



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Waiver to Allow Participation in Food and Drug Administration
Advisory Committee Meeting

DATE: November 14, 2008

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
Food and Drug Administration

THROUGH: Vince Tolino /S/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. /S/
Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. /S/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

Name of Advisory Committee Member: David Harrington, Ph.D.

Committee: Oncologic Drugs Advisory Committee

Meeting Date: December 16, 2008

Description of the Facts on Which the Waiver is Based:

Type, Nature, and Magnitude of Financial Interest(s):

David Harrington, Ph.D., is Chief, Division of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute. A faculty member in the division's Statistical Center has a subcontract with [REDACTED] to provide statistical analysis of data from a study of [REDACTED] in the treatment of colorectal cancer. The subcontract is funded indirectly by [REDACTED] through [REDACTED]. Dr. Harrington has no direct involvement in this activity. His only involvement is managerial as chief of the division. He does not receive any personal remuneration from the funds received. [REDACTED] is an approved competing product to Erbitux (cetuximab) and Vectibix (panitumumab), the two products to be discussed in the context of the types of studies and data needed to establish K-ras mutational status as predictive of response to drug therapy or as prognostic biomarker in colon cancer.

The magnitude of the financial interest is between \$0 - \$50,000.

Description of the Particular Matter to Which the Waiver Applies:

Discussion of Biologics License Application (BLA) 125084, trade name Erbitux (cetuximab), sponsored by ImClone Systems, Inc., and BLA 125147, trade name Vectibix (panitumumab), sponsored by Amgen, Inc., regarding types of studies and data needed to establish K-ras mutational status as predictive of response to drug therapy or as prognostic biomarker in colon cancer.

Additional Facts:

Erbitux (cetuximab) is an Epidermal Growth Factor Receptor (EGFR) inhibitor approved for the treatment of patients who have colorectal cancer that has spread to other parts of the body (1) as a single agent for patients whose disease has progressed after receiving both irinotecan and oxaliplatin for patients who are unable to tolerate chemotherapy with irinotecan; and, (2) in combination with another chemotherapy drug, irinotecan, for patients whose disease has progressed after receiving chemotherapy with irinotecan.

Vectibix (panitumumab) is an (EGFR) antagonist approved as a single agent for the treatment of metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine (i.e., capecitabine, floxuridine, or fluorouracil), oxaliplatin (Eloxatin), and irinotecan (Camptosar) chemotherapy regimens.

Recent study data suggest that colorectal cancer patients whose tumors have mutated K-ras genes do not benefit from treatment with EGFR-inhibitors, such as Erbitux (cetuximab) and Vectibix (panitumumab).

Basis for Granting the Waiver:

First, the funding from [REDACTED] is minimal and does not represent a substantial financial interest.

Second, Dr. Harrington himself has no personal financial interest in either [REDACTED] or [REDACTED]. The fact that this financial interest is imputed to him from his employer should lessen conflict of interest concerns in light of the essential need for his expertise.

Third, Dr. Harrington's only involvement in the project is managerial as Chief of the Division of Biostatistics and Computational Biology at the Dana-Farber Cancer Institute.

Moreover, it is unlikely that committee's recommendations and subsequent FDA action on the particular matter at issue will substantially affect the economic stability of [REDACTED] or its ability or willingness to fulfill its commitment to [REDACTED]. [REDACTED] is a leading global pharmaceutical company that develops and markets therapeutic products in the areas of [REDACTED], [REDACTED] and [REDACTED], as well as [REDACTED].

██████████ disorders and ██████████. In the third quarter of 2008, ██████████
██████████ posted net sales of \$ ██████████.

According to the review division, Dr. Harrington's participation is essential to this meeting because of his unique expertise. Dr. Harrington serves as Professor of Biostatistics at the Harvard School of Public Health and Chair of the Department of Biostatistics and Computational Biology in the Dana-Farber Cancer Institute. Along with his role as a statistician, Dr. Harrington is also a cancer researcher at the Institute. He is a member of the Institute of Mathematical Statistics and has been elected to the International Statistics Institute. His areas of expertise include: non-parametric methods for survival data and collaborative clinical trials. He has authored or co-authored numerous journal articles with areas of interest such as: non-Hodgkin's lymphoma, leukemia, lung cancer and myeloma.

Eleven other statisticians/biostatisticians were invited to this meeting with six of these individuals being unable to attend. Of the five able to attend, three individuals are cleared through conflict of interest screening. One individual requires a waiver.

Dr. Harrington, as the sitting member of the Oncology Drugs Advisory Committee, has a unique expertise for this meeting. The committee will discuss biologic license applications (BLA) 125084, trade name Erbitux (cetuximab), ImClone Systems, Incorporated, and BLA 125147, trade name Vectibix (panitumumab), Amgen, Incorporated, regarding types of studies and data needed to establish K-ras mutational status as predictive of response to drug therapy or as a prognostic biomarker in colon cancer. This is a precedence setting meeting where such issues are expected to recur in the future, and as such, a current member should be in attendance to provide continuity and consistency of statistical thought.

Missing data are common in both prospective and retrospective cohort studies, and simply ignoring cases with missing observations can lead to substantial biases in inference. Dr. Harrington's expertise is in methods for analyzing survival data when some covariates have missing observation. It is this last issue that is expected to be a major discussion point at the meeting. A considerable subset of patients had missing K-ras biomarker status data and Dr. Harrington is knowledgeable both about biomarker validation issues and special trial design considerations required for consideration of a biomarker as part of a clinical trial. He has expertise in the differential design requirements of a biomarker as a prognostic tool as compared to a predictive, and is unique in his ability to provide input, as compared to the other attending statisticians. In addition, his familiarity of the two products under consideration, their applications were discussed at previous Oncologic Drugs Advisory Committee meetings, will provide insights that consultants who were not in attendance cannot provide.

The division feels strongly that Dr. Harrington has the background and expertise to lead an appropriate and stimulating discussion during the meeting. His knowledge of clinical trial design and his experience as a biostatistician and cancer researcher will bring required knowledge to this meeting.

Accordingly, I recommend that you grant a waiver under 18 U.S.C. § 208(b)(3) for David Harrington, Ph.D., a member of the Oncologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. § 208(b)(a).

Certification:

The individual may participate – The need for the Special Government Employee's services outweighs the potential for a conflict of interest.

Limitations on the Regular Government Employee or Special Government Employee's Ability to Act:

Non-voting

Other (specify):

Denied – The individual may not participate.

RS/
Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy

11/25/08
Date