DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 7 2007

Sidney Wolfe, M.D.
Elizabeth Barbehenn, Ph.D.
Public Citizen Health Research Group
1600 20th Street, NW
Washington, DC 20009

Theresa P. Pretlow, Ph.D.
Thomas G. Pretlow, M.D.
Case Western Reserve University
10900 Euclid Avenue
Cleveland, OH 44106-7288

Re: Docket No. 2006P-0154/CP1 and SUP1

Dear Drs. Wolfe, Barbehenn, Pretlow, and Pretlow:

This responds to your citizen petition dated April 10, 2006 (Petition), and the supplement to your Petition dated June 5, 2006 (Supplement). Your Petition requests that the Food and Drug Administration (FDA or Agency) immediately remove Xenical (orlistat) from the market and not approve a new drug application (NDA) for an over-the-counter (OTC) formulation of orlistat. Your request is based on data described in FDA's pharmacology review of the Xenical NDA[1] and a recent study in rats that reported an association between orlistat and an increased incidence of colonic aberrant crypt foci (ACF),[2] which you describe as a precursor of colon cancer. Additionally, you contend that orlistat should not be permitted to "remain on the market for the long-term treatment of a non-lethal condition when it combines so little efficacy coupled with a still unresolved potential to cause breast and colon cancer" (Petition at 10).

We have carefully reviewed your Petition and Supplement, as well as the comments on the Petition submitted by a private citizen on May 22, 2006, and by Hoffman-La Roche Inc. (Roche) and GlaxoSmithKline Consumer Healthcare (GSK) on November 8, 2006. For the reasons described in detail in this response, we deny your requests that FDA immediately remove Xenical from the market and that FDA not approve an OTC formulation of orlistat. However, as with all FDA-approved products, FDA will continue to monitor and review available safety information related to orlistat throughout the drug product's lifecycle.

I. BACKGROUND

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

[1] Food and Drug Administration, Pharmacology Review of NDA 20-766 (orlistat), April 22, 1997.

[2] Garcia SB, Barros LT, Turatti A, et al. The anti-obesity agent orlistat is associated to [sic] increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett 2006;240:221-224.

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 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. At a dose of 120 milligrams (mg) taken three times daily (t.i.d.), orlistat inhibits dietary fat absorption from the small intestine by approximately 30 percent. This wasting of calories — the unabsorbed dietary fat is excreted in the stool — has been shown to promote weight loss under certain circumstances.

On April 23, 1999, FDA approved Roche's NDA for Xenical (orlistat) 120-mg capsules for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet. At the time of approval, Roche agreed to a postmarketing commitment to provide monthly updates of breast cancer diagnoses from ongoing phase 3b studies until the studies were completed. This commitment was satisfied in 2000.

In June 2005, GSK submitted an NDA for Alli (orlistat) 60-mg capsules for OTC use as a weight loss aid.[3] Today, the Agency approved GSK's NDA for Alli.

The Federal Food, Drug, and Cosmetic Act (the 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"

- "that 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."[4]

The Agency also will withdraw approval of an NDA based upon efficacy concerns if "(3) 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

[3] For purposes of this response, all references to the "sponsor" or to the "application" are intended to refer to Roche and the Xenical (orlistat) application, respectively, unless otherwise specified.

[4] Section 505(e)(1) and (2) of the Act (21 U.S.C. 355(e)(1) and (2)); see also 21 CFR 314.150. In addition, section 505(e) of the 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."

505(e) of the Act). Your Petition states that you seek withdrawal of the Xenical (orlistat) NDA pursuant to section 505(e)(3) of the Act (21 U.S.C. 355(e)).

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

II. DISCUSSION

Executive Summary

Your request that Xenical (orlistat) be withdrawn from marketing is based on the following information:

> (1) "findings from the pharmacology review of Roche's own data that orlistat causes aberrant crypt foci in the colon of rats," referring to the April 28, 1997, pharmacology review;
>
> (2) "a recent independent confirmation of the above finding that orlistat causes an increase in aberrant crypt foci in rats," referring to the study by Garcia and colleagues (Garcia Study);[5] and
>
> (3) "a large scientific literature that acknowledges the importance of aberrant crypt foci as the earliest identifiable neoplastic colonic lesion and putative precursor of colon cancer" (Petition at 2).

As discussed in sections II.A.1 and II.A.2 of this response, we have reviewed the literature cited in your Petition and submitted to the docket as the second supplement to your Petition (Supplement 2),[6] and conducted our own review of relevant literature related to aberrant crypt foci. We also have examined the following sources of data regarding the safety of orlistat with respect to colonic cell proliferation and aberrant crypt foci:

> (1) preclinical and clinical studies supporting approval of Xenical (see sections II.A.3 and II.A.4 of this response);
>
> (2) presentation of clinical study data to the Endocrinologic and Metabolic Drugs Advisory Committee (see section II.A.5 of this response); and
>
> (3) FDA's Adverse Event Reporting System (AERS) database (see section II.A.6 of this response).

Based on these data, we conclude that the available evidence concerning orlistat's safety does not support a causal relationship between orlistat and colorectal carcinoma, nor does any of this information meet the criteria for market withdrawal as set forth in section 505(e) of the Act.

---

[5] Garcia SB, Barros LT, Turatti A, et al. The anti-obesity agent orlistat is associated to [sic] increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett 2006;240:221-224.

[6] 2006P-0154/SUP2.

You also suggest that orlistat does not have a favorable risk/benefit profile for long-term use based on other adverse events described in product labeling and what you describe as a "still unresolved potential" to cause breast cancer and "minimal efficacy" for weight loss (Petition at 10). As discussed in section II.B of this response, the Agency rigorously evaluated the imbalance in the number of women treated with orlistat compared to placebo who were diagnosed with breast cancer during their participation in the preapproval phase 3 clinical trials (phase 3a studies), and the Xenical NDA was only approved after FDA determined there was adequate data to support a conclusion that orlistat does not increase the risk of breast cancer and that orlistat has a favorable risk/benefit profile. In addition, the Xenical NDA approval included a postmarketing commitment for Roche to provide monthly updates of breast cancer diagnoses from ongoing clinical studies (phase 3b studies) until the studies were completed. These updates further supported our conclusion that the available data does not provide evidence of an increased risk of breast cancer associated with orlistat.

In the Petition, you provide your own analysis of spontaneous adverse event reports in the AERS database of breast cancer associated with use of orlistat (Petition at 8 to 9). Our analysis of reports in the AERS database is set forth in section II.B.2 of this response. Based on our analysis of the totality of the data related to the risk of breast cancer, we do not consider these spontaneous adverse event reports to constitute a safety signal warranting further investigation at this time.

In your discussion of the risk/benefit profile, you briefly reference gastrointestinal (GI) symptoms relating to bowel movements as well as the loss of fat-soluble vitamins, both of which are associated with orlistat's mechanism of action (Petition at 7 to 8). As noted in section II.C of this response, these issues are adequately addressed in the product labeling. You also suggest that a postmarketing study should have been requested of the sponsor to evaluate the efficacy and safety of vitamin supplementation in orlistat users (Petition at 8). In section II.C.2 of this response, we describe data obtained in a postapproval study conducted in obese adolescents regarding the efficacy and safety of vitamin supplementation in conjunction with orlistat use.

Finally, we respond to your contention regarding the "minimal efficacy" of orlistat (Petition at 10). As discussed in section II.D of this response, the data in Roche's NDA for orlistat satisfied a recommended approach for demonstrating efficacy as described in the Agency's 1996 draft guidance on *Clinical Evaluation of Weight-Control Drugs* — the proportion of subjects who reached and maintained a loss of at least 5% of baseline body weight was significantly greater in the active drug group as compared with the placebo group after 1 year of treatment.[7] In addition, weight loss with orlistat generally was associated with improvements in blood pressure, fasting glucose and insulin, and total and LDL-cholesterol.

[7] See draft guidance on *Clinical Evaluation of Weight-Control Drugs* (September 1996), available on the Internet at http://www.fda.gov/cder/guidance/index.htm. This draft guidance is undergoing revision and will be reissued for comment in accordance with FDA's Good Guidance Practices and the recommendations of the Report of the Working Group on Obesity (March 12, 2004).

A. Colonic Aberrant Crypt Foci

1. Background Information on Colonic Aberrant Crypt Foci

In 1987, Ranjana P. Bird identified what became known as aberrant crypt foci (ACF) in the colonic epithelial cells of mice treated with the chemical carcinogen azoxymethane, a known initiator of colon cancer.[8] This led to the hypothesis — still a matter of some debate nearly 20 years later — that ACF are preneoplastic lesions, which under certain conditions progress stepwise to adenoma and carcinoma. The rodent ACF assay provides a relatively inexpensive method to screen for compounds (including dietary factors, environmental chemicals, and drugs) that promote or inhibit the progression of colorectal carcinoma following tumor initiation with a chemical carcinogen.[9] From a clinical standpoint, however, we currently consider ACF as an unvalidated, exploratory biomarker. ACF will remain as such until ongoing interventional and prospective observational trials like the ACF substudy of the National Cancer Institute's Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial define the natural history of ACF and qualify and quantitate the role ACF parameters play, if any, in predicting risk for colorectal carcinoma in humans.[10]

Colonic crypts are invaginations of the internal lining of the intestine into the underlying connective tissue of the GI tract. ACF are found only in the colon, principally the distal region, are up to three times larger than normal colonic crypts, are microscopically elevated, have increased pericryptal space, have oval or slit-like lumenal openings, and have a thickened epithelium that stains dark with methylene blue. Histologically, ACF are generally categorized as: (1) non-hyperplastic; (2) hyperplastic; (3) dysplastic; or (4) mixed.[11]

Some data suggest that short-term changes in certain ACF parameters correlate modestly well with the long-term development of colorectal tumors in rodents. For example, ACF that are dysplastic, large (e.g., ≥ 4 crypts per focus), contain multiple crypts per focus (crypt multiplicity), have aberrant β-catenin expression, or are depleted of mucin, correlate more strongly with tumor formation in rodents pretreated with a chemical carcinogen than the total number of ACF.[12] It is commonly accepted that dysplastic ACF harbor neoplastic potential.

---

[8] Bird RP. Observation and quantification of aberrant crypts in the murine colon treated with a colon carcinogen: preliminary findings. Cancer Lett 1987;37:147-151.

[9] Bruce WR. Counterpoint: From animal models to prevention of colon cancer. Criteria for proceeding from preclinical studies and choice of models for prevention studies. Cancer Epidemiol Biomark Prev 2003;12:401-404.

[10] See National Cancer Institute, Division of Cancer Prevention: Prostate, Lung, Colorectal & Ovarian Cancer Screening Trial (PLCO), available on the Internet at http://www.cancer.gov/prevention/plco.

[11] Alrawi SJ, Schiff M, Carroll RE, et al. Aberrant crypt foci. Anticancer Res 2006;26:107-120.

[12] Pretlow TP, O'Riordan MA, Somich GA, et al. Aberrant crypts correlate with tumor incidence in F344 rats treated with azoxymethane and phytate. Carcinogenesis 1992;13:1509-1512; Magnuson BA, Carr I, Bird RP. Ability of aberrant crypt foci characteristics to predict colonic tumor incidence in rats fed cholic acid. Cancer Res 1993;53:4499-4504; Femia AP, Dolara P, Caderni G. Mucin-depleted foci (MDF) in the colon of rats treated with azoxymethane (AOM) are useful biomarkers for colon carcinogenesis. Carcinogenesis 2004;25:277-281; Hao XP, Pretlow TG, Rao JS, Pretlow TP. [Beta]-catenin expression is altered in human colonic aberrant crypt foci. Cancer Res 2001;61:8085-8088.

A long list of dietary, chemical, and environmental factors have been shown to increase or decrease, by statistically significant amounts, ACF parameters in rodents exposed to a chemical carcinogen. For example, the total number of ACF may be increased by a number of factors in rodents pretreated with a chemical carcinogen, including high levels of saturated fat and sucrose, low levels of calcium, thermolyzed casein, green tea extracts, black tea extracts, sulfasalazine, beta-sitosterol, chenodeoxycholic acid, and even a single bout of exhaustive exercise.[13]

In your Petition, you state that "[t]he connection of ACF with carcinogenesis is so well recognized that the appearance of ACF in rats is used by many groups to test the potential carcinogenicity of chemicals. For example, the Environmental Protection Agency (EPA) uses an ACF assay in its tests of possible carcinogens" (Petition at 4). However, the references cited in support of your contention are two research papers by EPA investigators who used suspected rat colon carcinogens to test whether the ACF assay, which is thought to detect preneoplastic lesions, would show a positive signal in cases where the 2-year rodent bioassay did not. The EPA, to our knowledge, is not endorsing the use of the rodent ACF assay as a surrogate for a lifetime rodent bioassay to detect carcinogenicity.

Although ACF with certain features may have some correlation with the long-term development of colorectal tumors in rodents, there is no accepted definition of what constitutes a clinically significant increase or decrease in an ACF parameter (such as total number of ACF, ACF size, or crypt multiplicity) based on cancer risk in humans. In a study published in 1998, researchers from Japan analyzed ACF from the distal colon and rectum of 171 normal subjects, 131 individuals with colorectal adenoma, and 48 patients with colorectal cancer.[14] They found that 56% of normal subjects had ACF, compared with 88% and 100% of patients with adenoma and cancer, respectively. Dysplastic ACF were observed in 6% of normal subjects, 14% of subjects with adenoma, and 52% of the patients with colorectal cancer. Others have confirmed that the prevalence of ACF in the distal colon is higher in people with adenoma and carcinoma than in healthy, non-diseased adults.[15] Ongoing interventional and longitudinal observation studies, such as the ACF substudy of the PLCO Cancer Screening Trial discussed above, may eventually contribute data to address two important questions: What is the natural history of ACF, and what

---

[13] Rao CV, Hirose Y, Indranie C, Reddy BS. Modulation of experimental colon tumorigenesis by types and amounts of dietary fatty acids. Cancer Res 2001;61:1927-1933; Pierre F, Freeman A, Tache S, et al. Beef meat and blood sausage promote the formation of azoxymethane-induced mucin-depleted foci and aberrant crypt foci in rat colons. J Nutr 2004;134:2711-2716; Caderni G, Lancioni L, Palli D, et al. Dietary sucrose and starch affect dysplastic characteristics in carcinogen-induced aberrant crypt foci in rat colon. Cancer Lett 1997;114:39-41; Wargovich MJ, Jimenez A, McKee K, et al. Efficacy of potential chemopreventive agents on rat colon aberrant crypt formation and progression. Carcinogenesis 2000;21:1149-1155; Zhang XM, Stamp D, Minkin S, et al. Promotion of aberrant crypt foci and cancer in rat colon by thermolyzed protein. J Natl Cancer Inst 1992;84:1026-1030; Wargovich, MJ, Chen CD, Jimenez A, et al. Aberrant crypts as a biomarker for colon cancer: evaluation of potential chemopreventive agents in the rat. Cancer Epidemiol Biomark Prev 1996;5:355-360; Demarzo MMP, Garcia SB. Exhaustive physical exercise increases the number of colonic preneoplastic lesions in untrained rats treated with a chemical carcinogen. Cancer Lett 2004;216:31-34.

[14] Takayama T, Katsuki S, Takahashi Y, et al. Aberrant crypt foci of the colon as precursors of adenoma and cancer. N Engl J Med 1998;339:1277-1284. See also Petition at 6 to 7.

[15] Seike K, Koda K, Oda K, et al. Assessment of rectal aberrant crypt foci by standard chromoscopy and its predictive value for colonic advanced neoplasms. Am J Gastroenterol 2006;101:1362-1369.

role, if any, do ACF play in predicting risk for future development of colorectal cancer in humans.[16]

Much of your rationale for requesting that orlistat be removed from the market appears to rest on the assumption that ACF is a valid, predictive biomarker. (We note, however, that the Supplement to your Petition acknowledges that "aberrant crypt foci are far from being validated as a biomarker for either cancer or polyps" (Supplement at 2).) A biomarker is commonly defined as a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention."[17] A valid biomarker is quantifiable, reproducible, precise, accurate, and predictive of an outcome of interest, with sensitivity and specificity commensurate with its intended use, at which point it can be considered a surrogate marker and used in lieu of a clinical endpoint.[18] In the Supplement to your Petition, you opine that "in general, surrogate marker measurement should be given greater weight in measuring adverse events than surrogate markers in measuring efficacy" (Supplement at 3). However, judged by the above-referenced criteria, we view ACF as an unvalidated, exploratory biomarker, both from an efficacy (i.e., colorectal cancer chemoprevention) and safety perspective.

2. The Garcia Study

The allegations in your Petition are based, in part, on the Garcia Study, which you describe as "a recent independent confirmation . . . that orlistat causes an increase in aberrant crypt foci in rats" (Petition at 2). Garcia and colleagues studied the effects of orlistat, a high-fat diet, a chemical carcinogen (dimethyl-hydrazine (DMH)), and combinations thereof on the formation of colonic ACF and cell proliferation in rats.[19] As discussed below, this study provides limited data to evaluate the effect of these factors on colonic ACF formation and cell proliferation and, contrary to your assertion, does not provide confirmation of a causal relationship between orlistat and colonic ACF in rats. Indeed, no colonic ACF were detected in rats that received orlistat without administration of the chemical carcinogen DMH and, contrary to the study authors' assertion, proliferative indices did not differ significantly among DMH-exposed rats that received a standard diet alone, orlistat alone, a high-fat diet alone, or orlistat with a high-fat diet.

---

[16] A recently presented abstract concluded that "ACF are not a useful surrogate end-point biomarker (SEB) of adenoma risk or chemoprevention efficacy" in humans. Cho NL, Redston M, Carothers AM, et al. Predictive role of aberrant crypt foci (ACF) as surrogate endpoint biomarkers of colorectal cancer. American Association for Cancer Research Fifth Annual International Conference on Frontiers in Cancer Prevention Research, November 12-15, 2006.

[17] Biomarkers Definitions Working Group. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. Clin Pharmacol Ther 2001;69:89-95.

[18] Weir CJ, Walley RJ. Statistical evaluation of biomarkers as surrogate endpoints: a literature review. Statist Med 2006;25:183-203; Lesko LJ, Atkinson AJ. Use of biomarkers and surrogate endpoints in drug development and regulatory decision making: criteria, validation, strategies. Annu Rev Pharmacol Toxicol 2001;41:347-366.

[19] Garcia SB, Barros LT, Turatti A, et al. The anti-obesity agent orlistat is associated to [sic] increase in colonic preneoplastic markers in rats treated with a chemical carcinogen. Cancer Lett 2006;240:221-224.

Garcia and colleagues evaluated 8 groups each of which was composed of 10 male Wistar rats. Groups 3, 4, 7, and 8 received two weekly injections of DMH (25 mg/kg).[20] Groups 1 to 4 received standard rat food, and groups 5 to 8 received standard rat food enriched with 10% cotton oil (high-fat diet). The diets of rats in groups 2, 4, 6, and 8 also were supplemented with orlistat (200 mg/kg chow). However, the article does not report the amount of orlistat that rats in groups 2, 4, 6, or 8 actually consumed, and the basis for your assertion that the rats consumed orlistat "at a level 5 times the human exposure" is unclear (see Petition at 6). Thirty days after the second DMH injection, all rats were killed and their distal colons excised and examined to identify and quantify ACF and estimate colonic cell proliferation by the proliferative cellular nuclear antigen (PCNA) method.

Garcia and colleagues reported that ACFs were observed only in the colons of animals that received DMH. This absence of ACF formation in the colons of rats treated with orlistat alone indicates that orlistat did not induce ACF formation in the absence of the chemical carcinogen DMH within the study period. Among DMH-injected rats, rats that received DMH with a standard diet plus orlistat (group 4) or a high-fat diet without orlistat (group 7) had statistically significantly greater numbers of ACF per cm^2 of rat colon mucosa compared with rats that received DMH with a standard diet and no orlistat (group 3). Rats that received DMH with a high-fat diet plus orlistat (group 8) developed the largest number of ACF, with the differences compared with groups 3, 4, and 7 reaching nominal statistical significance. However, there is no basis to assert that the difference between 17 ACF per cm^2 of colon (group 8) and 12 ACF per cm^2 of colon (groups 4 and 7) has any clinical relevance. The absence of malignant colorectal tumors in rats and mice treated long-term with high doses of orlistat (see section II.A.3 of this response) strongly suggests that the ACF findings reported by Garcia and colleagues do not raise a concern.

Garcia and colleagues also evaluated colonic cell proliferation among the treatment groups. Proliferation of colonic epithelial cells is a normal, continuous process by which senescent cells are replaced by new cells. Proliferation was assessed using antibodies to proliferating cell nuclear antigen (PCNA). An increase in the PCNA labeling index[21] was observed among rats receiving orlistat (group 2), a high-fat diet (group 5), and a high-fat diet plus orlistat (group 6) when compared with rats in the control group (group 1). We do not believe that this difference in the PCNA labeling index in this relatively short study involving a relatively small number of rats has any clinical significance given that orlistat did not cause malignant colorectal tumors in numerous long-term studies of rats and mice. Further, there was not a statistically significant difference in proliferative indices among DMH-exposed rats that received a standard diet alone, orlistat alone, a high-fat diet, or orlistat plus a high-fat diet.

The conclusions that may be drawn from the Garcia Study are limited due to the lack of detail in the methodology and results sections of the article. Most importantly, the authors do not inform the reader about ACF size, crypt multiplicity, histology, location in the crypts where cell

[20] Your petition incorrectly describes the methodology of the Garcia study by stating: "All rats were treated with the carcinogen, 1,2-dimethylhydrazine..." (Petition at 6).

[21] The PCNA-labeling index was expressed as a ratio of positively stained nuclei to total nuclei counted per 100 crypts in this study.

replication was occurring, β-catenin expression, or degree of mucin depletion — characteristics that are believed to signal increased risk for malignant tumor development.[22]

Thus, the Garcia Study involves a relatively small number of rats treated for a relatively short period of time and provides limited data to evaluate orlistat's effects on ACF formation. We believe the data contained in the NDA provide a more appropriate basis for assessing the risk of colonic adverse events than the data reported by Garcia.

3. FDA Review of Preclinical Studies in the Xenical NDA

In the Petition, you reference certain inconsistent findings of colonic proliferative changes in mice and rats, and comment upon the substantial number of preclinical studies that the sponsor conducted to evaluate the effect of orlistat on colonic epithelial cells (Petition at 4 to 5, and Table 2). You allege that the interpretation of certain of these preclinical studies is impaired by the "lack of adequately high doses" and "lack of critical independent analyses" by FDA's pharmacology reviewer (Petition at 5). As discussed below, the Agency believes that review of the pharmacology studies was appropriate and followed standard procedures and that the orlistat doses selected for the two 24-month carcinogenicity studies were adequate.

Because orlistat increases the amount of dietary fat that reaches the colon, and some animal data suggest that this may stimulate colonic cell proliferation,[23] the Division of Metabolism and Endocrinology Products (Review Division) requested that Roche conduct a series of preclinical studies to specifically evaluate the effect orlistat has on colonic epithelial cells. Orlistat treatment was associated with "a dose-dependent, reproducible and reversible increase of colonic mucosal proliferation along with inhibition of fat absorption" in short-term studies of rats fed a high-fat, low-calcium diet, so the Review Division "requested the sponsor to conduct a longer term study."[24] The following sections of this response discuss data from two 9-month studies evaluating orlistat's effects on colonic cell proliferation and ACF in rats, and two 24-month carcinogenicity studies in rats and mice.

a. Nine-Month Studies in Rats Evaluating Orlistat's Effects on Colonic Cell Proliferation and Aberrant Crypt Foci

The sponsor conducted two 9-month studies to evaluate the effect of orlistat on colonic cell proliferation and aberrant crypt foci in rats fed a high-fat, normal-calcium diet or a high-fat, low-calcium diet. Each 9-month study was composed of 220 male and 220 female rats randomized equally to one of four treatment groups per gender: control, orlistat 70 parts per million (ppm) (low-dose), orlistat 140 ppm (mid-dose), or orlistat 280 ppm (high-dose) mixed in food. The amount of orlistat in the mid-dose group was intended to replicate the degree of inhibition of fat absorption observed in humans taking the prescription dose of orlistat (120 mg, three times

[22] See discussion in section II.A.1 of this response.

[23] See, e.g., Bird RP, Medline A, Furrer R, Bruce WR. Toxicity of orally administered fat to the colonic epithelium of mice. Carcinogenesis 1985;6:1063-1066; Stadler J, Stern HS, Yeung KS, et al. Effect of high fat consumption on cell proliferation activity of colorectal mucosa and on soluble faecal [sic] bile acids. Gut 1988;29:1326-1331.

[24] Food and Drug Administration, Pharmacology Review of NDA 20-766 (orlistat), April 22, 1997, at 53.

daily), rather than attain a dose multiple (as was evaluated in the two 24-month carcinogenicity studies described in section II.A.3.b of this response). The intake of orlistat ranged from approximately 3 to 15 mg/kg/day in male rats and approximately 4 to 22 mg/kg/day in female rats. Rats were provided ad libitum access to a diet comprised of approximately 40% of calories from fat and 1.0% calcium (high-fat, normal-calcium diet) or approximately 40% of calories from fat and 0.1% calcium (high-fat, low-calcium diet). The high-fat, low-calcium diet mimics the typical Western diet and represents a worst case scenario in terms of colonic cell stimulation.

All ACF samples were read by two pathologists blinded to treatment allocation per the sponsor. Cell proliferation was measured by labeling index and crypt grade[25] using slides stained for PCNA. Criteria used to define ACF included: one or more crypts that were at least 2-fold larger than surrounding crypts, with a slit-like luminal opening, increased size of crypts, increased space between crypts, increased staining intensity, and a slightly raised profile on the mucosal surface. The total number of ACF and the number of aberrant crypts per ACF (multiplicity) were recorded.

In the study of rats fed a high-fat, normal-calcium diet, there were no statistically significant differences between the orlistat and control groups in the mean labeling index at week 39. Mean crypt height for females in the orlistat 280 ppm group was statistically significantly greater as compared with the control group. There were no other statistically significant differences in mean crypt height among the groups. Mean crypt grades were essentially indistinguishable among the groups.

In the study of rats fed a high-fat, low-calcium diet, the mean labeling index at week 39 for males in the orlistat 140 ppm group and females in the orlistat 280 ppm group was statistically significantly lower as compared to the control group. The mean crypt heights for males in the orlistat 70 and 280 ppm groups were statistically significantly lower compared to controls, whereas mean crypt height for females in the orlistat 280 ppm group was statistically significantly greater compared with the control group. For females in the orlistat 140 ppm group, the mean crypt grade was statistically significantly lower compared to controls, whereas mean crypt grade for females in the orlistat 280 ppm group was statistically significantly greater compared with the control group.

Neither crypt multiplicity nor percentage of ACF with at least 4 aberrant crypts increased in a consistent dose-related manner in the orlistat versus control groups. Additional analyses of ACF data failed to identify consistent changes of concern in orlistat compared with control animals. None of the animals sacrificed at week 39 had malignant colorectal tumors, despite an extended study period and ACF formation in both the treatment and control groups.

b. Twenty-four-Month Carcinogenicity Studies in Mice and Rats of Orlistat

The sponsor also conducted two 24-month (lifetime exposure) carcinogenicity studies of orlistat in Wistar rats and NMRI mice, respectively. Each study was composed of 50 male and 50 female rodents per group assigned to each dose tested, with additional rodents per group

[25] The crypt grade was represented as a number from 1 to 6 with a grade of 3 indicating that labeled cells extend half the distance from the base to the mouth of the crypt.

designated for interim sacrifice. In both studies, orlistat was administered by dietary admixture in standard certified chow containing 22% fat and 0.98% calcium. In these studies, there was no evidence of carcinogenicity potential at doses up to 1000 mg/kg/day (38 times human exposure at the maximum recommended human dose (MRHD)) in rats and 1500 mg/kg/day in mice (46 times human exposure at the MRHD). These calculated exposures in rodents relative to humans are based on calculated area under the curve (AUC) comparisons of actual exposures, not on a body surface area comparison as suggested by the petitioner. In general, exposures based on actual data (i.e., AUC) are considered more accurate and relevant than exposures based on approximations of body surface area comparisons. These studies also evaluated colonic mucosal cell proliferation by PCNA immunohistochemical staining.

In the 24-month mouse carcinogenicity study, a minimal increase in colonic mucosal cell proliferation was observed in male mice receiving 1500 mg/kg/day orlistat after 26, 52, and 78 weeks of treatment. A similar increase was observed in female mice receiving 1500 mg/kg/day orlistat after 52 and 78 weeks of treatment. A minimal increase in colonic mucosal cell proliferation was also observed in male mice receiving 25, 375, and 750 mg/kg/day orlistat after 78 weeks of treatment and in female mice receiving 750 mg/kg/day orlistat after 52 weeks of treatment. However, there were no malignant colorectal tumors in any of the mice sacrificed at weeks 95 or 104.[26]

In the 24-month rat carcinogenicity study, orlistat treatment did not result in any increases in colonic mucosal cell proliferation following 26, 52, 78, and 104 weeks of treatment. However, mucosal cell proliferation of the rectum was increased in male and female rats receiving 500 or 1000 mg/kg/day orlistat after 52, 78, and 104 weeks of treatment. In animals sacrificed at week 78, one rat from the 150 mg/kg/day group was noted to have a malignant lymphoma of the colon. In animals sacrificed at week 104, one rat from the 150 mg/kg/day group was diagnosed with metastatic carcinoma of the rectum (the primary organ with cancer was unknown).

These carcinogenicity studies and the results were reviewed by the CDER Executive Carcinogenicity Assessment Committee (ECAC) and deemed valid, adequate assessments of a negative carcinogenic potential of orlistat. With reference to petitioners' allegations regarding the adequacy of the orlistat dose used in these studies, it is noteworthy that the 1500 mg/kg/day dose tested in the mouse bioassay represents the limit dose recommended for carcinogenicity testing in rodents as described in the ICH S1C and S1C(R) guidances, further supporting the adequacy of assessment.[27] Similarly, the 1000 mg/kg/day dose tested in the rat bioassay achieved very high systemic exposures, providing an AUC (0-24) exposure multiple of 1885-fold and 2292-fold for male and female rats, respectively. This AUC (0-24) dose multiple is significantly greater than the 25-fold ratio of rodent to human plasma AUC of parent compound recommended in the ICH S1C guidance for high dose selection for carcinogenicity studies of

[26] Male mice were treated for 104 weeks and female mice were treated for 95 instead of 104 weeks because of intercurrent mortality in all female dose groups, including the controls.

[27] ICH guidance for industry on *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995); ICH Addendum to guidance for industry on *S1C(R) Dose Selection for Carcinogenicity Studies of Pharmaceuticals: Addition of a Limit Dose and Related Notes* (July 1997).

non-genotoxic pharmaceuticals.[28] The results of the two carcinogenicity studies do not support the hypothesis that orlistat is an initiator or promoter of colorectal carcinoma.

Your Petition focuses on some inconsistent colonic proliferative changes observed in the toxicology studies and outlined in Table 2 of your Petition. Findings of colonic cell proliferation or perturbations in crypt height were not observed consistently across studies following chronic exposure to orlistat in animals fed standard certified chow. Some increases in cell colonic cell proliferation, perturbations in crypt height, and inconsistent changes in ACF number were seen in two 9-month studies in rats fed high-fat diets with either low or normal calcium levels. However, there was no evidence of carcinogenicity (including colon adenoma/carcinoma) following orlistat exposures, even for a life-time in rodents.

4. Clinical Study Evaluating Effect of Orlistat on Colonic Cell Proliferation

Your Petition asserts that the primary medical reviewer noted "observational studies that implicated high dietary fat levels on the occurrence of colon cancer" and expressed concern regarding colonic cell proliferation based on a 6-week clinical study of the effect of orlistat-induced fat malabsorption on colonic cell proliferation and fecal concentrations of free fatty acids and bile acids (Petition at 9). Our analysis of data from this 6-week clinical study and from other randomized, double-blind, placebo-controlled clinical trials of orlistat is described below.

The sponsor evaluated the effect of orlistat-induced fat malabsorption on colonic cell proliferation and fecal concentrations of free fatty acids and bile acids in a randomized, double-blind, placebo-controlled, 6-week study in 24 obese male and female volunteers. Stool samples for total fat, free fatty acid, bile acid, and pH were collected at daily intervals from day –7 to –1 and from days 36 to 42. Ten orlistat and twelve placebo subjects provided evaluable pharmacodynamic data. The fecal levels of total fat and free fatty acids increased by significantly greater amounts in the orlistat group relative to the placebo group. The level of bile acid decreased by a significantly greater amount in the orlistat group versus the placebo group. (The concentration of deoxycholic and lithocholic acid accounted for most of the reduction in total bile acid in the orlistat group.) Employing rectal biopsies at baseline (day –7) and week 6 (day 43), cell proliferation was assessed by examining changes in bromodeoxyuridine (BrdU), PCNA, and crypt mitotic count values (CMC). The changes from baseline to week 6 in these three biomarkers of cell proliferation did not differ by a statistically significant amount in the groups treated with orlistat compared with placebo.[29] However, the levels of BrdU and PCNA were numerically lower in the orlistat groups (a lower value indicates less proliferation).

The primary medical reviewer raised the possibility of a meaningful, but non-statistically significant, correlation between increased levels of fecal total fat and free fatty acids and increased activity of biomarkers for proliferation in the orlistat group, and requested a consult on these data from the Division of Gastrointestinal Drug Products (GI Division). Following review of these data, the consulting medical officer from the GI Division concluded that under the experimental conditions in this study, orlistat did not induce colonic epithelial cell proliferation

[28] ICH guidance for industry on *S1C Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (March 1995).

[29] We recognize, however, that statistical significance would be difficult to achieve in this small sample.

and the fecal concentrations of free fatty acids and bile acids did not reveal findings of concern under orlistat treatment as compared to the control group.[30]

In evaluating whether orlistat might increase the risk for colon cancer, the consulting medical officer from the GI Division further noted that, although "no one can, of course, answer this question with certainty," the following information appears to mitigate such concerns:

- Orlistat does not seem to have mutagenicity or genotoxicity potential . . .
- Because the unhydrolyzed [triglyceride] being offered to the colon is structurally normal, this situation is like in other malabsorption syndrome[s] . . . [and n]o effects of the fat on colonic architecture are expected.
- Although higher than before treatment, the amount/concentration of [free fatty acids] being offered to the colon does not increase much with orlistat [and n]ot much cytotoxic effect is expected . . .
- Orlistat's [pharmacodynamic] effects result in a significant decrease in total [bile acids], particularly [deoxycholic acid] not only in the stool, but — most importantly — the liquid phase of the stool. Orlistat shares this [pharmacodynamic] effect with compounds now being tested in the prevention of colorectal cancer, such as [ursodeoxycholic acid].
- Orlistat inhibits the secretory phospholipase A_2, an enzyme involved in the production of arachidonic acid, which is a substrate for the production of [prostaglandins] and [leukotrienes].[31]

We also analyzed data from randomized, double-blind, placebo-controlled clinical trials of orlistat, ranging from 6 months to 4 years in duration, for reports of colorectal cancer. In these clinical trials, one of 7912 (0.01%) subjects randomized to placebo and six of 9717 (0.06%) subjects randomized to orlistat 60 mg or 120 mg t.i.d. were diagnosed with colorectal cancer ($p=0.14$). Of the six reports of colorectal cancer in the orlistat-treated groups, the average age of the cases was 58 years (range: 47 to 70 years) and the mean duration on study drug prior to the diagnosis of colorectal cancer was 218 days (range: 26 to 694 days). We note that two of the cases of colorectal cancer in orlistat-treated patients were diagnosed within 4 months of starting the first dose of drug. If these two cases are removed from the statistical analysis, as many would advocate given the extremely short latency period, the p-value for the comparison of the proportion of cases of colorectal cancer in placebo versus orlistat-treated subjects increases from 0.14 to 0.39. We recognize, however, that the small number of events, particularly the single case among subjects randomized to placebo, renders statistical analyses of these data very unstable.

[30] Food and Drug Administration, Division of Gastrointestinal and Coagulation Drug Products Medical Officer's Consult regarding NDA 20-766 (orlistat), March 6, 1997, at 23.

[31] Id. at 21-22.

In your Petition, you comment on the lack of a postmarketing surveillance commitment to study orlistat use in individuals with risk factors for colon cancer, those with predisposing conditions, and those with premalignant lesions, as recommended by the consulting medical officer from the GI Division (Petition at 9). The consulting medical officer's recommendation for a phase 4 clinical study to investigate the GI effects of orlistat in obese subjects at increased risk for colorectal cancer (e.g., individuals with ulcerative colitis greater than 10 years or subjects with premalignant lesions such as dysplasia or adenomatous polyps) was not included as a study commitment because the Review Division did not believe that requesting such a study was scientifically justified given the absence of signals of concern from the preclinical studies and the clinical study that specifically examined orlistat's effects on colonic cell proliferation, ACF formation, and colorectal tumor development. It should be noted that based on data indicating that orlistat decreases levels of deoxycholic acid in the liquid and solid phases of the stool — potentially beneficial effects from the standpoint of colon cancer — the consulting medical officer also recommended that the sponsor conduct preclinical studies to examine whether the drug *inhibits* malignant colonic epithelial cells in vitro and in vivo.[32]

5. Presentation of Clinical Study Data Related to Colonic Cell Proliferation to Advisory Committees

The Supplement to your Petition contends that data from the Xenical NDA and the Garcia study regarding ACF formation should have been presented at the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Drugs Advisory Committee that convened on January 23, 2006, to discuss the NDA for an OTC formulation of orlistat (see Supplement at 1 to 3). As discussed below, issues related to clinical study data on colonic cell proliferation were openly presented to and addressed with the Endocrinologic and Metabolic Drugs Advisory Committee that convened to discuss the Xenical NDA on May 14, 1997. The limited findings of the Garcia study in rats, discussed previously in section II.A.2 of this response, did not warrant further Advisory Committee consideration on the issue of ACF and colonic cell proliferation.[33]

Findings from the clinical study discussed in section II.A.4 of this response, above, were presented in the briefing packages provided to the Endocrinologic and Metabolic Drugs Advisory Committee in advance of the Advisory Committee meetings on May 14, 1997, and March 13, 1998, to discuss the Xenical NDA. At the May 14, 1997, meeting, the Advisory Committee discussed, among other issues, orlistat's effects on the GI tract and possible risk for colon cancer. As one Advisory Committee member noted: "I read through very carefully a lot of data on that, which is very reassuring, about no changes in rates of differentiation of colonic cells, various markers for molecular events and colonic epithelium."[34] The consulting medical

---

[32] Food and Drug Administration, Division of Gastrointestinal and Coagulation Drug Products Medical Officer's Consult regarding NDA 20-766 (orlistat), March 6, 1997, at 24.

[33] A version of the Garcia study was posted on the Internet on December 27, 2005, less than one month before the January 23, 2006, Advisory Committee meeting, and the Garcia study was published on August 28, 2006.

[34] Food and Drug Administration, Endocrinologic and Metabolic Drugs Advisory Committee meeting transcript, May 1997 at 137, available on the Internet at http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3279t1.pdf (1997 Advisory Committee Transcript).

officer from the GI Division attended the meeting and presented his conclusions regarding the 6-week clinical study of the effect of orlistat-induced fat malabsorption on colonic cell proliferation and fecal concentrations of free fatty acids and bile acids. The consulting medical officer opined that "after administration of the recommended dose, 120 milligrams t.i.d. for six weeks, and looking into colonic events, such as cell proliferation -- and I realize that cell proliferation was controversial -- there were no findings of concern."[35] He further stated: "The most important finding was that actually, a decrease in the oxycholic acid, and this is a very interesting finding because there are two or three multi-center clinical trials in the United States, almost exclusively based on this pharmacodynamic finding. Decrease in the oxycholic acid in both the solid and the liquid phase of the stool, and this is supposed to be a very good parameter of anti-cancer compounds."[36]

6. Analysis of Reports Involving Colon Cancer in AERS Database

Finally, we have analyzed data from our Adverse Event Reporting System (AERS) database with respect to adverse drug experiences involving colon cancer associated with the use of orlistat.

A search of the AERS database from April 23, 1999 (date of approval of the Xenical NDA), through July 21, 2006, for reports of colon cancer in individuals exposed to orlistat identified a total of 20 unduplicated reports. Our search used the following *Medical Dictionary for Regulatory Activities* (MedDRA) terms: Colonic Neoplasms Malignant; Colorectal Neoplasms Malignant; Colorectal and Anal Neoplasms Malignancy Unspecified; Colon Adenoma; and Colonic Polyp. Eight reports were for colon polyps, two were for colon polyps/colitis, and two were for non-colon primary cancers that invaded the colon. Of the eight cases of colon cancer, six reports were foreign, and four occurred in women. Data regarding age at time of event was reported for 7 patients, and the mean age of the patients was 57 years (range: 45 to 68 years). The median duration of use of orlistat prior to the diagnosis of colon cancer was 211 days (range: 9 to 1813 days). For the reports that included information on the year of diagnosis, one case was detected in 2000, one in 2001, 3 in 2002, and 2 in 2005.

We recognize that passive drug safety reporting systems such as AERS are not well-suited to assessing latent events such as malignancies or whether a drug increases the risk for commonly occurring adverse events in the population for which the drug is approved. The risk for colon cancer appears to be increased by abdominal obesity in men and women,[37] and interpretation of spontaneous reports of colon cancer in individuals exposed to orlistat is difficult due to, among other things, confounding by indication. Based on our analysis of the totality of the data related to the risk of colon cancer among orlistat users, we do not consider this small number of spontaneous adverse event reports of colon cancer cases to constitute a safety signal warranting further investigation at this time.

---

[35] Id. at 196.

[36] Id. at 196 to 197.

[37] Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:920-931; Moore LL, Bradlee ML, Singer MR, et al. BMI and waist circumference as predictors of lifetime colon cancer risk in Framingham Study adults. Int J Obes 2004;28:559-567.

B. Breast Cancer Data

Your Petition correctly states that orlistat "was not approved initially because of an increase in breast cancer in the orlistat treated groups" (Petition at 8), but inappropriately characterizes this issue as "unresolved" (Petition at 10). As described in detail in section II.B.1 of this response, FDA analyzed available safety data related to the imbalance of breast cancer cases observed in the phase 3a studies, presented the issue to two Advisory Committees convened to discuss the Xenical NDA, and requested additional data from the sponsor (phase 3b studies) until the initial concerns were addressed. FDA also evaluated data submitted by the sponsor in accordance with its postmarketing commitment to provide monthly updates of breast cancer diagnoses from ongoing phase 3b studies. As with all marketed drug products, FDA continues to monitor and review available safety information related to orlistat.

1. Analysis of Data Related to Imbalance of Breast Cancer Diagnoses During Phase 3a Clinical Trials

There was an unexpected and initially inexplicable imbalance in the number of women treated with orlistat compared with placebo who were diagnosed with breast cancer during their participation in the preapproval phase 3 clinical trials (phase 3a studies): nine (1.2%) of the subjects randomized to orlistat 120 mg, one (0.3%) subject randomized to orlistat 60 mg, and one (0.2%) subject randomized to placebo. The possible explanations for this finding included detection bias, chance, or a causal relationship. Upon detailed review of the clinical data, the Review Division found no compelling evidence that the imbalance in breast cancer cases was due to detection bias. Although the imbalance was of nominal statistical significance, the finding lacked apparent biological plausibility based on the following:

- Preclinical studies did not indicate that orlistat was mutagenic or carcinogenic;
- There was no increase in breast tumors in the preclinical orlistat carcinogenicity studies in which animals were exposed to drug levels that were 800 times higher based on body surface area comparisons than those achieved in humans dosed with 120 mg three times daily;
- A negligible amount of the parent drug or its metabolites reach the systemic circulation;
- There was no obvious mechanism to explain a secondary effect of orlistat on breast cancer risk (levels of fat-soluble vitamins were within normal limits in the women diagnosed with breast cancer and the limited clinical data available did not suggest that orlistat increased endogenous estrogen levels);
- Five of the ten breast cancer cases were diagnosed within 6 months of starting orlistat — considered by some to be too short a period of time to meaningfully promote tumor growth.

The imbalance in the cases of breast cancer observed in the phase 3 clinical trials was one of the issues presented to the Endocrinologic and Metabolic Drugs Advisory Committee on May 14, 1997, when the Advisory Committee convened to discuss the orlistat NDA. The committee

voted unanimously (8 to 0) in favor of approving orlistat for the treatment of obesity. However, one Advisory Committee member, upon learning that the Review Division was planning to request additional analyses of the breast cancer data, stated that he would reserve his final vote on approvability pending the outcome of the additional analyses.

Following the first Advisory Committee meeting, the Review Division asked the sponsor to conduct a follow-up survey of all females aged 45 years or older at the time of randomization into the seven phase 3 clinical trials, including those who withdrew early, to obtain complete ascertainment of breast cancer cases. (Since a larger percentage of placebo as compared to orlistat subjects withdrew early from the clinical trials, the lower than expected incidence of breast cancer in the placebo groups could have been due to underreporting.) The sponsor obtained follow-up information on more than 90% of trial participants, and identified an additional three cases of breast cancer: two in subjects randomized to orlistat 120 mg and one in a subject randomized to placebo. Based on the information obtained during the telephone follow-up survey, there was no "catch-up" of breast cancer cases in the women randomized to treatment with placebo nor was there evidence of a detection bias. Thus, the follow-up survey did not alleviate the Review Division's concern regarding the imbalance in breast cancer cases in women randomized to orlistat in the phase 3a trials.

The Review Division consulted the Division of Oncology Drug Products (Oncology Division) to request their evaluation of the breast cancer data from the orlistat clinical trials. After reviewing the available information, a medical officer from the Oncology Division concluded that the "clinical information related to a possible association between orlistat use and the risk of developing breast cancer is inconclusive."[38] The principal reason for this conclusion was evidence suggesting that 9 of the 14 breast cancer cases were present prior to initiation of study drug (these 9 cases all were among subjects randomized to treatment with orlistat). The lack of a similar number of pre-existing cases in subjects randomized to placebo was most likely a chance finding, and the consulting medical officer from the Oncology Division recommended the collection of additional safety data until there is more confidence about the estimate of oncological risk, if any, with the use of orlistat.

On March 13, 1998, a second FDA Advisory Committee convened to discuss the orlistat NDA and interpretation of the breast cancer data. The advisory panel was composed of members of the Endocrinologic and Metabolic Drugs Advisory Committee, as well as a biometrics researcher from the National Cancer Institute and two breast cancer oncologists. At the end of the meeting, when asked to take into consideration the overall benefits and risks of orlistat and recommend whether orlistat should be approved for the treatment of obesity, the vote was split (5 for and 5 against approval). Regardless of their vote on approval, all panelists recommended additional study of the breast cancer issue.

Due to the need to resolve outstanding concerns regarding the imbalance of breast cancer cases in the phase 3a studies, the Review Division advised in its approvable letter dated May 12, 1998, that approval of orlistat was contingent upon submission and review of data from randomized,

[38] Food and Drug Administration, Division of Drug Oncology Products Medical Officer's Consult regarding NDA 20-766 (orlistat), January 16, 1998.

double-blind, placebo-controlled, parallel-group clinical studies that support a conclusion that the drug does not increase the risk of breast cancer.[39] The letter further stated that "[i]n the aggregate, these data should provide information on approximately as many women 45 years of age or older, and approximately as many women-years of treatment with orlistat 120 mg tid and with placebo, as did the clinical studies that showed an increase in the occurrence of breast cancer in women 45 years of age or older who were treated with orlistat."[40]

In January 1999, Roche submitted a response to the approvable letter (supplemented in March 1999) that met the Review Division's request for additional data. These new data were based upon 20 ongoing and 3 completed randomized, double-blind, placebo-controlled trials that did not have mammographic screening at baseline (phase 3b studies), 6 open-label studies that did not have mammographic screening at baseline, and one large ongoing randomized, double-blind, placebo-controlled study (the XENDOS study) that did have mammographic screening at baseline.[41] The Review Division gave preference to data from studies in which mammographic screening was not routinely done at baseline because the preapproval phase 3 studies that gave rise to the concern did not include mammographic screening. There were three cases of breast cancer reported from these datasets: one in a woman from the phase 3b studies who had been randomized to placebo and two in women from XENDOS, both randomized to placebo as well.

Your Petition incorrectly suggests that "in the end, the FDA accepted the sponsor's assurances that breast cancer was not a drug-related adverse event, and nothing about it appears in the label" (Petition at 8). The lack of replication of an increase in breast cancer cases in women treated with orlistat in a set of phase 3 clinical trials (phase 3b studies and the XENDOS study), coupled with the biological implausibility of an association between orlistat use and breast cancer risk, indicated that the imbalance observed in the phase 3a studies was not causally related to treatment with orlistat.[42] The Review Division ultimately concluded therefore that the imbalance in breast cancer cases in the phase 3a studies was a chance finding (i.e., there was an increased number of women with pre-existing malignant breast tumors in the orlistat compared with the placebo groups at baseline) and that orlistat was neither an initiator nor a promoter of breast cancer.[43]

Your petition notes that the medical officer from the Oncology Division previously consulted by the Review Division regarding breast cancer risk recommended in her January 1998 consult memorandum that "product labeling should 'address issues related to breast cancer risk' with language similar to that used for Premarin. She also recommended a postmarketing registry be established to collect tumor data" (Petition at 8). The orlistat labeling did not reference the breast cancer findings from the preapproval phase 3a trials because the Review Division did not

---

[39] Food and Drug Administration, Office of Drug Evaluation II "Approvable" Letter for NDA 20-766 (orlistat), May 12, 1998.

[40] Id.

[41] Food and Drug Administration, Division of Metabolic and Endocrine Drug Products, Medical Officer's Memorandum Regarding Review of Roche's Response to Approvable Letter Issued May 12, 1998, and Safety Update for NDA 20-766 (orlistat), March 22, 1999.

[42] Id.

[43] Id.

approve orlistat until after there was adequate evidence to conclude that the imbalance in breast cancer cases observed in the phase 3a studies was a chance finding and that orlistat was not associated with an increased risk of developing breast cancer.

To facilitate careful monitoring of data from ongoing studies, Roche agreed to provide monthly updates of breast cancer diagnoses from ongoing phase 3b studies and the XENDOS study until study completion as a phase 4 commitment. This commitment was satisfied in September 2000. In the phase 3b studies, in women 45 years of age or older at randomization, there were four cases of breast cancer during 1906 person-years of exposure in the orlistat groups compared with six cases during 1382 person-years of exposure in the placebo groups. In the XENDOS study, in women 45 years of age or older at randomization, there were zero cases of breast cancer during 808 person-years of exposure in the orlistat group compared with three cases during 808 person-years of exposure in the placebo group. These data further support the Review Division's conclusion that orlistat is neither an initiator nor a promoter of breast cancer.

2. Analysis of Reports Involving Breast Cancer in AERS Database

In the Petition, you provide your own analysis of spontaneous adverse event reports in the AERS database of breast cancer associated with use of orlistat (Petition at 8 to 9). You contend that "from the time of marketing through June 2005, there were 28 reported cases of breast cancer. Eight lacked information on duration of therapy and 3 were of a month or less" (Petition at 8). In Table 6 of your Petition, you describe the distribution of exposure for the remaining 17 reported cases of breast cancer from your analysis, 6 of which were in persons exposed to orlistat for a duration of 6 months or less (Petition at 8 to 9). Finally, you provide your own analysis of rates of spontaneous adverse event reports of breast cancer in individuals exposed to Xenical (orlistat) as compared with Meridia (sibutramine), another drug indicated for weight management, and assert that there was an "approximately 10-fold difference in reported cases per million prescriptions, based on IMS data" (Petition at 9). Our analysis of reports of breast cancer in the AERS database is set forth below. Based on our analysis of the totality of the data related to orlistat and the risk of breast cancer, we do not consider these spontaneous adverse event reports to constitute a safety signal warranting further investigation at this time.

A search of the AERS database from April 23, 1999 (date of approval of the Xenical NDA), through July 21, 2006, for reports of breast cancer in individuals exposed to orlistat identified a total of 30 unduplicated reports. Our search used the MedDRA high level group term "breast neoplasms malignant and unspecified" and extended more than 1 year beyond the search period described in your Petition. From the 30 reports, we excluded the following four cases from our analysis: two cases that occurred in women with a previous history of breast cancer, one case that was described as fibrocystic breast disease, and one case that was identified as a benign breast lump. This resulted in 26 reports for further evaluation, 19 of which were from foreign countries. The level of detail provided in these spontaneous reports varied. Data regarding age at time of event was reported for 21 patients, and the mean age was 56 years (range: 28 to 78 years). Twenty-five of the reported cases occurred in females. The median duration of use of orlistat prior to the diagnosis of breast cancer was 138 days (range: 7 to 870 days) based on information contained in 21 of the reports. Of the 21 reports which included a date of breast cancer diagnosis, 10 were diagnosed in 1999, 5 in 2000, 2 in 2001, 3 in 2002, and 1 in 2004.

When the number of domestic AERS reports of breast cancer for orlistat are adjusted for the number of domestic prescriptions dispensed, the reporting rate is approximately 0.6 cases per 1,000,000 prescriptions for orlistat.[44] This reporting rate is lower than the rate cited in your Petition (3.4 cases per 1,000,000 prescriptions for orlistat) presumably because you included foreign reports in your calculation. This is inappropriate given that the prescription-use data comprising the denominator pertain only to the United States. In addition, your Petition did not specify the AERS search term(s) that generated the data used in your analysis or whether the resultant number of cases were limited to unique patients or could include duplicates, and this also may have contributed to the difference between our calculated reporting rates. Finally, we note that the difference between our calculated reporting rates may be attributable to different sources of prescription data and different time periods for analysis of spontaneous adverse event reports.

Regardless of the approach taken to calculate the reporting rates, it is generally accepted that passive drug safety reporting systems such as AERS are not well-suited to assessing latent events such as malignancies or whether a drug increases the risk for commonly occurring adverse events in the population for which the drug is approved. The risk for postmenopausal breast cancer is increased by excess body weight.[45] Overweight and obese middle-aged women, many of whom are postmenopausal, represent a considerable segment of the population who use obesity drugs.[46] It would not be surprising, therefore, if FDA received spontaneous reports of breast cancer in overweight and obese middle-aged and older women taking orlistat. One reason that the Review Division did not approve orlistat until there was adequate evidence that the drug did not increase the risk for breast cancer (i.e., placebo-controlled data from phase 3b clinical trials), was concern that once orlistat was approved the Agency would indeed receive reports of breast cancer in overweight and obese postmenopausal women taking orlistat, and interpretation of such reports would be extremely difficult due, among other things, to confounding by indication. In this setting, the small difference in domestic reporting rates of breast cancer among women exposed to orlistat as compared with women exposed to sibutramine (approximately 0.6 cases per 1,000,000 prescriptions for orlistat versus approximately 0.1 cases per 1,000,000 prescriptions for sibutramine,[47] calculated as described earlier in this section) is not informative.

C. GI Symptoms and Levels of Fat-Soluble Vitamins and Beta-Carotene

In your discussion of the risk/benefit profile, you briefly reference GI symptoms relating to bowel movements as well as the loss of fat-soluble vitamins (Petition at 7 to 8), both of which are associated with orlistat's mechanism of action. As discussed below, it is FDA's position that these issues are adequately addressed in the product labeling.

---

[44] Verispan Vector One®: National, Data extracted July 31, 2006.

[45] See, e.g., Morimoto LM, White E, Chen Z, et al. Obesity, body size, and risk of postmenopausal breast cancer: the Women's Health Initiative (United States). Cancer Causes Control 2002;13:741-751.

[46] Khan LK, Serdula MK, Bowman BA, Williamson DF. Use of prescription weight loss pills among U.S. adults in 1996-1998. Ann Intern Med 2001;134:282-286.

[47] Verispan Vector One®: National, Data extracted July 31, 2006.

1. GI Symptoms

The most common adverse events reported by subjects taking orlistat in the preapproval trials were oily spotting, flatus with discharge, fecal urgency, and oily evacuation. These events are expected with fat malabsorption, do not pose a threat to patient safety, and are adequately described in Xenical product labeling.

2. Levels of Fat-Soluble Vitamins and Beta-Carotene

In your Petition, you also observe that loss of fat-soluble vitamins (beta-carotene and vitamins A, D, E, and K) was a concern related to orlistat's mechanism of action, and suggest that a postmarketing study should have been requested of the sponsor to evaluate the safety and efficacy of vitamin supplementation (Petition at 8).

Orlistat was expected to reduce the absorption of fat-soluble vitamins based on its mechanism of action. In preapproval clinical trials of up to 2 years' duration, in which adult subjects did not receive routine vitamin supplementation, a larger percentage of subjects treated with orlistat versus placebo developed two or more consecutive low levels of vitamins A, D, E, and beta-carotene (Table 1). The changes in prothrombin time (PT), which was used as a surrogate measure of vitamin K status, from baseline to year 2 did not differ between the subjects treated with orlistat versus placebo. Although subjects were not specifically questioned about signs or symptoms of fat-soluble vitamin deficiencies, there was no evidence from spontaneous adverse event reporting or routine physical examinations to suggest that any of the subjects developed signs or symptoms of vitamin A, D, E, or K deficiency. Nonetheless, because a larger proportion of subjects treated long-term with orlistat versus placebo had two consecutive low serum levels of vitamins A, D, E, and beta-carotene, the Xenical product labeling strongly encourages all users to take a multivitamin once daily.

Table 1

Incidence of Low Vitamin Values on Two or More Consecutive Visits Adults Treated for up to Two Years

	Placebo	**Xenical**
Vitamin A	1.0%	2.2%
Vitamin D	6.6%	12.0%
Vitamin E	1.0%	5.8%
Beta-carotene	1.7%	6.1%

The primary medical reviewer did recommend that a postmarketing study be conducted to evaluate the efficacy and safety of vitamin supplementation. Although the Agency chose not to request that the sponsor conduct such a study at the time of approval, important information regarding the efficacy and safety of vitamin supplementation was obtained in a postapproval study conducted in obese adolescents. Compared to the incidence of two or more consecutive low serum fat-soluble vitamin levels in subjects not supplemented with a daily multivitamin (Table 1), obese adolescent subjects who took a daily multivitamin while being treated with 120

mg of orlistat, three times daily, for up to 1 year had very small absolute and relative rates of low serum fat-soluble vitamin levels when compared with placebo-treated subjects (Table 2).

Table 2

Incidence of Low Vitamin Values on Two or More Consecutive Visits Adolescents Treated for up to One Year

	Placebo	Xenical
Vitamin A	0.0%	0.0%
Vitamin D	0.7%	1.4%
Vitamin E	0.0%	0.0%
Beta-carotene	0.8%	1.5%

The Xenical labeling strongly encourages 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 at least once a day.

D. Efficacy of Orlistat for Obesity Management, Including Weight Loss and Weight Maintenance

You have suggested 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 earlier in this response and its "minimal efficacy" for weight loss (Petition at 10). In support of your contention, you reference two studies that were published after approval of the Xenical NDA in 1999: the 4-year XENDOS study and the 1-year Kelley study (Petition at 7). Data from these and other studies are discussed below. Collectively, these data support the efficacy of orlistat in accordance with the recommended approach for demonstrating efficacy described in the Agency's 1996 draft guidance on *Clinical Evaluation of Weight-Control Drugs* (Draft Obesity Guidance).[48]

The Agency's 1996 Draft Obesity Guidance described two methods to demonstrate the efficacy of a new weight-loss drug: (1) the mean drug-associated weight loss exceeds the mean placebo weight loss by at least 5% after 1 year of treatment, or (2) the proportion of subjects who reach and maintain a loss of at least 5% of baseline body weight is significantly greater in the active drug group as compared with the placebo group after 1 year of treatment.[49] It is generally accepted that weight loss of 5% or more is associated with improvements in cardiometabolic risk factors.[50]

---

[48] See draft guidance on *Clinical Evaluation of Weight-Control Drugs* (September 1996), available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

[49] Id. at 5 to 6.

[50] Goldstein DJ, Potvin JH. Long-term weight loss: the effect of pharmacologic agents. Am J Clin Nutr 1994;60:647-657; Food and Drug Administration, Endocrinologic and Metabolic Drugs Advisory Committee meeting transcript, January 19-20, 1994.

The sponsor conducted seven placebo-controlled phase 3 trials in approximately 3000 overweight and obese subjects in support of the weight-loss indication. Four studies were 2 years in duration, one study was 18 months long, and two studies were of 1-year duration.[51] Two doses of orlistat, 120 mg t.i.d. and 60 mg t.i.d., were evaluated in the seven phase 3 trials. All subjects were instructed to consume a low-calorie diet that contained approximately 30% of total calories from fat during the first year of treatment. Those subjects who took part in the 2-year studies were instructed to consume a eucaloric diet (i.e., a diet that would maintain weight based on caloric intake) during the second year of treatment.

The mean percent change in body weight from baseline to year 1 in subjects treated with placebo was approximately –3.0% compared with –6.0% in subjects who received orlistat 120 mg ($p<0.001$). Fifty-seven percent of orlistat-treated subjects versus 30% of placebo-treated subjects lost at least 5% of baseline body weight following treatment for up to 1 year ($p<0.01$). The mean percent change in body weight from baseline to year 2 in subjects treated with placebo was –1.0% compared with –4.0% in subjects who received orlistat 120 mg ($p<0.001$). Forty percent of orlistat-treated subjects lost at least 5% of baseline body weight after 2 years of treatment as compared with 24% of subjects treated with placebo ($p<0.01$).

Although orlistat did not satisfy the first efficacy criterion based on mean changes in body weight, the drug was considered efficacious because a significantly larger proportion of subjects who received the drug lost at least 5% of their baseline body weight compared with subjects who received placebo. All eight members of an FDA advisory committee that convened on May 14, 1997, to discuss the orlistat NDA concluded that orlistat was efficacious. FDA's approval of orlistat on April 23, 1999, reflects our determination that orlistat has a favorable risk/benefit profile.

The two studies referenced in your Petition were published after the drug's approval in 1999. In the first trial, a 1-year study of overweight and obese type 2 diabetics, the orlistat group lost approximately 4.0% of baseline body weight compared with an approximate 1.0% reduction in the placebo group.[52] Your Petition did not mention that nearly 33% of the subjects randomized to orlistat lost at least 5% of baseline weight versus 13% of subjects randomized to placebo. As demonstrated in this study, for reasons that are unclear, overweight and obese subjects with type 2 diabetes tended to lose less weight on orlistat compared with non-diabetic overweight and obese subjects.

In the second study cited in your Petition (the XENDOS study), obese, non-diabetic subjects treated for four years with orlistat lost approximately 5.3% of baseline body weight compared with a 2.7% reduction in the placebo group.[53] Approximately 53% and 37% of orlistat and

---

[51] Food and Drug Administration, Division of Metabolic and Endocrine Drug Products, Medical Officer's Review of NDA 20-766 (orlistat), April 30, 1997.

[52] Kelley DE, Bray GA, Pi-Sunyer FX, et al. Clinical efficacy of orlistat therapy in overweight and obese patients with insulin-treated type 2 diabetes. Diabetes Care 2002;25:1033-1041.

[53] Torgerson JS, Hauptman J, Boldrin MN, Sjostrom L. Xenical in the prevention of diabetes in obese subjects (XENDOS) study. Diabetes Care 2004;27:155-161.

placebo subjects, respectively, lost at least 5% of baseline body weight. During the last 3 years of the trial subjects from both treatment groups regained some of the weight they lost in the first year. Nevertheless, after 4 years of treatment, subjects on orlistat still weighed significantly less than those on placebo. Moreover, despite regaining a portion of initially lost weight — a phenomenon common to all weight-loss drugs — therapy with orlistat reduced the cumulative incidence of developing type 2 diabetes, the primary efficacy endpoint of the study, from 9% to 6% ($p<0.05$).

Comprehensive assessments of orlistat's efficacy have recently been published. These meta-analytic and systematic reviews involving more than 20 clinical trials indicate that long-term treatment with orlistat is associated with an average weight loss of 2.75 kg relative to placebo.[54] More important, based on clinical trial data one would expect approximately 54% of orlistat-treated versus 30% of placebo-treated subjects to lose at least 5% of baseline body weight, which is generally accompanied by favorable changes in blood pressure, total and low density lipoprotein cholesterol, and, in individuals with type 2 diabetes, improvements in glycemic control.[55]

Thus, when viewed in aggregate, data available prior to and following orlistat's approval support the conclusion that the drug is effective — that is, a significantly greater percentage of subjects treated long-term with orlistat lose at least 5% of baseline body weight compared with those treated with placebo.

E. OTC Formulation of Orlistat

FDA has concluded that a 60-mg dose strength orlistat product 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. All relevant statutory and regulatory criteria regarding OTC marketing have been met for the OTC orlistat product (see section 503(b) of the Act and 21 CFR 310.200(b)).

None of the data provided in your Petition alters our favorable assessment of the risk/benefit profile of a 60-mg, non-prescription dose strength of orlistat. As discussed above, the Agency has found the 120-mg dose strength of Xenical (orlistat) to be safe and effective for obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced-calorie diet by obese patients with an initial body mass index ≥ 30 kg/m^2 or ≥ 27 kg/m^2 in the presence of other risk factors (e.g., hypertension, diabetes, dyslipidemia), and there is no reason to anticipate safety concerns associated with the lower 60-mg dose strength. This conclusion is based on data establishing that the 60-mg dose strength causes less excretion of fat compared to the 120-mg dose strength. While this means some degree of decreased efficacy, it also reduces the likelihood of other adverse events reflective of decreased tolerability.

---

[54] Li Z, Maglione M, Tu W, et al. Meta-analysis: pharmacologic treatment of obesity. Ann Intern Med 2005;142:532-546.

[55] See Padwal R, Li SK, Lau DCW. Long-term pharmacotherapy for obesity and overweight. Cochrane Database of Systematic Reviews. 2004.

III. CONCLUSION

Based upon our review of all of the available evidence (including preclinical data, preapproval clinical studies, data from the sponsor's postmarketing commitment, and postmarketing spontaneous adverse event reporting), we have not found that orlistat is "unsafe for use under the conditions of use upon the basis of which the application was approved" nor have we found "that 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" (section 505(e)(1)-(2) of the Act). Further, we have not found "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" (section 505(e)(3) of the Act). Accordingly, we deny your Petition requesting that FDA withdraw approval of the Xenical NDA and not approve an NDA for an OTC formulation of orlistat. As with all FDA-approved products, FDA will continue to monitor and review available safety information related to orlistat throughout the drug product's lifecycle.

Sincerely,

Steven K. Galson, M.D., M.P.H.
Director
Center for Drug Evaluation and Research