

Attachment 1 of 3

**Summary of Comments in Opposition to Public Citizen's
Petition Requesting Withdrawal of Prescription Xenical
from the Market and the Rejection of Approval of Orlistat
Capsules for Over-the-Counter Use
(FDA Docket No. 2006P-0154 and 2006P-0154/Sup 1)**

General Background for Attachments 1-3

On April 10, 2006, Public Citizen filed a citizen petition (Docket No. 2006P-0154/CP 1) to the United States Food and Drug Administration (FDA) requesting that FDA take immediate action to remove Xenical[®] (orlistat) Capsules, 120 mg, from the US market. The Petition further suggested that FDA should not approve GlaxoSmithKline's pending new drug application for the use of orlistat 60 mg capsules as an over-the-counter weight loss aid (alli[™] orlistat 60 mg Capsules).

A Supplement to the Citizen Petition (Supplement) was submitted to FDA on June 5, 2006 to further Public Citizen's position presented in the original April 10 petition. The supplement did not provide additional data for consideration but alleged that there was a lack of transparency by FDA and GSK regarding the issue of aberrant crypt foci (ACF) at the January 2006 Advisory Committee hearing reviewing the safety and efficacy of orlistat as a potential OTC product.

To address the issues raised in the Petition and Supplement, which both Roche and GSK take very seriously, Roche and GSK (collectively referred to as the "Sponsors") have reviewed the current body of preclinical, clinical and post-marketing safety data, including the ACF data, to assess the potential risk of developing colon cancer as a result of orlistat therapy. In addition, a review of epidemiology data was conducted to identify risk factors for colorectal cancer in humans.

The Sponsors' assessment of the scientific issues, which reflects the combined scientific opinion of GSK and Roche, is provided in three documents designated as Attachments 1, 2 and 3 respectively.

- Attachment 1 is a point-by-point assessment of overall general issues raised in the Petition and Supplement.
- Attachment 2 is a detailed summary of the orlistat preclinical and clinical data and colon cancer. Attachment 2 addresses both the data referenced by Public Citizen in their Petition and includes additional preclinical and clinical data not discussed in the Petition.
- Attachment 3 is the report of an independent expert task force (referred to herein as the "Colon Scientific Advisory Board") who reviewed the relevant preclinical and clinical orlistat data and concluded that there is no evidence that orlistat increases the risk of colon cancer in humans.

1 A Brief Overview of the Regulatory History of Orlistat

Roche received approval by the United States Food and Drug Administration (FDA) in 1999 to market Xenical (orlistat) Capsules, 120 mg for the treatment of obesity. Orlistat is currently approved in more than 145 countries and has been used safely and effectively by more than 26 million patients worldwide since its first approval in 1997. Orlistat's foreign marketing experience includes 6 countries where Xenical® (120 mg) has recently been reclassified from prescription to OTC status as a 'pharmacy-only' medicine.

Following initial US approval, as part of the mandatory regulatory process for maintaining market status for all Rx approved drugs, the safety of orlistat has been monitored on an ongoing basis and reported to FDA as per the Code of Federal Regulations.

Roche received approval for Xenical in the US in April 1999 for the indication of obesity management, including weight loss and weight maintenance, when used in conjunction with a reduced calorie diet as well as the reduction of weight regain after prior weight loss. Other major labeling supplements to NDA 20-766 included the submission of data in pediatric patients aged 12 to 16 years (June 2003) and data from the 4 year Xendos study (December 2003) for the prevention of diabetes. Both of these supplements were approved and data from these applications are included in the approved Xenical label.

In June 2005, GSK submitted an NDA for the use of orlistat 60 mg capsules as an over-the-counter weight loss aid (alli™ orlistat 60 mg capsules). In support of the OTC application, an FDA Advisory Committee hearing was held on January 23, 2006 to specifically consider the safety and efficacy of orlistat in an over-the-counter environment. At the conclusion of the proceedings, the committee members voted 11 to 3 that orlistat was safe and effective for OTC use to promote weight loss in overweight adults when used along with a reduced calorie and low fat diet.

GSK received an approvable letter for this application in April 2006.

2 Background to Issues Raised in Petition and Supplement

In two preclinical studies conducted by Hoffmann-La Roche (Roche) in support of the original development program for Xenical®, an increase in total aberrant crypt foci (ACF) has been observed. Some scientists are of the opinion that ACF may be a potential biomarker for the development of colon cancer.

The Petition supposes that an increase in ACF (aberrant crypt foci) in a rodent model is an accepted biomarker for human colon cancer and notes the observation of increased total ACF in some short-term rodent studies with orlistat. Based on these factors, the Petition concludes that orlistat can cause colon cancer in humans.

The Petition raises other issues relative to the established safety and efficacy profile of orlistat capsules which includes the conduct of the carcinogenicity studies, recent preclinical study conducted by Garcia et al, EPA and its use of ACF as a biomarker, colonic proliferation data, post-marketing surveillance, breast cancer, data regarding chemoprevention, FDA review process in general, information provided to the joint Advisory Committee in January, 2006 and obesity and mortality. These are the issues that are specifically addressed by the Sponsors in Attachment 1. The preclinical and clinical data for orlistat and colon cancer are addressed in detail in Attachment 2.

3 Summary of Specific Issues Raised in Petition and Supplement

The April 10, 2006 petition and the June 5, 2006 supplement raise several issues and reach certain conclusions regarding orlistat. The Sponsors of the Rx and OTC regulatory applications have considered each of these issues and a summary of our assessment for each issue is provided below. The overall preclinical and clinical data for orlistat and colon cancer are provided in detail in Attachment 2. Based on the results of our assessments of these issues, we conclude that treatment with orlistat does not increase colon cancer risk and there is no change in the overall benefit/risk assessment of orlistat as either an Rx or potential OTC product.

3.1 Validity of Orlistat Carcinogenicity Studies

Citizen's Petition: The carcinogenicity studies are not valid due to inappropriate dose selection.

Sponsors' Assessment: The carcinogenicity studies in rat and mouse for orlistat are valid and were conducted at appropriate doses. The doses for the orlistat carcinogenicity studies were discussed with and agreed to by FDA prior to initiation of the studies and were in accordance with current International Conference on Harmonization (ICH) guidelines for high dose selection for carcinogenicity studies (ICH 1994) for non-genotoxic agents. Dose selection for the rat and mouse carcinogenicity studies was based on animal to human AUC (0-24h) exposure ratios (not on the maximum tolerated dose), with the doses far exceeding human exposure. The highest doses of orlistat used in the carcinogenicity studies were 79- and 62-fold greater than the human exposure in the mouse study for males and females respectively and 1185- and 2292-fold greater than human exposure in the rat study for males and females.

3.2 ACF as a Biomarker

Citizen's Petition: ACF in a rodent model is an acceptable biomarker for human colon cancer.

Sponsors' Assessment: ACF has not been validated as a biomarker nor is there consensus in the scientific community that total ACF can be used as an accurate predictor of colonic tumor development in humans.

Notably, the Supplement acknowledges that ACF are “far from being a validated biomarker for either cancer or polyps”, thus supporting the assertion that the general status of ACF as a “biomarker” is not universally accepted by the scientific community.

In the case of orlistat specifically, ACF cannot be considered a well accepted biomarker for the development of colon cancer based on the fact that two 2-year carcinogenicity studies, specifically designed to determine oncogenicity potential in two species of rodents exposed to a wide range of doses showed no evidence of colonic carcinoma. Although not related to orlistat, the Environmental Protection Agency (EPA) had similar issues regarding the findings of an increase in colonic ACF in rats and the corresponding lack of tumor development in two year carcinogenicity studies with dibromochloromethane in the same strain of rat, see section 3.4.

Also in a 6-week randomized, double blind, placebo controlled study in obese patients receiving orlistat, 120 mg tid, multiple rectal biopsies were taken to assess colonic cell proliferation. The results of this study indicated no increase in colonic cell proliferation with orlistat-treated subjects.

Based on the preclinical and clinical data for orlistat, observations of ACF in a rodent model do not meet the criteria for a valid biomarker as defined in the March 2005 FDA Guidance for Industry on *Pharmacogenomic Data Submissions*[1]. Roche and GSK also support the FDA recommendation in this guidance that observational or exploratory biomarkers are insufficient for making regulatory decisions. In addition, there is no data showing that orlistat is associated with the development of cancer.

3.3 Garcia Study

Citizen’s Petition: This study shows orlistat increases ACF formation in a rodent model.

Sponsors’ Assessment: The Petition cites the results of a recent publication by Garcia et al [2] as fundamental support for its position. This study evaluated the formation of colonic ACF in rats following 30 days of treatment with various combinations of orlistat, the carcinogen dimethyl hydrazine (DMH) and a high fat diet supplemented with 10% cotton oil. ACF were observed only in the colons of animals treated with the carcinogen DMH.

The results of this 30 day study are not inconsistent with some of Roche's preclinical studies. That is, in short-term studies (generally less than 4 weeks), orlistat can cause an increase in ACF in rodents. Importantly, however, additional preclinical data submitted within the original NDA demonstrates that this increase is not observed in studies of longer duration (generally nine months).

Further, the relevance of this publication on a non-validated biomarker is questionable based on the results of long term carcinogenicity studies that demonstrate no increased risk of tumor development with orlistat administration (See Section 3.1).

3.4 EPA use of ACF testing

Citizen's Petition: EPA uses ACF to test possible carcinogens.

Sponsors' Assessment: The Petition suggests that the EPA uses ACF testing as the single testing methodology for the determination of possible carcinogens. EPA does not use ACF as a sole test for oncogenicity potential but considers the weight of the experimental evidence in animal models that are relevant to humans. In the EPA Office of Water report entitled, "*Drinking Water Criteria Document for Brominated Trihalomethanes*", dated November 15, 2005, the EPA summarized findings regarding the use of ACF assays for brominated trihalomethanes (references 18 and 19 in the April 10, 2006 petition) as follows:

"Studies of induction of aberrant crypt foci (ACF) show that bromodichloromethane, dibromochloromethane, and bromoform given in drinking water significantly increase the number and focal area of ACF in the colons of male F344 rats, Eker rats and strain A/J mice but not in the colons of B6C3F1 mice. The biological significance of this induction is unclear, as intestinal tumors have not been observed either in the colons of F344 rats treated with dibromochloromethane by corn oil gavage or in the colon of rats exposed to bromodichloromethane in the drinking water for two years. Administration of individual brominated trihalomethanes in a high animal fat diet did not significantly increase the number of ACF when compared to a diet containing normal levels of fat."

For the data specifically referenced in the petition, the EPA concluded that the biological significance of findings of an increase in ACF is unclear due to the lack of intestinal tumors in the carcinogenicity studies.

3.5 Colonic cell proliferation

Citizen's Petition: Raises concerns related to colonic cell proliferation and review by FDA's GI Division.

Sponsors' Assessment: A 6-week randomized, double blind, placebo controlled study in obese patients receiving orlistat, 120 mg tid, was conducted which included multiple rectal biopsies to assess colonic cell proliferation. The design of this study was based on the input received from FDA and several external consultants with expertise in colon cancer and colonic proliferation. The results of this multiple dose study indicate that inhibition of dietary fat absorption by orlistat did not adversely alter or change the proliferative status of the colonic epithelium in these obese subjects.

The petition mentions and acknowledges that the orlistat review division requested a consult from the FDA's Division of Gastrointestinal and Coagulation Drug Products (GI Division) regarding the data. The GI division found the endpoints in the clinical study conducted were appropriate, the cell proliferation evaluations were well executed, and under the experimental conditions of the study, the reviewer concluded there was no colonic cell proliferation.

3.6 Post-marketing surveillance

Citizen's Petition: There is a lack of post-marketing surveillance regarding colon cancer.

Sponsors' Assessment: Post-marketing safety surveillance has been conducted and continues to be conducted with respect to orlistat in accordance with 21CFR 314.80. Roche has an extensive post-marketing safety surveillance program in place for all their approved drugs including orlistat which starts immediately upon approval and continues as long as the drug is marketed anywhere in the world. The objectives of this safety surveillance program includes updating health authorities regarding the safety profile of the drug and to revise the approved label, if necessary, to incorporate information from pharmacovigilance/post-marketing safety surveillance or data from post-marketing studies revealing new safety information.

Roche's pharmacovigilance program monitors and assesses all newly acquired safety information in accordance with Good Pharmacovigilance Practices with regular reviews and evaluations of safety data. Briefly this program includes single case evaluations, review of listings of suspected and unexpected serious adverse reactions

and events, regular cumulative data review through evaluation of proportional reporting ratio (PRR) and cumulative listings, review of similar cases if a signal is identified, and periodic reporting to FDA and other health authorities as required by their specific regulations. The mandatory periodic reporting to FDA requires safety information for drugs to be reviewed periodically and submitted to FDA quarterly for the first three years, and then annually thereafter. For orlistat, Roche submitted these periodic reports on a quarterly basis to the FDA between 1999-2002 and after 2002, has submitted and continues to submit the reports on an annual basis. These reports include all spontaneous cases (serious and non-serious) and all serious and unlisted cases are discussed in detail under the relevant System Organ Class (SOC).

The specific results of this extensive post-marketing surveillance program for orlistat relative to the development of colon or rectal carcinoma clearly indicate that no signal for colon or rectal cancer has been observed based on the estimated 26 million patient treatments with orlistat to-date. In addition, any cases of colon or rectal cancer are reported and will continue to be reported to all health authorities, including FDA within 15 days of Roche's receipt of the case. Post-marketing surveillance will be continued for the orlistat Rx and is the responsibility of Roche. GSK will be responsible for the post-marketing safety surveillance of orlistat as an OTC product. Both companies have a collaborative pharmacovigilance agreement in place to ensure appropriate exchange of safety information for the Rx and OTC products among the two companies and regulatory agencies.

3.7 Breast Cancer

Citizen's Petition: The breast cancer issue is unresolved.

Sponsors' Assessment: As part of the original drug review process for Xenical, there were discussions related to breast cancer. All questions regarding this topic have since been resolved with all health authorities including FDA. Breast cancer was discussed in two public forums at two Advisory Committee meetings during the regulatory review and approval of Xenical. These meetings included numerous consultants and cancer experts who reviewed the data in detail. The transcripts for the Advisory Committee hearings and approval letter for Rx orlistat are also publicly available. The approval letter for orlistat dated April 1999 included a Phase IV commitment requesting Roche to provide monthly reports of breast cancer which included data from a large aggregate database of placebo controlled clinical trials. The aggregate database showed no difference in incidences of breast cancer between the placebo and orlistat treatment groups. Roche completely complied with this

Phase IV commitment and was notified by FDA in 2000 of its fulfillment of this commitment. Therefore the Sponsors consider this issue to be resolved.

3.8 Orlistat and Chemoprevention

Citizen's Petition: Evidence to promote tumor growth is greater than evidence to prevent cancer.

Sponsors' Assessment: With respect to orlistat use, the petition states that the evidence to cause cancer is much stronger than the ability to prevent cancer. Based on the extensive review of relevant orlistat data, both preclinical and clinical, there is no evidence to support such a statement. In a section entitled "Other potential uses of orlistat," the petition refers to studies showing that orlistat inhibits fatty acid synthase (FAS), and may thereby inhibit tumor growth [3, 4]. The Sponsors agree that these findings of orlistat selectively reducing the tumorigenicity of several cell lines including colon cancer cell lines adds to already existing evidence of the safety of orlistat. Actually this is only one of a number of lines of evidence that orlistat may actually reduce the risk of cancer. Others include:

- an indirect effect by reducing BMI and waist circumference of the obese which has recently been associated with a reduced risk of colon cancer [5]
- directly by inhibiting secretory phospholipase A1 which is linked to decreases in cancer-enhancing prostaglandins [6, 7]
- directly by reducing the concentration of secondary bile acids in the colon; increased levels of secondary bile acids have been associated with increased colon cancer risk [8]
- indirectly by decreasing luminal pH; a more acidic pH is expected to lower the solubility of bile acids and thus reduce their deleterious effects on the colonic mucosa [8, 9, 10]

While the Sponsors do not maintain that an anti-cancer effect has been demonstrated for orlistat, Kridel et al. go so far as to say "We have found orlistat to block FAS and induce apoptosis in a number of colon cancer cell lines, so treating patients at high risk for colon cancer in a prophylactic manner could be considered" [3]. When combined with the lack of genotoxicity, no evidence of carcinogenicity in the 2-yr carcinogenicity studies in both rats and mice, and the lack of a safety signal from either the FDA or the Roche Safety databases concerning human exposure, the above

information concerning the potential mechanisms for cancer prevention provide further evidence of the safety of orlistat.

3.9 FDA Review Process

Citizen's Petition: Criticism of FDA review process for orlistat.

Sponsors' Assessment: From the Sponsors' perspective, the FDA did conduct a comprehensive review of the safety and efficacy of orlistat for its intended indications. The safety of both Xenical 120 mg and orlistat 60 mg capsules has been extensively reviewed by several FDA medical reviewers and by independent Advisory Committees.

In addition, Roche also had numerous external consultants involved in the design and review of the preclinical and clinical data for orlistat on an ongoing basis. Additionally, to support the OTC application, a separate and distinct review process was undertaken which included two Divisions of FDA and a third Advisory Committee meeting. This panel was convened to specifically consider issues deemed to potentially impact the safety and efficacy of orlistat in an over-the-counter environment.

In consideration of the number of FDA scientists and external consultants involved in the review of the safety and efficacy of orlistat, the Sponsors conclude that the review process was rigorous and comprehensive.

3.10 Joint Advisory Committee Meeting (23 January 2006)

Supplement to Petition: Information available to the Advisory Committee was lacking.

Sponsors' Assessment: The Supplement to the Petition raises a concern that participants of the January 23, 2006 Joint Meeting of the Nonprescription Drugs Advisory Committee and Endocrinologic and Metabolic Drugs Advisory Committee to discuss orlistat 60 mg capsules for use as an over-the-counter (OTC) weight loss aid were not aware of the increase in ACF and colonic proliferation observed in some preclinical studies with orlistat.

The issue of colonic proliferation was discussed at the May 13, 1997 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee considering the Rx use of Xenical 120 mg capsules. The FDA's GI consulting reviewer was an active participant in the meeting. In addition, the FDA briefing document for the 1997

meeting included the complete assessment written by the GI consulting reviewer. There were no recommendations or outstanding issues raised by the Advisory Committee relative to this issue.

Because the issue was already presented to a previous Advisory Committee for review and comment, and because there is no new substantive data regarding this issue, it was therefore considered by the Sponsors as previously resolved prior to the approval of the prescription drug product (Xenical). For this reason GSK did not include this issue in its briefing document or in its presentation at the January 2006 Advisory Committee hearing to consider the over-the-counter use of orlistat 60 mg capsules.

3.11 Obesity and Mortality

Citizen's Petition: Obesity is a non-lethal condition.

Sponsors' Assessment: The Petition states that "obesity is a non-lethal condition". Obese patients are at a significantly increased risk for premature death. The Center for Disease Control (CDC) lists obesity as the 2nd leading cause of preventable deaths in the US after smoking, due to its co-morbid risk factors. Overweight and obesity are a significant and escalating public health problem in the U.S. The prevalence of overweight and obesity has steadily increased over the last 40 years among both men and women of all ages, all racial/ethnic groups, and at all educational levels [11]. Nearly one in three American adults (30.4%) is considered obese (BMI \geq 30) [12]. An additional 34% of American adults are considered overweight (BMI 25.0 – 29.9). Excess weight contributes to a myriad of health problems including cardiovascular disease, diabetes, hypertension, osteoarthritis, gall bladder disease, dyslipidemia, musculoskeletal problems and certain cancers including endometrial, colon, kidney, gallbladder and postmenopausal breast cancer [13]. Adults who are overweight but not obese (BMI between 25.0 and 29.9) are significantly more likely than their leaner peers to develop a number of co-morbidities including diabetes, cardiovascular disease and cancer [13, 14].

4 Colon Scientific Advisory Board

Based on the fact that some of the original data on orlistat and colon cancer risk dates back almost 10 years, GSK sought expert opinion regarding the medical validity of these conclusions in the context of current science. To that end, an independent Advisory Board of experts was convened to examine the issues raised in the citizen petition and to discuss current science in this area. The panel members, considered experts in the fields of cancer research, gastroenterology, toxicology and obesity included:

- Peter Holt, MD
Professor of Medicine, Columbia University
- C. Richard Boland, MD
Chief of Gastroenterology, Baylor University Medical Center
- Samuel Klein, MD
Director, Center for Human Nutrition, Washington University School of Medicine
- Robert Sandler, MD, MPH
Professor Cancer Epidemiology, Cancer Prevention and Control
University of North Carolina Cancer Hospital
- Michael Wargovich, PhD
Professor of Pathology, Microbiology and Immunology
University of South Carolina School of Medicine

The Colon Scientific Advisory Board met over a period of 2 days during which time there were presentations and discussion on topics including orlistat, colon cancer, biomarkers, ACF and dietary fat. A background package including up-to-date relevant preclinical and clinical data for orlistat as well as relevant published literature was provided to the experts in advance of the meeting. Representatives of Roche, GSK, and other outside experts participated in this open session. Following the open session, the Advisory Board were presented with a series of specific questions regarding orlistat and colon cancer and asked to debate these questions in a closed session. A summary of the Advisory Board meeting and their response to the questions debated by the Board is included in Attachment 3. The overall conclusion, as agreed to by all panel members, is that there is no evidence that orlistat increases the risk of colon cancer in humans.

5 Conclusion

Based on a comprehensive review of orlistat preclinical, clinical and post-marketing surveillance data, the Sponsors conclude that there is no evidence of a causal link between the use of orlistat and colorectal cancer. Long term carcinogenicity studies in rodents are considered the "gold standard" for assessing cancer risk for drug approval, as compared to shorter term trials that utilize a surrogate biomarker. Based on the absence of colorectal cancer in appropriately conducted rodent carcinogenicity studies, an increase in total ACF noted in preclinical studies is not a valid predictor of human colonic tumor development.

Other issues that were raised in the Petition and Supplement were also assessed by the Sponsors. Based on the Sponsors' comprehensive assessment of the scientific evidence discussed above, no change in labeling or marketing status of Rx orlistat is warranted. The overall benefit-risk profile of orlistat remains favorable and appropriate for an over-the-counter drug product and a delay in the approval and subsequent marketing of 60 mg orlistat as an OTC product is not warranted.

6 References

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