FDA Conference Call: August 13, 2002

FDA Personnel:

Jeri El-Hage, Toxicology Team Leader
Jena Weber, Project Manager

TPNA Personnel:

David Baron, Ph.D., Director, Nonclinical
Janet Haskins, Manager, Regulatory Affairs
Pat Frank, Ph.D., TPNA Consultant

The purpose of this conference call was so that Dr. El-Hage, could express her concerns and findings regarding the nonclinical data shared with TPNA during the July 31, 2002 conference call.

Dr. El-Hage noted that in light of the fact that several compounds that are dual PPAR agonist have discontinued development due to transitional cell tumors in the bladder and kidneys of male and female rats and in male mice, the Division is becoming concerned. She also noted that in follow-up studies, there was no irritation or formation of calculi noted.

Dr. El-Hage then noted that a promoter-model study was conducted by another company in which pioglitazone was given. The study was designed as follows:

- BBN was given to Fisher rats in their drinking water for four-weeks
- Groups are:
  - Pioglitazone 40 mg/kg/day plus BBN
  - Their compound (no dosages given, but Dr. El-Hage noted it was multiple) plus BBN
  - The control group just received the BBN.
- Duruation was 32-weeks
- Results:

- 85% of the animals in the pioglitazone and the other company's compound group had tumor formation. Either group had calculi formation.
- 15% of the animals in the control group had tumor formation, with around 50% of those having calculi formation.

Based on these findings, and the fact that the other dual PPAR agonist have discontinued from development, the Division does not feel that the general population is being adequately informed about the possible risk of dual PPARs. Dr. El-Hage shared with TPNA that before the other dual PPAR agonist discontinued development they were being required to monitor for bladder tumors in their clinical studies. She noted that the Division's internal consultant suggested screening urine for NMP-22, which Dr. El-Hage believes is approved for screen of bladder tumors and is commercial available.

Finally Dr. El-Hage noted that she is trying to bring these findings to the CAC board in mid-September. She will inquire if they feel that the pioglitazone package insert adequately addresses our data and the data that the Divisions has. She suggested that TPNA might consider adding the following sentence to our package insert: "Increase bladder and renal transitional cell tumors were seen in other compounds in the same class of drugs."