Attachment 3

Attachment 3 of 3

Summary of the Colon Scientific Advisory Board

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 about how these conclusions would hold up under 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.[1] 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 relevant questions on 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 provided in the following pages.

The key conclusion, as agreed by all panel members, is that there is no evidence that orlistat increases the risk of colon cancer in humans.

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[1] Advisory board members have been compensated by GSK pursuant to its commercial practices policies on advisory boards.

Report of the Colon Scientific Advisory Board Meeting
New York, New York, July 14-15 2006

Participants:
Peter R. Holt – Chairperson
Richard Boland
Sam Klein
Robert Sandler
Mike Wargovich

As background for responding to a series of questions, the advisory board heard presentations by several of their members, as well as by individuals cognizant of both the preclinical and clinical data that had been gathered by Roche and GSK in their presentations to the FDA.

Dr. Klein provided background information which covered the clinical efficacy and side-effects reported in Orlistat clinical trials.

Dr. Sandler and Dr. Holt discussed the evidence for a relationship between dietary fat intake and colorectal cancer development in epidemiologic and experimental studies. Data from epidemiological studies have repeatedly demonstrated a very rapid increase in the incidence of colorectal cancer in populations that migrate from low incidence to high incidence areas of the world, indicating the importance of the environment in this process. As a whole, the reasons given for this rapid increase is the Westernized lifestyle which includes diet, obesity, and inactivity, amongst others. The epidemiologic information about diet shows little evidence that an increase of dietary fat in the absence of increased energy intake is associated with an increase in colorectal neoplasia. Instead, meat rather than fat is associated with colorectal cancer, and there is some evidence that charred and grilled meats are the major culprits. Dr. Sandler found no evidence that disorders that result in fat malabsorption per se were associated with an increase in colorectal neoplasia. Furthermore, neither three prospective studies that evaluated the incidence of adenoma recurrence, nor the Women's Health Initiative that evaluated the incidence of colorectal cancer showed a beneficial effect of reducing the amount of fat in the diet.

Data from studies conducted in rodent models that used tumors and aberrant crypt foci (ACF) as endpoints have shown that high fat diets increase tumorigenesis to differing degrees depending on the fat fed. For example, dietary corn oil is more tumorigenic than dietary fish oil. However, this data appears to apply to the rodent, but does not hold in human studies.

Dr. Wargovich described the history, appearance, and differences in ACF, emphasizing that large ACF with multiple crypts were associated with neoplasia and that crypts could be hyperplastic, dysplastic, or have one or a number of genetic mutations, and these crypts were more important than total crypt numbers in assessing risk for colon cancer. In the rodent, data from studies involving carcinogen induction of neoplasia indicate that ACF are associated with the development of colorectal cancer. In experimental studies, ACF of multicrypt foci are associated with the subsequent development of tumors. Generally chemopreventive agents reduce aberrant crypt foci, but this is not always associated with a reduction of colonic tumors. In humans, ACF

increase with age, are associated with the presence of cancer, are not always associated with adenomas, and some ACF's have genetic features that have some similarity with the genetic changes in human colon cancers.

Data from both preclinical and clinical studies that were presented to the FDA by Roche during the original submission for Orlistat approval were described. Wargovich presented the results of a double-blind study conducted in human subjects treated with Orlistat 120mg three times daily [or matching placebo] for six weeks. Colonoscopies and multiple biopsies were performed at the beginning and end of the study, and fecal samples were collected for the last six days of the study periods. The subjects were fed a low-calorie diet [1900 kcals containing 73g fat a day]. Primary endpoints were proliferation assays using BrDU, PCNA, and whole crypt mitotic indices. Secondary endpoints were evaluation of fecal chemistry. The results of the proliferation assays clearly showed no increase in proliferation and some suggestion for a reduction in proliferation in the mid-crypt zones in subjects treated with Orlistat. Fecal excretion data showed some reduction in the secondary bile acids in subjects taking Orlistat, accompanied by a significant fall in fecal pH. The results of this human study certainly indicated no increase in proliferation and possibly a beneficial effect by a reduction of secondary bile acids and fecal pH.

The advisory board was asked to answer a series of questions related to the effects of Orlistat on the colon.

Question 1: Does a high fat diet or fat malabsorption syndromes increase the risk of colorectal cancer in humans?

In rodent models, a high fat diet given in conjunction with an initiating carcinogen, such as AOM or DMH, is associated with an increase in colorectal tumorigenesis. The extent of the induction of colorectal tumors varies depending upon the dietary fat that is fed.

In human observational studies and clinical trials dietary fat does not increase the risk of colorectal neoplasia. There is no evidence that fat-malabsorptive disorders are associated with an increase in colorectal cancer, but the evidence on this topic is limited.

Question 2: What is the relevance of changes in colorectal proliferation and aberrant crypt foci in a rat model to human cancer risks? Is there sufficient evidence to determine that total ACF's in rodents is a validated biomarker for cancer risk in humans?

Changes in epithelial cell proliferation and in total ACF in rodent models provide inconsistent data related to human colon cancer development. It is unlikely that total ACF itself is associated with an increased risk of colon cancer. However, multi-crypt ACF's and the presence of dysplasia in ACF's are likely to increase the risk of cancer.

Animal data on ACF's often are irrelevant to human data on colorectal neoplasia.

In humans, colorectal proliferative data may not be relevant and may be misleading with respect to human colorectal cancer. Although ACF's in humans have been associated with the presence of colorectal neoplasia [and aging], the implications of this finding are yet unknown.

Question 3: What is the relevance of the manuscript by Garcia, et al. in *Cancer Letters* regarding the effect of Orlistat to human cancer risk?

The data presented in this manuscript is consistent with data obtained by Roche in preclinical studies. Namely, short-term (generally less than 4 weeks) orlistat therapy can cause an increase in ACFs in rodents. Data from studies of long duration (generally greater than 9 months) did not show an increase in ACFs. The methods used by Garcia, et al. in their study reported in *Cancer Letters* are not typical of those used in most rodent studies to assess the risk of an intervention [usually a chemopreventive intervention] on colorectal neoplasia. These differences include the type of fat used in the diet (cottonseed oil), method of analysis, and absence of information about food intake.

Furthermore, data obtained in human subjects (unpublished human studies of D.G. Pace, et al.) that were made available to the advisory board showed no effect of Orlistat on colonic proliferation, and suggested a reduction in proliferation in subjects treated with Orlistat compared with placebo.

Question 4: In the scientific advisory board's judgment, does Orlistat increase the risk of colon cancer in humans?

In our judgment there is no evidence that Orlistat increases the risk of colorectal cancer in humans. The reasons for these opinions are:

1. The lack of support and relevance of ACF data in rodent models to human disease.

2. The consensus of evidence from clinical epidemiologic studies that indicate there is no increased risk of colorectal cancer when consuming a high fat diet.

3. Data from study conducted by Pace, et al. which found Orlistat did not increase colorectal proliferation in humans.

Question 5: In our judgment, does Orlistat reduce the risk of colorectal cancer in humans?

In our judgment, there is no evidence that Orlistat reduces the risk of colorectal cancer in humans. However:

1. A reduction in obesity might be accompanied by a reduction in colon cancer in humans.

2. There is a suggestion that orlistat-induced changes in fecal chemistry (i.e. decreased bile acids and decreased pH) might be beneficial in reducing the risk of colorectal neoplasia.