Summary Minutes of the
Oncologic Drugs Advisory Committee Meeting
February 8, 2011
Location: FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the February 8, 2011 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on ___April 7, 2011_____.

I certify that I attended the February 8, 2011 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

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Nicole Vesely, Pharm.D.	Wyndham Wilson, M.D., Ph.D.
Designated Federal Officer, ODAC	Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on February 8, 2011 at the FDA White Oak Campus, Building 31, the Great Room, White Oak Conference Center (Rm. 1503), 10903 New Hampshire Avenue, Silver Spring, MD 20993-0002. Prior to the meeting, members and invited consultants were screened and cleared for conflict of interest, and provided copies of the background material from the FDA and the sponsors. The meeting was called to order by Wyndham Wilson, M.D., Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Officer). There were approximately 150 persons in attendance. There were zero (0) speakers for the Open Public Hearing session.

Issue: The committee heard updates on new drug applications (NDAs) and biologics license applications (BLAs) approved under 21 CFR 314.500 and 601.40 (subpart H and subpart E, respectively, accelerated approval regulations) prior to January 1, 2009. These updates will provide information related to the status of phase IV clinical studies and to difficulties associated with completion of phase IV commitments. Phase IV studies are postmarketing studies to confirm clinical benefit of a drug after it receives accelerated approval.

Specifically, the committee received updates on the following products: (1) BLA 125084, trade name ERBITUX (cetuximab), application submitted by Imclone Systems Inc., used in combination with the anticancer agent irinotecan and indicated for the treatment of epidermal growth factor receptor (EGFR)-expressing colorectal cancer that has metastasized (spread beyond the colon or rectum) in patients for whom chemotherapy using irinotecan alone is ineffective or less effective; (2) supplemental BLA (sBLA) 125011/24, trade name BEXXAR (tositumomab and Iodine I 131 tositumomab), application submitted by SmithKline Beecham Corp. doing business as (d/b/a) GlaxoSmithKline, indicated for the treatment of patients with varieties of non-Hodgkin's lymphoma known as CD20 antigen-expressing relapsed or refractory, low grade, follicular, or transformed non-Hodgkin's lymphoma, who have not received the drug Rituximab; (3) NDA 21-673, tradename CLOLAR (clofarabine) for intravenous infusion, application submitted by Genzyme Corp., indicated for the treatment of pediatric patients 1 to 21 years old with acute lymphoblastic leukemia (ALL) whose disease has not responded to or has relapsed following treatment with at least two prior chemotherapy regimens; (4) NDA 21-877, tradename ARRANON (nelarabine) Injection, application submitted by GlaxoSmithKline, indicated for the treatment of patients with types of leukemia or lymphoma known as T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens; (5) BLA 125147, tradename VECTIBIX (panitumumab), application submitted by Amgen Inc., indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens; and (6) sNDA 21-588/025, tradename GLEEVEC (imatinib mesylate) tablets, application submitted by Novartis Pharmaceuticals Corp., indicated for the adjuvant (additional) treatment of adult patients following complete gross resection (removal) of a form of cancer known as Kit (CD117) positive gastrointestinal stromal tumors (GIST).

Based on the updates provided, the committee had a general discussion centering on possible ways to improve the planning and conduct of trials to confirm clinical benefit (post marketing requirements). The overall goal will be the optimization of the accelerated approval process with a focus on decreasing the amount of time to confirm (or fail to confirm) clinical benefit while continuing to provide early availability of promising oncology products.

Attendance:

Oncologic Drugs Advisory Committee Members Present (Voting):

Ralph Freedman, M.D., Ph.D., William Kelly, D.O., Patrick Loehrer, Sr., M.D., Brent Logan, Ph.D., Virginia Mason, R.N. (Consumer Representative), Mikkael Sekeres, M.D., M.S., Wyndham Wilson, M.D., Ph.D. (Committee Chair)

Special Government Employee Consultants (Temporary Voting Members):
Frank Balis, M.D., Ralph D'Agostino, Ph.D., Gary Lyman, M.D., M.P.H., Silvana Martino, D.O., Musa Mayer, M.S. (Patient Representative), Joanne Mortimer, M.D., Ronald Richardson, M.D.

Regular Government Employee Consultants (Temporary Voting Members):
Malcolm Smith, M.D., M.P.H

Oncologic Drugs Advisory Committee Member (Non-Voting):
Gregory Curt, M.D. (Industry Representative)

Guest Speaker (Non-Voting, Presenting Only):
Hilde Boone, Pharm. MSc

Oncologic Drugs Advisory Committee Members Not Present:
Jean Grem, M.D., F.A.C.P.
Margaret Tempero, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Anthony Murgo, M.D., M.S., Paul Kluetz, M.D., Lee Pai-Scherf, M.D. (Erbitux Only), Ruthann Giusti, M.D. (Bexxar & Vectibix Only), Suzanne Demko, P.A.-C. (Erbitux, Bexxar & Vectibix Only), Martin Cohen, M.D. (Clolar, Arranon & Gleevec Only), John Johnson, M.D. (Clolar, Arranon & Gleevec Only)

Designated Federal Officer:
Nicole Vesely, Pharm.D.

The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D., Ph.D.** Chair, ODAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Officer, ODAC
Opening Remarks	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER, FDA
FDA Presentation Accelerated Approval (AA) for Oncology Drug Products: An Update and Regulatory Overview	**Paul Kluetz, M.D.** Medical Officer, Division of Drug Oncology Products
FDA Presentation Accelerated Approval Overview of HIV Drug Approvals	**Jeff Murray, M.D., M.P.H.** Deputy Director, Division of Antiviral Products
Sponsor Presentation	**Eli Lilly and Co. – Erbitux**

Erbitux (cetuximab): Erbitux in the treatment of metastatic colorectal carcinoma (mCRC)	**Colleen Mockbee, Pharm.D.** Senior Director, Regulatory Affairs Eli Lilly & Company

Questions from Committee to Sponsor

Sponsor Presentation Bexxar Therapeutic Regimen (Tositumomab and Iodine I 131 Tositumomab) Post-marketing Commitments	**GlaxoSmithKline – Bexxar** Thomas S. Lin, M.D., Ph.D. Director, Clinical Development GSK Oncology

Questions from Committee to Sponsor

Sponsor Presentation Clolar® (clofarabine) Pediatric Relapsed/Refractory Acute Lymphoblastic Leukemia	**Genzyme Corp. – Clolar** **Mark Hayes, Ph.D.** Group Vice President Genzyme Regulatory Affairs

Questions from Committee to Sponsor

Sponsor Presentation Arranon (nelarabine) Injection Accelerated Approval Update	**GlaxoSmithKline – Arranon** **Mark Russo, M.D., Ph.D.** GSK

Questions from Committee to Sponsor

Sponsor Presentation Vectibix®(panitumumab) Accelerated Approval Status	**Amgen, Inc. – Vectibix** **Paul Eisenberg, M.D., M.P.H.** Global Regulatory Affairs & Safety, Amgen, Inc.

Questions from Committee to Sponsor

Sponsor Presentation Gleevec Adjuvant GIST Accelerated Approval ODAC	**Novartis Pharmaceuticals Corp. – Gleevec** **Laurie Letvak, M.D.** Vice President, Global Program Head Novartis Pharmaceuticals Corp.

Questions from Committee to Sponsor

Speaker Presentation Conditional Marketing Authorisations in the European Union (EU)	**Hilde Boone, Pharm, MSc (Guest Speaker)** European Medicines Agency Liaison Official at the US FDA

Questions to the ODAC and ODAC Discussion

Questions to the ODAC and ODAC Discussion (continued)

Questions to Committee:

The Oncologic Drugs Advisory Committee will discuss the accelerated approval process. To focus the discussion, the following non-voting questions will be posed to committee members. The first question pertains to studies supporting the initial accelerated approval. The remaining questions apply to post-marketing studies designed to confirm clinical benefit.

1. SINGLE ARM TRIALS TO GAIN ACCELERATED APPROVAL

Single arm trials have formed the basis for 29/49 or over half of the accelerated approvals for oncology drugs to date. While single arm trials often require less resources and time to complete, they provide limited data on clinical benefit and safety. Single arm trials for accelerated approval have usually been performed in refractory populations where no available therapy exists. As a greater number of drugs are approved, identification and documentation of a refractory population is increasingly problematic. In addition, marginal response rates observed in single arm trials in a refractory setting make it difficult to determine whether the findings are "reasonably likely" to predict clinical benefit.

Alternatives to a single arm trial in a refractory population include randomized trials in a less refractory population against an active control using a surrogate endpoint analyzed at an earlier time point or a randomized trial in a refractory population comparing the investigational agent to best supportive care or various agents selected by investigators. Randomized trials provide the opportunity to look at a wider variety of endpoints and allow for an improved characterization of safety.

DISCUSS: Given the problems with single arm trials, discuss scenarios where a randomized study should be required for accelerated approval. Alternatively, please discuss situations where single arm trials may be appropriate to support an accelerated approval.

Overall, members agreed that randomized controlled trials should be the standard and that single arm trials should be the exception. Committee members commented that single arm trials may be used in the following situations: 1) rare diseases and 2) high level of activity of the agent or pronounced treatment effect. It was also mentioned that the toxicity of the agent must be taken into account in a risk/benefit analysis in the situations in which single arm trials may be used. Committee members noted that it would be helpful to have a definition of rare diseases. Members also noted that the bar for accelerated approvals should not be lowered to move products on to the market faster through single arm trials, but rather single arm trials should only be used in certain situations and randomized controlled trials should be the standard.

Please see transcript for detailed discussion.

2. NUMBER OF CONFIRMATORY TRIALS

The time from either successful completion of a required post-marketing study or withdrawal of the indication can be prolonged. For drug approval in most therapeutic areas outside of oncology, two well-designed randomized trials are usually required. In oncology, the FDA has frequently approved drugs on the basis of a single well-conducted trial. The FDA usually receives proposals for a single trial to be conducted post-approval to demonstrate clinical benefit for drugs receiving accelerated approval. However, in the setting of accelerated approval, when only one confirmatory post-marketing trial is conducted, there is the increased risk that clinical benefit will not be demonstrated in a timely manner if

that single trial fails to confirm a benefit or does not accrue patients as rapidly as planned. This may lead to either withdrawal of the indication or the need to conduct a second trial, resulting in substantial delays.

DISCUSS: Discuss whether applicants should be required to conduct at least two adequate and well-controlled clinical trials as their accelerated approval commitment to verify clinical benefit.

Overall, members agreed that at least two controlled trials should be needed for accelerated approval commitments. Most members agreed with this statement with the caveat that in rare diseases and pediatrics this may not be feasible. Members commented that only conducting one trial that ends up lacking robust results would further delay time to meeting commitments as a second trial would then need to be planned and conducted. Members then noted that a prospective, well designed development plan is also needed to decrease the time to meet accelerated approval commitments.

Please see transcript for detailed discussion.

3. TIMING OF CONFIRMATORY TRIALS

Accelerated approval regulations clearly state that post-marketing trials "**would usually be underway at the time of accelerated approval**." Once a drug gains accelerated approval in a refractory disease stage, accrual to a confirmatory trial in the same setting is difficult. Pursuing a confirmatory clinical trial in a less refractory setting can potentially circumvent this problem. However, changes in science, accrual challenges and other hurdles may lead to delays. The FDA believes that more timely completion of accelerated approval confirmatory trials can be enhanced if accelerated approval is granted when the confirmatory trial is on-going.

DISCUSS: Given the regulations state that confirmatory trials would usually be underway at the time of accelerated approval, discuss whether an approval should be delayed until such trials are ongoing, keeping in mind that access to not yet marketed drugs could be accomplished under expanded access programs if a delay is anticipated.

Overall, members felt that a well designed development plan is needed prior to the application being filed. Most also preferred that the sponsor have studies already ongoing at the time of application.

Please see transcript for detailed discussion.

4. THE USE OF COOPERATIVE GROUPS TO CONDUCT CONFIRMATORY TRIALS

The FDA recognizes that cooperative groups, both in the United States and Europe, are critical to drug development and encourages their participation throughout the drug discovery process.

Applicants may engage a cooperative group to design and execute a confirmatory trial to fulfill their regulatory obligation. However, the ultimate responsibility of completing the confirmatory trial with due diligence rests with the applicant. This fact may hold added importance to sponsors with the introduction of substantial financial penalties (2007 FDAAA) for lack of timely completion of these trials at the agreed upon dates.

DISCUSS: Please discuss the use of a cooperative group to conduct the trial(s) required to demonstrate clinical benefit to fulfill their accelerated approval obligation. If a cooperative group

is used, discuss whether an additional trial(s) should be conducted under the direct supervision of the applicant to ensure adherence to completing post marketing require

Members agreed that it is the responsibility of the sponsor to meet their post marketing requirements. If sponsors decide to use a cooperative group to meet these requirements, it is the responsibility of the sponsor to ensure that the requirement is met, not the cooperative group(s). Members also noted that cooperative groups are a useful mechanism, however, in situations where timelines must be met and penalties may be enforced, cooperative groups may not always be the appropriate mechanism. Members also noted that changes are being put in place within cooperative groups that may lessen some of the issues that have arisen in cooperative group trials. As in question 2, members overall agreed that two well-controlled trials should be needed for accelerated approval commitments and in addition, members commented that one of these trials could be a cooperative group trial. It was also noted that cooperative groups should be included prospectively in the development design plan for the agent.

Please see transcript for detailed discussion.

Meeting adjourned at approximately 4:45 p.m.