Summary Minutes of the Oncologic Drugs Advisory Committee
September 6, 2006:

The summary minutes for the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee were approved on September 13, 2006.

I certify that I attended the September 6, 2006 meeting of the Oncologic Drugs Advisory Committee and that these minutes accurately reflect what transpired.

/s/	/s/
Johanna Clifford, M.Sc., RN Executive Secretary, ODAC	Maha Hussain, M.D., Acting Chair, ODAC

The meeting of the Oncologic Drugs Advisory Committee was held in the Maryland Ballroom, Hilton Washington DC/Silver Spring, Silver Spring, MD. Approximately 150 people were in attendance. The meeting was chaired by Maha Hussain, M.D.

The committee met to discuss new drug application (NDA) 20-287, proposed trade name FRAGMIN ® (dalteparin sodium) Injection, Pfizer, Incorporated, with proposed indication for the extended treatment of symptomatic venous thromboembolism (VTE), proximal deep vein thrombosis (DVT), and/or pulmonary embolism (PE) to reduce the recurrence of VTE in patients with cancer.

Attendance:
Oncologic Drugs Advisory Committee Members Present (voting):
Ronald Bukowski, M.D., Maha Hussain, M.D. (Chair), David Harrington, Ph.D., Pamela Haylock, M.D., Alexandra Levine, M.D., Michael Perry, M.D., Maria Rodriguez, M.D.,

Oncologic Drugs Advisory Committee Consultants (voting):
Stephen George, D. Sc.; William Hiatt, M.D. (Cardio-Renal Committee); Karl Schwartz (patient representative); Michael Link, M.D., Gary Lyman, M.D., MPH.

Industry Representative (non-voting):
Antonio Grillo-Lopez, M.D.

Oncologic Drugs Advisory Committee Members Absent:
James Doroshow, M.D., S. Gail Eckhardt, M.D., Joanne Mortimer, M.D.

FDA Participants:
Richard Pazdur, M.D., Rafel Rieves, M.D.; Andrew Dmytrijuk, M.D.; Kathy Robie-Suh, M.D.; Jyoti Zalkikar, Ph.D.

Open Public Hearing Participants:
Frank Burroughs & Steve Walker, Abigail Alliance

The agenda proceeded as follows:

Sponsor Presentation	**Pfizer, Inc**
Introduction	Connie Newman, M.D. Therapeutic Area Head, CVMED Worldwide Regulatory Affairs and Quality Assurance
Background on VTE and Cancer	Craig Eagle, M.D., Senior Director Head of Worldwide Medical Oncology
CLOT Study Design & ITT Results	Agnes Y.Y. Lee, M.D., M.Sc., FRCPC Associate Professor, Medicine, McMaster University Hamilton Health Sciences Henderson Hospital Hamilton, ON
CLOT Study Further Analyses	Craige Eagle, M.D.
Conclusion	Craig Eagle, M.D.

FDA Presentation
FDA Review of Clinical Data:
Fragmin for treatment of VTE
in cancer patients

NDA 21-986
Amdrew Dmytrijuk, M.D., Medical Officer
Division of medical Imaging and Hematology
OODP, CDER, FDA

Questions from the Committee

Open Public Hearing

Questions to the Committee

MEETING QUESTIONS

1. Safety: The FDA review of the CLOT study cited a potentially important mortality safety signal related to the study drug discontinuation findings. Discontinuation of the assigned study drug due to death was twice as common among patients receiving Fragmin as it was among patients receiving OAC. The cause for this imbalance is unclear and not explained by findings within the CLOT study database. For example, the database did not show an excess in fatal hemorrhage among patients receiving Fragmin. Post-hoc hypotheses, such as the possibility of informative censoring, have been proposed to account for the study drug discontinuation finding. Regarding the excessive number of Fragmin discontinuations due to death:

VOTE: Do you regard the study drug discontinuation due to death finding as sufficient to preclude the approval of the application until the issue is resolved with additional clinical studies?

Yes = 0 ***No = 12***

Overall the committee felt that the explanation provided for deaths and study drug discontinuation in both arms of the study was sufficient, although misleading, due to coding issues, differing patient management in either arm, etc. The committee felt that based on this aspect alone (study drug discontinuation), ruling out approval was not appropriate.

2. Efficacy: In order to rely on a single clinical study for definitive evidence of safety and efficacy, the primary efficacy endpoint result should be a robust finding. Special considerations in evaluating the CLOT study's primary endpoint result include the open label nature of the study, the differing anticoagulation management between the study groups, the endpoint's competing risk with mortality, possible bias in VTE symptom detection and inconsistencies in exploratory analyses of the primary endpoint result.

VOTE: Considering these endpoint limitations, does the CLOT study provide substantial evidence of effectiveness?

Yes = 12 ***No = 0***

The committee voted unanimously that despite the endpoint limitations, the study provided substantatial evidence of effectiveness. Although there were multiple reservations noted. Specifically, that the study has not proved the long-term use (additional 5 months) of the product and that the study could have been "cleaner" with respect to anticipation of the high mortality rate and more standardization of VTE ascertainment between the study groups.

3. Safety and Efficacy: If you provide favorable responses to the preceding safety and efficacy questions ("no" to safety question 1 and "yes" to efficacy question 2):

VOTE: Does the totality of the CLOT study's safety and efficacy results provide a benefit to risk relationship sufficient to warrant approval of this supplemental marketing application?

Yes = 12 ***No = 0***

Although the committee felt that the data presented does, in fact, warrant concern by the committee and the FDA, with further explanation of the death due to the disproportionate "on treatment" censorship of the deaths, the committee felt comfortable with the overall death curves presented in the data and thus overwhelming felt that the evidence provided in the CLOT study's result did warrant approval of the product.

4. Label Considerations: The CLOT study included predominantly patients with advanced (metastatic) cancer. Exploratory subset analyses did not support an apparent treatment effect within the subsets of patients with hematological malignancies or patients with non-metastatic cancer.

a. VOTE: If marketing approval is recommended, should the product label limit the indicated patient population to a subset of "cancer patients" (for example, only patients with metatstatic, non-hematologic cancer)?

Yes = 2 ***No = 10***

The committee felt that there was not enough evidence to limit the patient populations in the labelling to those with particular malignancies, expressing some concern with the subgroup analysis which they felt were difficult to interpret and not really valid. In addition, the committee expressed an interest in seeing post marketing data in the specific categories of patients with more limited disease.

b. DISCUSSION: If you vote to limit the indicated patient population, please discuss any important patient population limitations.

5. Additional Clinical Studies: The CLOT study was conducted among "cancer patients" and included predominantly patients with advanced (metastatic cancer). Limitations in the study design were cited above.

DISCUSSION: If marketing approval is not recommended, please describe the types of clinical data the sponsor should submit to support approval, including any important study design considerations and the potential need for study of patients without cancer or the study of specific cancer patient populations.

The committee did not address this question.

The meeting adjourned at approximately 5:00 p.m.