



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 /5/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. /5/
Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. /5/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

Name of Advisory Committee Member: Derek Raghavan, M.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):

Dr. Derek Raghavan's employer, the Cleveland Clinic Taussig Cancer Institute, has a contract with [REDACTED] for a study of [REDACTED] in advanced colorectal cancer for second line therapy. Dr. Raghavan's only involvement in the study is managerial as chair and director of the Cleveland Clinic Taussig Cancer Institute. He does not receive any personal remuneration or salary support from the funds received.

[REDACTED]
[REDACTED] in colon cancer.

The magnitude of the financial interest is between \$50,001 - \$100,000.

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 portion of the Cleveland Clinic's total research budget. In 2007, the Clinic's total grant and contract revenue was \$ [REDACTED].

Second, Dr. Raghavan himself has no personal financial interest in [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. Raghavan's only involvement in the study is managerial as chair and director of the Cleveland Clinic Taussig Cancer Institute.

Moreover, it is unlikely that committee's recommendations and subsequent FDA action on the particular matter at issue will substantially affect the [REDACTED] sponsored trial or the economic stability of firm. [REDACTED] is a global [REDACTED] company that markets human therapeutic products in the areas of [REDACTED], [REDACTED], and [REDACTED]. In the third quarter of 2008, the company reported global sales of \$ [REDACTED].

Further, according to the Office of Oncology Drug Products, Dr. Raghavan's participation is necessary to afford the advisory committee essential expertise. Dr. Raghavan currently holds the position of the M. Frank and Margaret Domiter Rudy Distinguished Chair in Translational Cancer Research at the Cleveland Clinic. He currently serves as a Member on the Genitourinary Task Force of the American Joint Committee on Cancer and is a member of the Southwest Oncology Group. Dr. Raghavan has published over 200 journal articles in such journals as the *New England Journal of Medicine* and *Lancet*.

Dr. Raghavan's expertise is in Medical Oncology. Seven Medical Oncologists were invited to this meeting. However, two of these individuals were recused through conflict of interest screening and another did not respond to the invitation. Of the four able to attend, one needs a waiver.

Dr. Raghavan is a past member of the Oncologic Drugs Advisory Committee (ODAC), serving as an ad-hoc member for one year and as an official member of the committee from 1997-2000, thus he is well-acquainted with the standards used by FDA for new regulatory claims. He is also an expert in clinical trial design as evidenced by his service on multiple review committees and as chair/principal investigator for numerous phase 1, 2, and 3 clinical trials. In addition, Dr. Raghavan is an expert in the field of genitourinary cancers, a field in which the use of genetic and phenotypic tumor characteristics are regularly evaluated for consideration of appropriate therapy and treatment decisions. Because the use of tumor markers has not been utilized to characterize prognosis or treatment management in colon cancer, there is a need to include experts on the committee with such experience in other cancer types where these issues have been considered for several decades. Of note, Dr. Raghavan is a recognized expert having served as the Chair for the American Society for Clinical Oncology, Subcommittee on Practice Guidelines for Locally Advanced Prostate Cancer, an author on the National Comprehensive Cancer Network (NCCN) urothelial cancer practice guidelines, and as a member of the NIH Prostate Specialized Programs of Research Excellence (SPORE) Review Committee, 1992. He has written extensively in peer reviewed literature on the topics relating to the use of assay methods and interpretation of such assays for use in treatment and prognosis of urothelial tumors including interpretation of marker protein assays, prognostic factors in clinical stage I non-seminomatous germ-cell tumors of the testis, assessment of serum alpha-fetoprotein in seminoma, detection of tumor-associated membrane proteins in prostate and bladder carcinomas by means of protein blotting, and molecular biology of urological cancer and has authored numerous chapters on tumor markers used in the management of male and female genitourinary tumors.

Locating qualified individuals without disqualifying financial interests to serve on this advisory committee has been difficult, even after screening all committee members and numerous special Government employees. It is imperative that the committee have a sufficient number of members with an expertise in Medical Oncology and the use of tumor markers in order to have a meaningful discussion at the meeting. The Office of Oncology Drug Products feels strongly that Dr. Raghavan brings essential experience and expertise to this meeting and wish to have him act as chair for this meeting. In

