a warning for acute pancreatitis.[40] This case is possibly attributable to sitagliptin, although a contributing role for orlistat cannot be ruled out.

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[35] Napier, S and M Thomas, 2006, 36 year old man presenting with pancreatitis and a history of recent commencement of orlistat case report, Nutr J., 5:19; Ahmad, FA and S Mahmud, 2010, Acute pancreatitis following orlistat therapy: report of two cases, J Pancreas (online), 11:61-63; Garg, R, C Hussey, and S Ibrahim, 2010, Pancreatitis associated with the use of sitagliptin and orlistat combination: a case report, Diabetic Med., 27:485-488; and Aguilera, XG, CT Sanchez-Vegazo, LC Perez, et al., 2008, Acute pancreatitis induced by orlistat, Medicina Clinica, 130:557.

[36] Napier S, et al., 2006; and Ahmad FA et al., 2010.

[37] Aguilera XG, et al., 2008.

[38] Ahmad FA, et al., 2010.

[39] Garg R, et al., 2010.

[40] See sitagliptin labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s023lbl.pdf.

In the Petition, you provide your own analysis of spontaneous adverse event reports in the AERS database for acute pancreatitis that reportedly occurred with the use of orlistat[41] (Petition at 10-11 and 20). The Agency conducted a safety review focusing on the possible association of orlistat and pancreatitis in 2006. At that time, we concluded that there may be an association between orlistat and pancreatitis, and pancreatitis was added to the Postmarketing Surveillance subsection of the Xenical label.[42] As part of our evaluation of the issues you raised, we reviewed AERS data in light of the concerns discussed in the Petition. We identified 25 additional cases of pancreatitis since 2006. Of these, 6 occurred in patients who were taking Xenical, and 19 with alli. There were no death reports, although most patients (19/25) were hospitalized. No severe acute pancreatitis cases (necrotizing or hemorrhagic) were reported, and most case reports (19/25; Xenical n=5; alli n=14) said acute pancreatitis was improved. All of the Xenical and 32% (6/19) of the alli cases were foreign reports. Concomitant medications labeled for pancreatitis were reported in 24% of the cases (6/25; Xenical n=3; alli n=3). In total, there are 59 cases of pancreatitis associated with orlistat in FDA's AERS database from orlistat's approval in 1999 through April 21, 2011. Given the large number of people exposed to orlistat and the limited number of reports to date, the rate of orlistat-associated pancreatitis appears to be low.

Acute pancreatitis is a complex clinical entity with multiple etiologies. The orlistat target population (overweight patients) is prone to co-morbidities that increase the risk for pancreatitis such as gall bladder disease, hypertrigylceridemia, and diabetes. As highlighted by the case reports discussed above, even when certain details of medical history, including the identification of other medications being used, are available, it is difficult to identify the precise cause of pancreatitis in this population. Consequently, spontaneous adverse event reports are of limited usefulness in characterizing the risk of acute pancreatitis associated with orlistat.

d. Current Labeling Adequately Addresses the Risk of Acute Pancreatitis

We agree that there may be an association between pancreatitis and orlistat use, but no causal relationship has been shown. This was our conclusion after our review in 2006, and your Petition and our updated review have not revealed any new information that results in a different conclusion. You appear to disagree with the labeling (stating that the warning is "not helpful" (Petition at 21)), but do not describe what specifically you find lacking or needing revision. As noted above, Xenical labeling includes the following in the Postmarketing Surveillance subsection:

- Pancreatitis has been reported with the use of XENICAL in postmarketing surveillance. No causal relationship or physiopathological mechanism between pancreatitis and obesity therapy has been definitively established.[43]

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[41] Because we are providing our own analysis of the AERS data for a similar time period, we will not discuss the details of your analysis.

[42] See Xenical labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/020766s022lbl.pdf.

[43] See most recent approved Xenical labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf.

Language for pancreatitis was included in the Drug Facts labeling for alli at the time of approval in 2007.[44] The current alli Drug Facts labeling directs patients to:

- **Ask a doctor before use if you have** ever had pancreatitis, and
- **Stop use and ask a doctor if** severe or continuous abdominal pain occurs. This may be a sign of a serious medical condition."[45]

(Emphasis in original.)

The background pancreatitis rates cannot be reliably estimated in an obese population with multiple risk factors, but given the large number of people exposed to orlistat and the limited number of adverse event reports to date, the rate of orlistat-associated pancreatitis appears to be low. Based on our analysis of the totality of the data related to the risk of acute pancreatitis among users of orlistat, we conclude that this risk is appropriately and adequately managed by the current labeling and continued monitoring.

3. Risk of Acute Oxalate Nephropathy and Kidney Stones

You state that orlistat can cause acute renal failure (ARF) secondary to acute oxalate nephropathy, and calcium oxalate nephrolithiasis (kidney stones) (Petition at 1). You refer to selected results from nonclinical studies and a statement in the review of the Xenical NDA as support for the biological plausibility of a link. You also describe case reports from the medical literature and provide your analysis of AERS data (Petition at 11-15, 21-22). The Petition also states that orlistat labeling lacks a warning for kidney stones (Petition at 22). Each of these points is discussed below.

We agree that there may be an association between orlistat use and acute oxalate nephropathy and kidney stones. As discussed below, in early 2012 (after the date of your Petition), FDA addressed these risks by approving kidney warnings on the labeling for Xenical and alli. We believe that the current labeling for orlistat drug products adequately addresses the risks of acute oxalate nephropathy and kidney stones.

a. Biological Plausibility

You refer to information from the nonclinical studies in the Xenical NDA and citations from the scientific literature as evidence of orlistat's renal toxicity (specifically oxalate nephropathy and oxalate nephrolithiasis or kidney stones). As discussed below, we agree that there is biological

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[44] See alli approved labeling, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf.

[45] Prior approved Drug Facts for alli is available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf. The most recently FDA-approved Drug Facts for alli is not publicly available on FDA's Web site. References to the prior approved Drug Facts are to text in the originally approved Drug Facts (available by the Web site link provided) that remains unchanged in the currently approved Drug Facts.

plausibility for a role of orlistat in the formation of calcium oxalate stones and in the development of oxalate nephropathy.
In the Petition you state:

> Regarding pre-clinical studies submitted as part of the NDA for Xenical (orlistat), in rats treated for 6 or 9 months with oral orlistat while fed a high-fat, normal calcium diet, kidney mineralization, pelvic dilation, and progressive nephropathy were commonly observed pathologic lesions on post-mortem histopathology examination. Likewise, in female dogs treated for one year with oral orlistat while fed a high-fat diet, medullary mineralization of the kidney was seen on post-mortem histopathology examination.

(Petition at 11-12.)

Although the findings you describe were seen in the treated group, the results from the control groups in these studies need to be considered as well. The cited FDA review goes on to state, "[h]istopathological findings for treated [animals] were similar to that of controls."[46] Consequently, these kidney findings were not considered to be related to treatment.

Of the more than 10 animal studies submitted to the Xenical NDA, there were 2 that had findings in the kidney that could be reasonably linked to treatment. In the 13-week rat[47] study using very high oral doses, fatty infiltration was noted in the kidney; this finding followed the same pattern as fatty infiltration in the liver and is likely related to pharmacodynamic effects. In the 2-year rat study,[48] kidney findings included a slight increase in kidney weight (range 12-21%) and an increase (in females only) in the incidence of the common background lesion of chronic renal pathology. Notably, there were no treatment-related kidney changes in dogs (which are predisposed to having calcium oxalate renal stones), even in studies using low-calcium diets. Unlike the case in rats, dogs are often found to have calcium oxalate renal stones as a background finding (i.e., irrespective of treatment). In addition, none of the nonclinical studies showed evidence of kidney stones or acute oxalate nephrology.

You also cite the literature to support your argument for orlistat-related kidney toxicity (Petition at 12). The first article you cite[49] describes an increase in urinary oxalate excretion in rats that were given a diet rich in soy oil, sodium oxalate, or both. High urinary oxalate excretion is positively associated with oxalate kidney stones. Orlistat further increased urinary oxalate excretion in experimental groups that were administered an excessive amount (2% of diet) of dietary oxalate, but had negligible effects in the other experimental groups. There was no

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[46] See Xenical Pharmacology Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P3.pdf at 31.

[47] See Xenical Pharmacology Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf at 59-60.

[48] See Xenical Pharmacology Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P2.pdf at 15.

[49] Ferraz, RRN, HG Tiselius, and IP Heiberg, 2004, Fat malabsorption induced by gastrointestinal lipase inhibitor leads to an increase in urinary oxalate excretion, Kidney International, 66: 676-682.

evidence of kidney stone formation or mineralization in the histopathology examination of the kidneys at the end of the study. If the rats in this study consumed all the food they were offered (20 grams (g)/day), the oxalate-supplemented groups would have consumed approximately 8.7 g/m^2 of oxalate daily, which is much higher than the 0.2 g/m^2 of oxalate measured in self-selected diets of human subjects.[50] This difference makes extrapolating these results to more realistic dietary scenarios which would involve significantly lower levels of oxalate intake problematic.

You cite several studies in the literature as providing evidence for a risk of kidney stones related to fat malabsorption.[51] As discussed in section II.A.5., orlistat, by design, leads to decreased absorption of fat in the GI tract. There are reports in the literature that malabsorbed fat increases the clinical risk of oxalate kidney stones due to excess binding of calcium by lipids in the GI tract, leading to unbound free oxalate being absorbed systemically, allowing it to bind to calcium and precipitate in the kidney.[52] This risk may be increased in patients with other GI disorders such as ileal disease (e.g., Crohn's disease and short bowel). These reports support the biological plausibility of a role of orlistat in the formation of calcium oxalate stones.

The biological plausibility for a role for orlistat in the development of kidney stones was considered in the Xenical and alli medical reviews. As you note, results from a study submitted to the Xenical NDA showed levels of urinary oxalate that were higher in the orlistat group compared to the control group, but the difference did not reach statistical significance. You state that a statistically significant higher number of subjects in the orlistat group had elevated levels of 24-hour urine oxalate levels in comparison to control subjects. As you point out, the clinical review of Xenical states that "[t]hese data provide biological plausibility with which to link the use of orlistat with the development of nephrolithiasis [kidney stones]" (Petition at 12-13). The clinical review for alli also posited that the incidence of oxalate stones may be increased in the real-world situation in which compliance with the direction for a low-fat diet is not monitored.[53]

In summary, we continue to believe that there is biological plausibility for a role of orlistat in the formation of calcium oxalate stones and in the development of oxalate nephropathy, although, as discussed above, no evidence of this type of renal pathology was seen in the nonclinical studies.

b. Cases From the Literature and FDA's Analysis of Cases From AERS

You assert in the Petition that there is a risk of ARF secondary to acute oxalate nephropathy and nephrolithiasis associated with orlistat. This assertion was based in part on a review of the

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[50] Holmes, RP and M Kennedy, 2000, Estimation of the oxalate content of foods and daily oxalate intake, Kidney International, 57(4): 1662-1667.

[51] Petition at 12.

[52] Dharmsathaphorn, K, DH Freeman, HJ Binder et al., 1982, Increased risk of nephrolithiasis in patients with steatorrhea, Digestive Disease Science, 27(5): 401-405.

[53] See alli Clinical Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_MedR_P5.pdf at 107.

literature and in part on your analysis of cases of nephrolithiasis associated with orlistat from the AERS database (Petition at 13-15; 21-22).

With regard to the literature, you cite several published reports of patients taking orlistat in whom calcium oxalate crystals resulted in ARF (Petition at 13-14). These published reports describe patients presenting with ARF that was temporally associated with orlistat, and who were found to have acute tubular necrosis and oxalate stone deposition on renal biopsy. Resolution after orlistat discontinuation was variable: in at least one case, renal function normalized, while in other cases, the result was chronic kidney disease where patients remained dialysis-dependent. There was one fatal outcome. From the case reports, it appears that patients who are at risk for this event may be those with underlying renal disease, or at risk for renal disease, such as those with diabetes or on other nephrotoxic agents. As described in subsection II.A.1.c. below, the approved labeling for Xenical and alli now includes warnings for those with, or at risk for, kidney disease, including kidney stones.

You also base your characterization of kidney-related risks on your analysis of the AERS database for cases of orlistat-induced nephrolithiasis (Petition at 13-15; 21-22). FDA performed an analysis of the AERS data using what we believe is a more comprehensive approach. Specifically, we reviewed all reports of ARF in orlistat users (including reports of nephrolithiasis). Because we are providing FDA's analysis of the AERS data, which looked at ARF, we will not discuss your AERS analysis in detail.

Our review of the AERS database included 21 cases (Xenical n = 15; alli n = 6) of ARF in association with orlistat. The demographics of this group of patients was as expected; the majority were over 50 years of age with hypertension, diabetes, or both, and were taking anti-hypertensives such as ACE inhibitors and diuretics and/or medications for their diabetes. The baseline renal function was not provided in a majority of the case reports.

This AERS case series included eight patients presenting with ARF that was temporally associated with orlistat use who were found to have oxalate stone deposition on renal biopsy. However, no cases of oxalate nephropathy were reported with alli. The outcomes for those who used Xenical and experienced oxalate nephropathy were serious: four patients (one of whom was approved for renal transplant) experienced acute tubular necrosis; and four were treated with hemodialysis (one of the four died).

There were 13 non-oxalate cases of acute renal failure (Xenical n=7; alli n=6). The available data did not detail whether oxalate nephrolithiasis contributed to ARF in these cases. These patients presented with renal dysfunction that was temporally associated with orlistat use. Information regarding baseline renal function was available only in the Xenical case reports, and in most of them there were confounding factors. The outcomes of the non-oxalate cases were serious: in one case there was probable acute tubular necrosis (though this was confounded by concurrent rhabdomyolysis, which can lead to the development of ARF independently), and in four cases (one with Xenical and three with alli) hemodialysis was required. Patients with Xenical-associated, non-oxalate ARF were reported to have orlistat-induced diarrhea (n=3), hypertension (which did not exist prior to orlistat usage (n = 1)), and ARF of unknown causes (n = 3). In four of the six alli non-oxalate cases of ARF, there were confounding factors: antibiotic

usage (n = 1); angiotensin II receptor blocker (ARB) usage (n = 1); liver failure (n = 1), and rhabdomyolysis (n = 1). For the remaining two alli non-oxalate cases, there was limited medical documentation.

Based on the temporal relationships and the biological plausibility, the case reports support the conclusion that ARF may develop secondary to orlistat-related oxalate deposition. In patients with predisposing factors, the ARF also may be associated with acute tubular necrosis. From the case reports, it appears that patients with underlying renal disease or at higher risk for renal disease – such as those with diabetes and those on other nephrotoxic agents – represent a population that may be more susceptible than those without these predisposing factors, particularly those using Xenical, which may be more likely to be used by those patients who have comorbidities and are under the care of a physician who would prescribe Xenical. However, based on our analysis of the totality of the data related to orlistat and the risk of ARF, we do not consider these spontaneous adverse event reports to constitute a safety signal warranting further investigation at this time.

c. Current Labeling Adequately Addresses the Risk of Acute Oxalate Nephropathy and Kidney Stones

We agree that there may be an association between orlistat use and acute oxalate nephropathy and kidney stones. In January 2012, FDA approved a revision to Xenical's labeling to, among other changes, add information to the WARNINGS AND PRECAUTIONS section describing cases of oxalate nephrolithiasis and oxalate nephropathy with renal failure while taking Xenical.[54] The Patient Information labeling for Xenical advises patients to tell their doctor before taking Xenical if they have had kidney problems or diabetes.[55]

Drug Facts for alli includes the following:

> **Ask a doctor before use** if you have ever had
> • gallbladder problems • kidney stones • pancreatitis[56]

(Emphasis in original.)

Based on our analysis of the totality of the data related to the risks of acute oxalate nephropathy and kidney stones among users of orlistat, we continue to believe that current labeling for Xenical and alli is appropriate and adequate to address these risks.

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[54] See letter from FDA dated January 20, 2012, at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/020766s029ltr.pdf.

[55] See most recent approved Xenical labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf.

[56] See prior approved Drug Facts for alli at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf.

4. Risk of Masked Pain of Acute Pancreatitis or Renal Colic

You state that orlistat commonly causes significant abdominal pain because of its local effects on the GI tract, and state that this is an important safety issue because abdominal pain could mask pain that is caused by concurrent mild acute pancreatitis or renal colic (Petition at 15). In support of this argument, you cite preclinical animal studies from the Xenical review in which oral administration of orlistat to rats and dogs caused a significant increase in fecal fat excretion, leading to loose or soft stools. You also note that the Xenical labeling identifies GI effects as one of the four major general categories of adverse events from orlistat, with the most common GI adverse events being oily spotting, fecal urgency, flatus with discharge, and (in about 25% of patients) abdominal pain (Petition at 15).

In the original NDA clinical review, it was noted that in the first year of treatment, 21% of patients in the Xenical group (out of 1913 patients total) and 16% of patients in the placebo group (out of 1466 patients) experienced abdominal pain. After two years of treatment, 23% of patients in the Xenical group (out of 613 total) and 24% of patients in the placebo group (out of 524 patients) experienced abdominal pain.[57] Because the incidence of abdominal pain in the treatment group is similar to that in the placebo group, it is difficult to conclude the abdominal pain was attributable to orlistat.

The situation is complicated by the fact that the target population for orlistat (overweight or obese patients) may be at risk for several clinical conditions associated with abdominal pain, including diverticulitis, diverticulosis, pancreatitis, cholelithiasis, and renal colic. The more serious clinical conditions, however, are likely to cause severe, recurrent, or progressive symptoms. It is unlikely that these more serious conditions would be masked except in mild cases or very early in the clinical course. Most serious causes of abdominal pain, such as pancreatitis, cholelithiasis, diverticulitis, or renal colic, can be identified via a laboratory test or imaging procedure and these evaluations would be directed by a medical provider.

The review of adverse events associated with orlistat at the time of the submission for alli (2006) showed the incidence of GI adverse events was moderately higher in the orlistat treatment groups than in the placebo group. The biggest discrepancies between orlistat and placebo were for the adverse events of fecal urgency, oily spotting, flatus with discharge, fatty/oily stool, oily evacuation, and fecal incontinence. These adverse events are primarily related to the drug's mechanism of action – malabsorption of fat. Abdominal pain may be associated with these events and would generally be mild and transient, and decrease with time, as was noted in the clinical trials.[58]

In conclusion, we do not agree that abdominal pain associated with use of orlistat is likely to mask a more serious clinical condition and interfere with the diagnosis. Abdominal pain that is

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[57] See Xenical Medical Officer's Review available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P2.pdf at 16 .

[58] See http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_prntlbl_P2.pdf at 12.

persistent or of increasing frequency or worsening severity would indicate a more serious problem and should be evaluated. Current alli labeling directs patients to **"Stop use and ask a doctor if** severe or continuous abdominal pain occurs. This may be a sign of a serious medical condition."[59] We believe the GI risks for consumers whose use of orlistat are not being managed by a prescribing medical professional are appropriately and adequately managed by the current labeling.

5. Safety Concerns Due to Interference With Absorption of Fat Soluble Vitamins and Lipophilic Drugs

You describe interference with the absorption of fat-soluble vitamins and lipophilic drugs as a safety issue posed by orlistat. You state that data from nonclinical animal studies and clinical studies demonstrate that absorption of fat-soluble vitamins is diminished in animals and humans taking orlistat daily. You also assert that orlistat can cause cyclosporine and amiodarone levels to be lowered and their efficacy decreased because of their binding to lipid that is not absorbed and leaves the body with feces, and that orlistat use can result in lowering of Vitamin K levels, which can interfere with warfarin absorption. Finally, you assert that although effects on the levels of other fat-soluble drugs and supplements have not been tested, their levels presumably would be similarly affected (Petition at 15-17, 22).

As discussed below, and in our response to the 2006 Petition, generally we agree with your position that orlistat can interfere with fat-soluble vitamin absorption. The absorption of fat-soluble vitamins (e.g., A, D, E, and K) and beta-carotene, as well as lipophilic drugs, depends on efficient absorption of dietary fat in the small intestine. The decreased levels of fat absorption in the GI tract in orlistat-treated patients could reduce absorption of fat-soluble vitamins and drugs. For this reason, labeling for both Xenical and alli advises patients taking orlistat to also take a multivitamin and warns against concomitant use of cyclosporine.[60] On October 16, 2013, FDA approved revisions of Xenical's labeling to incorporate information on the possible interaction between Xenical and anti-epileptic drugs.[61]

You reference preclinical animal studies, the FDA clinical reviews for Xenical and for alli, and the Joint Committee discussion of alli before the approval of the alli NDA (Petition at 15-18). We discuss each of your references below, as well as labeling related to vitamin absorption.

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[59] See prior approved Drug Facts for alli at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf. (Emphasis in the original).

[60] See prior approved Drug Facts for alli at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf and approved Xenical labeling at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf .

[61] See letter from FDA at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2013/020766Orig1s033ltr.pdf.

a. Nonclinical Animal Studies

In the Petition, you state:

> In spite of supplementation, hepatic stores of vitamin E decreased in all three species treated with oral orlistat in long-term studies (mice, rats, and dogs), and hepatic stores of vitamin A decreased in dogs. Even with supplementation, vitamin E levels in liver decreased by 60% to 70% in male and female rats. Although plasma levels appeared little affected, the liver reservoirs were depleted. In rats, plasma vitamins A and E decreased while in dogs, plasma vitamins D and E decreased. These decreases occurred because the fat-soluble vitamins are excreted along with the unabsorbed fat (Petition at 15-16).

We agree with your description of these study results. In the longest pivotal studies in mice, rats, and dogs, supplementation was successful in some species but not in others. There were decreases in the liver stores of Vitamin A in dogs and male rats. There was a slight (< 25 percent) decrease in hepatic stores of Vitamin A in male rats, but absolute Vitamin A levels in plasma were not affected in rats of either sex. Lower Vitamin E levels were seen in mice and rats.[62] There are, however, additional nonclinical data that suggest that vitamin supplementation adequately reduces the incidence of significant decreases. Another study[63] performed concurrently with the rat carcinogenicity study specifically examined the effectiveness of the vitamin supplementation on rats given 1,000 mg/kg/day of orlistat for 15 months. Animals were given 690 mg Vitamin A, 40 mg Vitamin E, 2.8 mg Vitamin D_3, 560 mg Vitamin K, and 2.8 mg β-carotene each week. There were no consistent adverse effects on plasma levels of Vitamins A, D, and E. Liver levels of vitamin A were slightly lower (by 20%) in males but not females, and hepatic vitamin E was 56-70% lower than in controls. Thus, in rats, it appears that it is possible to maintain adequate plasma levels of these vitamins with supplementation, even if liver depots of vitamins are somewhat depleted.

b. FDA's Clinical Safety Reviews of Xenical and alli

You reference discussions in the NDA clinical reviews of Xenical and alli about the potential of orlistat to interfere with the absorption of fat-soluble compounds, including the fat-soluble vitamins (e.g., A, D, E, and K) and lipophilic drugs (e.g., cyclosporine and amiodarone) (Petition at 16). As we stated in the response to your 2006 Petition, orlistat is expected to reduce the absorption of fat-soluble vitamins based on its mechanism of action. The effect of orlistat on vitamin E absorption is well established based on the clinical pharmacology study and the safety and efficacy trials in the Xenical NDA.[64] These studies demonstrated that administration of

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[62] See e.g., Xenical Pharmacology Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_medr_P2.pdf at 18 and http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P5.pdf at 61.

[63] See Xenical Pharmacology Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_phrmr_P4.pdf at 40-41 .

[64] See Sections 5.2 and 7.2 of Xenical labeling available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/020766s033lbl.pdf .

orlistat, 120, mg three times daily reduced vitamin E absorption by about 80%. The effects on vitamins A, D, and K were evaluated based on safety and efficacy trial data and were not as conclusive.

The possibility of interference with absorption of Vitamin A was raised in the FDA review[65] based on the dedicated drug-drug interaction (DDI) study results for beta-carotene (a pro-vitamin A carotenoid), which showed 30 to 40 percent reduction in extent of exposure (area under the curve) of beta-carotene upon coadministration with orlistat.

There has been extensive evaluation of the issue of interference with absorption of fat soluble vitamins since the approval of Xenical, including consideration of data regarding the efficacy and safety of vitamin supplementation that was obtained in a postapproval study conducted in obese adolescents.[66] As we described in the 2006 Petition Response, obese adolescent subjects who took a daily multivitamin while being treated with 120 mg of orlistat, three times a day, for up to 1 year, had very small absolute and relative rates of consecutive low serum fat-soluble vitamin levels when compared with placebo-treated subjects.

You specifically express concern about interference with the safe use of warfarin because of a decrease in vitamin K levels caused by orlistat (Petition at 22). Clinical pharmacology studies demonstrated that orlistat did not alter warfarin pharmacokinetics, but post-marketing reports of both prolonged prothrombin time and bleeding with concomitant drug use were noted.[67]

The DDI studies of orlistat and other orally administered drugs were reviewed under the Xenical and alli NDAs. A significant DDI was noted with cyclosporine. The serum concentrations of cyclosporine were reduced with coadministration with orlistat.[68] The potential for drug interactions exists whenever orlistat is coadministered with lipophilic drugs, and the issue may be critical for lipophilic drugs that have narrow therapeutic indices or when therapeutic drug monitoring is required. The labeling for Xenical provides information regarding spacing lipophilic vitamins and drugs from orlistat administration and specifically lists cyclosporine, levothyroxine, and warfarin. The alli labeling directs patients not to use alli if they are taking cyclosporine and to consult a doctor or pharmacist before taking the drug if they are: "taking warfarin (blood thinning medicine), or taking medicine for diabetes or thyroid disease. Your medication dose may need to be adjusted."[69]

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[65] See Xenical Clinical Pharmacology Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020766a_xenical_clinphrmr_P4.pdf at 16.

[66] See Xenical Medical Review for altered patient population, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/020766_S018_XENICAL_CAPSULES_AP.pdf.

[67] See FDA Briefing Document, available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_02_03-FDA-Clinical-Review.pdf at 67-69.

[68] Id.

[69] See prior approved Drug Facts for alli, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2007/021887lbl.pdf.

c. Advisory Committee Discussions

You note that members of the Joint Committee that considered alli expressed concern about the potential for orlistat to interfere with the absorption of vitamins and lipophilic drugs (Petition at 17). The potential interaction of orlistat and cyclosporine and other lipophilic medications was discussed at the Joint Committee meeting for alli.[70] The Joint Committee that considered alli also discussed the OTC labeling, and specifically whether consumers would read and follow the labeled instructions regarding multivitamins and the cyclosporine warning. You quote portions of the Joint Committee discussion in which concerns were raised by the members because of poor outcomes on some aspects of the initial Label Comprehension studies conducted for alli. These concerns were adequately addressed by later Label Comprehension[71] studies using revised proposed labeling. Specifically, at the time of approval of alli, the Social Scientist's review noted that 88.3% of the general population and 79% of the low-literacy group demonstrated understanding of the need to take a multivitamin, once daily at bedtime, while taking alli, and that when the cyclosporine warning was revised to exclude all organ transplant patients, regardless of the specific immunosuppressive therapy, 98.3% of subjects made a correct self-selection decision.[72]

d. Current Labeling Is Adequate

In summary, we agree that orlistat may interfere with absorption of fat-soluble vitamins and certain lipophilic drugs. The Xenical and alli labeling strongly recommends that all users take a multivitamin supplement that contains fat-soluble vitamins and beta-carotene. The supplement is to be taken once daily at least 2 hours before or after the administration of orlistat, such as at bedtime. Data indicate that in non-vitamin-supplemented subjects, the risk of developing a low-serum, fat-soluble vitamin level with long-term use of orlistat is low. This risk is further reduced if users adhere to the labeled recommendation and take a multivitamin supplement once a day.

After reviewing the information provided in the Petition and other relevant information, we conclude that the labeling regarding vitamin absorption and lipophilic drugs for Xenical and alli is appropriate and adequate.

B. Risk-Benefit Profile of Orlistat for Obesity Management, Including Weight Loss and Weight Maintenance

You suggest that orlistat does not have a favorable risk-benefit profile for long-term use based on the presumed risks described in your Petition and addressed above, and based on what you characterize as its minimal efficacy for weight loss (Petition at 17-18). In support of this

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[70] See Joint Committee transcript, available at http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4201T.pdf at 92-93.

[71] See Social Scientist Reviews available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_SocScienceR.pdf .

[72] See Social Scientist Review dated December 18, 2006, at p. 11, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2007/021887s000_SocScienceR.pdf .

argument, you describe the efficacy data from the Xenical and alli NDAs and quote statements from the review of alli and from the Joint Committee that considered alli before approval. As discussed below, we continue to believe that orlistat is effective for its approved indications and that it has a favorable risk-benefit profile.

1. Demonstrating Efficacy of Weight Loss Drugs

Under FDA's February 2007 draft guidance *Developing Products for Weight Management* (the 2007 Guidance), efficacy for a weight loss drug can be demonstrated if one of two primary weight loss benchmarks is met – after 1 year of treatment:[73]

i. The difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, or

ii. The proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.

These criteria are based on the principle that a 5 percent or greater weight loss is associated with metabolic and cardiovascular benefits. It is also anticipated, therefore, that weight loss due to a drug will be associated with commensurate improvements in other markers of cardiometabolic health, such as glucose metabolism, blood pressure, and blood lipids.

The Agency's 1996 Guidance (which was current at the time the Xenical and alli NDAs were approved) described two methods to demonstrate the efficacy of a new weight-loss drug:

i. The mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5 percent after 1 year of treatment, or

ii. The proportion of subjects who reach and maintain a loss of at least 5 percent of baseline body weight is significantly greater in the active drug group as compared with the placebo group after 1 year of treatment.[74]

2. Efficacy of Xenical

As previously described in detail in our response to your 2006 Petition, the sponsor of Xenical conducted seven placebo-controlled phase 3 trials in approximately 3,000 overweight and obese subjects in support of the weight-loss indication. Collectively, these data support the efficacy of

[73] The 2007 Guidance is available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071612.pdf.

[74] See FDA Briefing Document, available at http://www.fda.gov/ohrms/dockets/ac/06/briefing/2006-4201B1_02_03-FDA-Clinical-Review.pdf .

orlistat in accordance with the recommended approach for demonstrating efficacy described in the 1996 Guidance.

The mean placebo-subtracted weight loss at years 1 and 2 for Xenical was approximately 3%, as you note in the Petition (Petition at 17-18). The development program for Xenical and review of the NDA was conducted before the availability of the 2007 Draft Guidance on weight loss drugs. At the time of approval, Xenical met the recommended criterion from the 1996 Guidance that the proportion of subjects with at least 5% weight loss was significantly greater in the active group.[75]

In addition to meeting the 1996 Guidance recommendation for efficacy, the data included in the Xenical NDA are consistent with the second clinical recommendation for approval under the 2007 Guidance, which was based on the results of the Xenical primary care study 14161 (Xenical 37% versus placebo 16%), which is considered the most reflective of Xenical's "real-world" use.

The results of study 14161 and others are included in the Xenical labeling as shown in Table 1. Four out of five studies (Table 1) meet the 2007 "approximately double" compared to the placebo group recommendation. These weight loss results, in addition to the beneficial risk factor changes shown in Table 2, provide further evidence of the drug's efficacy.

Table 1. Percentage of Patients Losing ≥ 5% of Body Weight Randomization After Treatment for 1-Year After Randomization*

Study No.	Xenical n	Placebo n	p-value
114119B	35.5% 110	21.3% 108	0.021
14119C	54.8% 343	27.4% 340	< 0.001
14149	50.6% 241	26.3% 236	< 0.001
14161†	37.1% 210	16.0% 212	< 0.001
14185	42.6% 657	22.4% 223	< 0.001

* Treatment designates XENICAL 120 mg three times a day plus diet or placebo plus diet. Analyses were performed using the intention to treat approach and the last-observation-carried-forward imputation method.
† Study 14161 was conducted with primary care physicians.

As shown in Table 2 below (also from the Xenical labeling), the changes in risk factors associated with obesity after treatment with Xenical reflect changes that would be expected because of weight loss.

Table 2. Mean Change in Risk Factors From Randomization Following 1-Year Treatment*

Risk Factor	XENICAL 120 mg†	Placebo†
Metabolic		
Total Cholesterol	-2.0%	+5.0%
LDL-Cholesterol	-4.0%	+5.0%
HDL-Cholesterol	+9.3%	+12.8%
LDL/HDL	-0.37	-0.20
Triglycerides	+1.34%	+2.9%
Fasting Glucose, mmol/L	-0.04	+0.0

[75] The details of our evaluation of the original NDA efficacy data and the recommendations under the 1996 Guidance are set forth in more detail in our response to your 2006 Petition.

Risk Factor	XENICAL 120 mg†	Placebo†
Fasting Insulin, pmol/L	-6.7	+5.2
Cardiovascular		
Systolic Blood Pressure, mmHg	-1.01	+0.58
Diastolic Blood Pressure, mmHg	-1.19	+0.46
Anthropometric		
Waist Circumference, cm	-6.45	-4.04
Hip Circumference, cm	-5.31	-2.96
* Treatment was XENICAL 120 mg three times a day plus diet or placebo plus diet. LDL = low-density lipoprotein; HDL = high-density lipoprotein. † Intent-to-treat population at week 52, observed data based on pooled data from five studies.		

As also described in detail in our response to the 2006 Petition, additional data were submitted to the Xenical NDA in an efficacy supplement in 2004.[76] The XENDOS trial (XENical in the prevention of Diabetes in Obese Subjects) was a randomized, double-blind, placebo-controlled 4-year study of Xenical in 3305 obese (BMI > 30 kg/m^2) male and female subjects with normal or impaired glucose tolerance (IGT) living in Sweden. Primary endpoints were time to onset of type 2 diabetes mellitus and change in body weight.

At the completion of the 4-year trial, the adjusted cumulative rates of diabetes in the overall population were approximately 8.3% in the placebo group and 5.5% in the Xenical group ($p = 0.008$). This statistically significant delay in the development of diabetes was driven by the results from patients with IGT at baseline. Of the subjects with IGT, the adjusted cumulative rates of diabetes over 4 years were 27.2% in the placebo group and 18.7% in the Xenical group ($p = 0.005$). Of the subjects with normal glucose tolerance at baseline, approximately 1.4% of the placebo patients and 1.7% of the Xenical subjects developed diabetes ($p=0.8$).

After 1 year of treatment, the mean change in body weight was -7.46 kg for the placebo group compared to -11.37 kg for the Xenical group (nominal $p < 0.001$). After 4 years, the mean change in body weight was -4.09 kg for the placebo group compared to -6.90 kg for the Xenical group (nominal $p < 0.001$). At 4 years, 53% of Xenical patients and 37% of placebo patients achieved at least a 5% reduction in baseline body weight, and 26% and 16% of Xenical- and placebo-treated patients, respectively, lost at least 10% of baseline body weight.

Xenical does not have an indication for the prevention of diabetes mellitus in patients with impaired glucose tolerance. The delay of diabetes information, however, as well as the 4-year weight loss data, is presented in the Clinical Studies section of the Xenical label. FDA considers these data to be supportive of the clinical benefit of Xenical.

In conclusion, the totality of the available data for Xenical supports its efficacy as a weightloss drug.

[76] See Xenical Supplement Clinical Review, available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/020766_S019_XENICAL_CAPS_AP.pdf.

3. Efficacy of alli

Evidence of the efficacy of alli for weight loss is based on a subset of the clinical trials (those that included the 60-mg dose) from the database that supported the approval of Xenical.

The primary efficacy analysis of the two pooled pivotal trials was conducted at 6 months. At 6 months, placebo-subtracted mean weight loss for alli was 2.4% ($p < 0.001$), and 42% of subjects treated with alli versus 23% of those treated with placebo achieved a weight loss of $\geq 5\%$ ($p < 0.001$). In a separate 4-month trial in patients with a BMI between 25 and 28 kg/m^2, the placebo-subtracted mean weight loss with alli at 4 months was 1.6% ($p < 0.001$), and 36% of alli-treated subjects versus 28% of placebo-treated subjects achieved a weight loss of $\geq 5\%$ ($p = 0.104$).

At the January 23, 2006, meeting of the Joint Committee, the committee members concluded that efficacy of orlistat had been demonstrated for both the 60-mg and 120-mg doses in the nonprescription setting for overweight and obese individuals.

FDA has concluded that a 60-mg dose strength orlistat product (i.e., alli) is safe and effective for OTC use for weight loss in overweight adults, 18 years and older, when used along with a reduced-calorie and low-fat diet. Further, FDA has concluded that a requirement for prescription-only status for 60-mg orlistat is not necessary for the protection of the public health.

None of the data provided in your Petition alters our assessment of the efficacy of a 60-mg, nonprescription dose strength of orlistat.

C. Claims in the Marketing of alli

You assert that the current Web site for alli misleadingly states "[N]ew studies show that overweight and obese people using alli® (orlistat 60 mg) with a reduced calorie lower-fat diet can significantly reduce weight, visceral fat, and waist circumference and therefore may reduce their risk of type 2 diabetes, hypertension, heart disease and stroke" (Petition at 6). To the extent that you are requesting that we take enforcement action against GSK because it has made misleading claims about alli on the alli website, your request is not appropriate for a citizen petition. Decisions with respect to initiating enforcement actions are generally made on a case-by-case basis and are within the discretion of the Agency. As stated in 21 CFR 10.30(k), § 10.30 does not apply to "referral of a matter to a United States attorney for the initiation of court enforcement action and related correspondence . . . ." Agency decisions to take, or refrain from taking, enforcement actions are decisions related to referral of a matter to a United States attorney for the initiation of court enforcement action for violations of the FD&C Act. Therefore, your request that FDA take action concerning GSK's marketing claims for alli is denied. As with any drug product, we will monitor product claims and take action as we believe appropriate.

III. CONCLUSION

Based upon our review of all of the available evidence (including nonclinical data, preapproval clinical studies, data from the Xenical sponsor's postmarketing commitment, and postmarketing spontaneous adverse event reporting), we continue to believe that orlistat's benefits outweigh its risks for its approved indications, and that its risks are adequately addressed by the current labeling. We have not found that the criteria for market withdrawal are met for orlistat. Accordingly, we deny your Petition requesting that FDA withdraw approval of the Xenical NDA and the alli NDA. As with all FDA-approved products, FDA will continue to monitor and review available safety information related to orlistat throughout the drug product's life cycle.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research