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Joan Claybrook, President

June 5, 2006

Andrew von Eschenbach, M.D., Acting Commissioner
U.S. Food and Drug Administration
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Dear Dr. von Eschenbach:

This letter, based on an investigation published in the current issue of the *Cancer Letter* ("FDA Didn't Tell Advisors About Data Linking Obesity Drug With Precancerous Lesions", attached), supplements our April 10th petition this year to ban the prescription version of orlistat (Xenical) and our January 23rd testimony that opposed making orlistat available over the counter. Four researchers interviewed by the *Cancer Letter* objected to the fact that FDA advisory committee members who met on January 23rd to consider the over-the-counter switch of orlistat were not informed at or prior to the meeting about pre-cancerous changes (aberrant crypt foci or ACF) induced by orlistat in the colon of animals, an outcome documented in two studies.

"This [induction of ACF by orlistat] is the first I've heard of it," Neal Benowitz, a member of the FDA Nonprescription Drugs Advisory Committee told the *Cancer Letter*. Benowitz is a professor of Medicine, Psychiatry, and Biopharmaceutical Sciences at the University of California San Francisco who took part in the Jan. 23rd FDA advisory committee meeting. "This was not in any of the documents that we reviewed. Unless it gets reported by the manufacturer or FDA, or unless someone brings it up who gives testimony, we may not know about this."

In the case of making orlistat available without a prescription, the agency should stay true to its tradition of caution, said Bernard Levin, vice president for cancer prevention at M.D. Anderson Cancer Center told the *Cancer Letter*. "ACF may be an incomplete surrogate marker, [yet] it still points you in the direction that there is something there of concern," "The issue is, how much is it of concern?" The citizen petition filed by Public Citizen makes a compelling argument, Levin said. "The presence of ACF should have been discussed with the advisory

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committee earlier this year" and added "The panel should have an opportunity to develop its conclusions based on all the evidence available." "I respectfully suggest that it would have been prudent for the FDA to seek expert guidance." Levin also told the *Cancer Letter* that the drug should not be available over the counter.

A third researcher, University of Chicago gastroenterologist Marc Bissonnette agreed. "In my estimation, it's [ACF] a reasonable intermediate biomarker to raise concern, if not alarm," Bissonnette told the *Cancer Letter*. He said the agency's apparent decision not to consult advisors on ACF is consistent with its recent failures to detect toxicity in drugs. "That's clearly concerning," he said. "It reminds me of the Vioxx story, unfortunately, and lots of other stories like it."

A fourth researcher interviewed by the *Cancer Letter*, C. Richard Boland, chief of gastroenterology at Baylor University Medical Center in Dallas, said "Regardless of my lukewarm feelings about ACF, if FDA had the data and they withheld it, I think there is a problem there. Obviously, they are bringing the panel in to give them advice, and if you select the data you give them, they are going to give you whatever you've selected for."

Though aberrant crypt foci are far from being validated as a biomarker for either cancer or polyps, "there are substantial data in carcinogen-induced animal models suggesting that ACF correlate with development of more advanced tumors," Monica Bertagnolli, associate professor of surgery at Harvard University, a research scientist at Strang Cancer Prevention Center, and the principal investigator in the NCI study of Celebrex for prevention of recurrence of polyps told the *Cancer Letter*. "Human data to support this, however, are far from conclusive," Bertagnolli said. "The available studies suggest an association between human ACF and the presence of adenomas and/or cancers in the colorectum, but do not show that these lesions are causally linked."

Referring to orlistat's causing an increase in precancerous ACF, the *Cancer Letter* asked, "Should biomarkers that have the misfortune to pop up on the toxicity side be treated differently than those that could represent surrogates for efficacy?" "This is a no-brainer," answered Robert Sandler, professor of Cancer Epidemiology and Cancer Prevention and Control at the University of North Carolina Lineberger Cancer Center. "There are biomarkers for the good, and there are biomarkers for the bad. You have to be even-handed when you deal with them."

Increasingly, the FDA is relying upon surrogate markers of efficacy in approving new drugs. Examples include tumor shrinkage (instead of mortality) for cancer drugs and bone mineral density (instead of fractures) for osteoporosis drugs. Public Citizen has raised questions about the validity of these surrogate markers for efficacy.

We believe that, everything else being equal, surrogate markers for safety rest on a stronger clinical and statistical foundation than surrogate markers for efficacy for three reasons.

- Unless there is a clear demonstration of efficacy, a drug should not be approved. In contrast, safety is a relative concept; it can be evaluated only in the context of the degree of efficacy that has been demonstrated.

- The incidence of an efficacy endpoint is likely to be considerably higher than the incidence of a serious adverse event, making the need for a surrogate marker for efficacy endpoints less critical.

- The multiplicity and diversity of potential adverse events (compared to only one or a few efficacy outcomes) makes measuring adverse events in all cases impractical and necessitates reliance on surrogate adverse event markers. Indeed, many safety concerns are already measured by surrogate markers, e.g., liver function tests and creatinine levels.

For these reasons, we believe that, in general, surrogate marker measurement should be given greater weight in measuring adverse events than surrogate markers in measuring efficacy.

In summary, the FDA (and Glaxo's) decision not to bring to the January 23, 2006 advisory committee the information from the two independent sources that demonstrated that orlistat promotes the formation of ACF shows a recklessness and indifference to the public's health on the part of the agency and the company. Advisory committees are charged with protecting the public health, but they can not do so when drawing from a partial, stacked deck. There is more than enough evidence to take orlistat off the market as a prescription drug and thereby end the process of switching it to over-the-counter status.

Sincerely,

Sidney M. Wolfe MD, Director

Elizabeth Barbehenn

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