Teleconference Minutes

Date: July 30, 2001 **Time:** 1:00-1:40 PM, EDT **Location:** Parklawn; 17B-43

NDA 21-319 **Drug:** dutasteride **Indication:** Benign prostatic hyperplasia

Sponsor: Glaxo SmithKline

Type of Meeting: Clarification

Meeting Chair: Ameeta Parekh, Ph.D., Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, OCPB @ DRUDP (HFD-580)
Sayed Al-Habet, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Munir Abdullah, Ph.D. - Product Director, Regulatory Affairs
Linda Haberer, Ph.D. – Clinical Pharmacokineticist IV, GlaxoWellcome
Benedicte Ricci, Ph.D. – Clinical Pharmacokineticist IV, GlaxoWellcome
Ross Yager, Ph.D. - Drug Metabolism and Pharmacokinetics

Meeting Objective: To obtain further clarification regarding the metabolism studies.

Background: The sponsor submitted NDA 21-319 on December 21, 2000, for dutasteride soft-gelatin capsules to be used for the treatment of symptomatic BPH in men with an enlarged prostate gland. In support of this NDA, the sponsor submitted three Phase III trials, ARIA 3001, ARIA 3002 and ARIB 3003. During the December 5, 2000, pre-NDA meeting, the sponsor indicated that quantification of the metabolite was anticipated by the first quarter of 2001, and that mutagenicity testing would be conducted by the middle of 2001. The April 20, 2001, 120-day Safety Update Report included an update of the non-clinical and clinical studies that were ongoing at the time of the NDA submission. In the May 8, 2001, teleconference, the sponsor agreed to: "submit results of metabolite data from the blood samples from the carcinogenicity studies quantitating dutasteride metabolites in June 2001, preliminary data estimating the percentage of metabolites in human serum, preliminary results of a 90-day rat study and of an Ames test in July 2001, and final results of metabolite exposure study in rats in August 2001." In the July 20, 2001, correspondence the sponsor submitted changes to the proposed label; an overview on safety considerations on the

metabolism of dutasteride and metabolite data information from recently completed nonclinical studies; and a final study report to evaluate the metabolic fate of dutasteride.

Discussion:

- the sponsor clarified the following:
  - while quantitative data is available only for the 4-hydroxy metabolite, only qualitative data is available for the two major metabolites and the two minor metabolites of dutasteride; analytical standards to quantify the minor metabolites are not available
  - there is no evidence at this time indicating that the concentration of any of the metabolites is greater than that of the parent compound
  - summary report addressing qualitative assessment of dutasteride metabolites is located in the July 20, 2001 submission (Study RD 2001-00-969-00) (it was noted that this is a one page summary related to the metabolism in rats)
  - as agreed in the May 8, 2001 teleconference, only summaries would be provided since the final study reports (with data) could not be provided prior to the NDA goal date
- regarding urine and feces concentration of dutasteride and its metabolites, it was clarified that:
  - fluorine NMR testing indicates that the amount of the parent compound and its metabolites is not significant in urine, particularly when compared to feces, even though these results are qualitative and not quantitative
  - report RD 1999/02818/00, included in the April 20, 2001, 120-day safety update, includes data regarding the percentages of the metabolites recovered in the feces; this study lists only peak ratios, not quantitative measures because the actual amounts have not been identified
  - approximately 42 to 45% of the dose was recovered in the feces, based on steady state data that was averaged over two 3-day collection periods; there is about 55% of the dose that is unaccounted for, due to technical difficulties
- the sponsor indicated that there is one IV study, but metabolites were not monitored; lack of recovery of metabolites is not considered a safety concern, based on animal studies, recovery was about 97% in mass balance studies in dogs
- according to the sponsor, *in vitro* metabolic studies indicate that the CYP 3A4 isoenzymes are the primary isoenzymes for dutasteride metabolism; the sponsor also indicated that CYP 3A4 is responsible for only 4% of the metabolism of the drug *in vitro*; no other isoenzymes were known to be involved in the metabolism of the drug
  - verapamil, diltiazem and amlodipine were the only concomitant drugs taken by subjects analyzed in the population PK studies; there is no data on ketoconazole or other strong CYP 3A4 inhibitors, as concomitant drugs from the population PK studies
  - DRUDP recommends that the sponsor provide scientific rationale to indicate the contribution of the CYP 3A4 isoenzymes, and what the effect of potent CYP 3A4 inhibitors will be on the concentrations of dutasteride and its metabolites
  - DRUDP recommends also that the sponsor submit data on the activity of dutasteride metabolites; the sponsor indicated that data on the activity of some of the metabolites have been submitted previously in the April 20, 2001 and the July 20, 2001 submissions
  - DRUDP has concerns about a potential drug interaction with ketoconazole or other CYP 3A4 inhibitors assuming that dutasteride is extensively metabolized by CYP 3A4
- *in vitro* data does not agree with results in humans; language in the proposed label was included to conform with the language recommended by the FDA
- it would be helpful if the sponsor would submit the results of the sparse sampling study electronically; the sponsor indicated that the population PK analysis was submitted in February 2001 in manuscript form; population PK studies did not include renal and hepatic impaired patients

Decisions made:

- the sponsor will provide the scientific rationale indicating the contribution of the CYP 3A4 isoenzymes, the effect of potent CYP 3A4 inhibitors on the concentration of dutasteride and its metabolites, as well as the activity of dutasteride metabolites
- the sponsor will submit the results of the sparse sampling study electronically if necessary

Action Items:

- minutes will be sent to the sponsor in 30 days
- the sponsor will submit a rationale for the contribution of CYP 3A4 on the metabolism of dutasteride, and the effect of potent CYP 3A4 inhibitors on dutasteride metabolism

Minutes Preparer **Concurrence, Chair**

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

MEMORANDUM OF TELECON

DATE: August 2, 2001

APPLICATION NUMBER: NDA 21-319, dutasteride

BETWEEN:

Name: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs
Phone: 919-483-9318
Representing: Glaxo SmithKline

AND

Name: Evelyn R. Farinas, Regulatory Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: request for additional toxicology information

The following information was faxed to the sponsor subsequent to the August 2, 2001 teleconference:

The Carcinogenicity Assessment Committee has just reviewed your response to the CAC's request for historical data for liver tumors in B6C3F1 mice for Dutasteride, NDA #21319. CAC would like to see the dietary carcinogenicity study controls for the same strain and time period for the contract facility used, if gavage studies were not performed during that period. CAC would like to see those data and other data used to support lack of statistical significance submitted in the form of means and standard deviations, as well as ranges, or they would like to see the data as tabulated lists of results from individual studies.

Evelyn R. Farinas
Regulatory Project Manager

Teleconference Minutes

Date: August 3, 2001 **Time**: 2:30-2:45 PM, EST **Location**: PKLN; 17B45

NDA 21-319 **Drug**: dutasteride **Indication**: BPH

Sponsor: Glaxo SmithKline

Chair: Laurie McLeod, Ph.D, Toxicology Reviewer, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

Minutes Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA attendees:
Laurie McLeod, Ph.D. - Toxicology Reviewer, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. - Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Munir Abdullah, Ph.D. – Product Director, Regulatory Affairs
Jackie Greene – Project Director
James Myers – Safety Assessment

Objective: To clarify recent request for submission of statistical data.

Background: The sponsor was asked to submit historical data for liver tumors in B6C3F1 mice for review by the Carcinogenicty Assessment Committee (CAC). As follow up, the CAC requested that the sponsor submit the dietary carcinogenicity study controls for the same strain and time period for the contract facility used, if gavage studies were not performed during that period. In addition, the sponsor was asked to submit any other data used to support lack of statistical significance. This data should be submitted in the form of means and standard deviations, as well as ranges, or as tabulated lists of results from individual studies. These requests were faxed to the sponsor on August 2, 2001.

Discussion:

- DRUDP clarified that:
  - in order to complete the statistical analysis of the historical data, the CAC needs data from gavage studies or from dietary studies from the same period in B6C3F1 mice; these studies should provide the standard deviation, not just the range
  - the CAC needs data that shows that the figures provided are within range statistically
  - the sponsor should submit as many studies from that period as possible (at least five or six studies), including the number of animals per control group, and the number of animals with tumors (not the range nor the average)
- the sponsor indicated that:
  - the available data is from three older dietary studies (started in 1986, 1991, and 1993, respectively); this data includes combined histophathology summary totals and historical control databases with the number of animals and the percentage of animal affected

- additional information in support of their findings was derived from a 1998 NIEHS article

Decisions made:

- the sponsor will submit the information from the three dietary studies to DRUDP, and the article from NIEHS as supporting evidence
- the sponsor will verify with [redacted] if additional rat dietary studies have been conducted
- DRUDP will accept the NIEHS publication in lieu of individual studies as supporting evidence, if this article shows standard deviation data from individual studies

Action items:

- data from the three dietary studies, as well the 1998 NIEHS article, will be sent to DRUDP by the sponsor (*facsimile received on August 3, 2001, containing data from the three dietary studies and selected excerpt from the NIEHS articles containing liver tumor specific information)*
- minutes to be sent to the sponsor in 30 days

Minutes Recorder

Chair

Note to the sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Minutes

Date: September 25, 2001 **Time:** 3:00-3:30 PM, EDT **Location:** Parklawn; 17B-43

NDA 21-319 **Drug:** dutasteride **Indication:** symptoms of benign prostatic hypertrophy

Sponsor: Glaxo SmithKline

Type of Meeting: Guidance

Meeting Chair: Jean Salemme, Ph.D., Chemist, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Bekki Komas, Assistant Director, Regulatory Affairs, US CMC Submissions, Worldwide Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Jean Salemme, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Participants:
Bekki Komas – Assistant Director, Regulatory Affairs, US CMC Submissions, Worldwide Regulatory Affairs, Glaxo SmithKline
Ralph Caricofe - Glaxo SmithKline
Steve Meyerhoffer - Glaxo SmithKline

Meeting Objective: To discuss and further clarify for the sponsor the deficiencies listed in the August 20, 2001, FDA Information Request Letter.

Background: In a letter to Glaxo SmithKline, dated August 20, 2001, DRUDP provided a list of 13 deficiencies regarding CMC issues for this NDA. The sponsor was asked to address these 13 deficiencies, in order for DRUDP to continue the timely evaluation of this NDA. (The 13 deficiencies are listed in the Addendum to these minutes.) The sponsor's responses were received in the Amendment of September 7, 2001. This teleconference was scheduled to discuss the sponsor's responses to deficiencies #5 and #7, and to answer any questions the sponsor had regarding deficiency #9.

Discussion:

- Regarding deficiency #9:
  - it was clarified that the current Office of New Drug Chemistry (ONDC) policy is to request that the first three production batches produced post-approval be placed in the stability program, as indicated in the Guidance
- Regarding deficiency #7:
  - there is a concern that the [redacted] stability study did not represent a full 36-month stability period
  - the assay method for dutasteride in the drug product is not specific for dutasteride because an impurity from the drug substance, the [redacted] with dutasteride. In their

response to this deficiency, the sponsor stated that the [redacted] is not a degradant, and that the amount present is controlled in the drug substance; thus, the sponsor states that they should not have to either improve the [redacted] method so that dutasteride does not [redacted] with any other compound, or determine the amount of [redacted] present by the impurity method and then subtract this amount from the assay value to report a true value for dutasteride
    - DRUDP stated that if the sponsor could demonstrate that no [redacted] was present under the assay peak for dutasteride in the 36-month stability samples of the primary drug product stability batches, then this data would be sufficient to establish that the [redacted] was not a degradant; as such, the regulatory method provided in the NDA would be acceptable
- regarding #5:
    - DRUDP accepts the proposed limit of [redacted]

Action items:

- another teleconference will be scheduled one day from this teleconference to discuss the 36-month data that the sponsor states they can provide

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Teleconference Minutes

Date: September 26, 2001 **Time:** 4:00-4:30 PM, EDT **Location:** Parklawn; 17B-43

NDA 21-319 **Drug:** dutasteride **Indication:** symptoms of benign prostatic hypertrophy

Sponsor: Glaxo SmithKline

Type of Meeting: Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D., Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Bekki Komas, Assistant Director, Regulatory Affairs, US CMC Submissions, Worldwide Regulatory Affairs

Meeting Recorder: Evelyn R. Farinas, RPh, M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Moo-Jhong Rhee, Ph.D. - Team Leader, DNDC II @ DRUDP (HFD-580)
Jean Salemme, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager. DRUDP (HFD-580)

External Participants:
Bekki Komas – Assistant Director, Regulatory Affairs, US CMC Submissions, Worldwide Regulatory Affairs, Glaxo SmithKline
Ralph Caricofe - Glaxo SmithKline
Steve Meyerhoffer - Glaxo SmithKline

Meeting Objective: To discuss deficiency #7 and how it should be addressed by the sponsor.

Background: In a letter to Glaxo SmithKline, dated August 20, 2001, DRUDP provided a list of 13 deficiencies regarding CMC issues for this NDA. The sponsor was asked to address these 13 deficiencies, in order for DRUDP to continue the timely evaluation of this NDA. The sponsor responded to the deficiencies in the amendment of September 7, 2001. Deficiencies #5 and #7 were discussed during a teleconference on September 25, 2001. Today's teleconference was scheduled to discuss deficiency #7 in greater detail.

Discussion:
- DRUDP's review of the NDA indicates that the analytical method to detect to detect dutasteride in the drug product is not adequate, nor sufficiently specific nor robust
- DRUDP stated that the 36-month data from the primary drug product stability batches, as discussed in the September 25, 2001, teleconference, will not adequately address the fact that the assay method for dutasteride in the drug product is not demonstrating specificity.

- DRUDP stated that as an option the sponsor use the proposed analytical method as an interim method and commit to submit within a short time frame as an amendment to the NDA a more specific method to assay the drug substance in the drug product
- the sponsor indicated that the CMC section of the NDA contains Methods A and B which can be used to determine the exact amount of [redacted] in the drug substance
- DRUDP stated that the methods A and B are methods for the drug substance, not the drug product; specificity can be addressed in the drug product method if the amount of [redacted] present in the drug substance used to make the drug product is subtracted from the assay value determined by the drug product assay method
- the sponsor stated that the [redacted] will be quantitated for the drug substance using Methods A and B, and this amount will be subtracted from the assay value of the drug substance in the drug product; if several batches of drug substance are used in making the drug product, the highest amount of [redacted] present will be subtracted from the assay value

Action items:

- the sponsor will revise the method for the assay of dutasteride in the drug product to subtract out the amount of [redacted] that is in the drug substance used to make the drug product; if more than one batch of drug substance is used to make the drug product, the highest impurity content of the drug substance batches will be subtracted from the assay
- the revised method will be faxed to DRUDP by 3-Oct-2001 for a review; if the revised method is satisfactory to DRUDP, then the sponsor will amend the NDA with a revised method; additionally, the sponsor will update the methods validation packages with the new method, and forward three copies of the revised methods validation packages to DRUDP

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting minutes.

Teleconference Minutes

Date: October 10, 2001 **Time:** 1:30-1:45 PM, EST **Location:** PKLN; 13B45

NDA 21-319 **Drug:** dutasteride **Indication:** BPH

Sponsor: GlaxoSmithKline

Type of Meeting: Guidance

Meeting Chair: Moo-Jhong Rhee, Ph.D., Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs, GlaxoSmithKline (GSK)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, DNDC II @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Munir Abdullah, Ph.D. - Product Director, Regulatory Affairs, GSK

Meeting Objective: To address lack of tradename for dutasteride.

Background: The sponsor submitted NDA 21-319 on December 21, 2000, for dutasteride soft-gelatin capsules to be used for the treatment of symptomatic BPH in men with an enlarged prostate gland. The sponsor was notified that OPDRA does not recommend the use either of the proposed tradenames (i.e., Duagen and Zygara) on the basis of the potential for confusion with approved proprietary names. To date, the sponsor has not proposed additional tradenames for dutasteride.

Discussion:
- the sponsor indicated that another tradename would not be proposed prior to the goal date
- the sponsor was asked to submit an amendment stating that if this NDA is approved without a tradename, a tradename would be submitted for review and approval as a Prior Approval labeling supplement, or, as part of an efficacy supplement

Decisions made:
- the sponsor will comply with the Division's request, pending approval by GSK's management

Action Items:

- the sponsor will fax a letter agreeing to the Division's recommendations, as soon as it is approved by GSK's management *(hard copy received October 16, 2001; see addendum)*
- minutes of this teleconference will be sent to the sponsor within 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

Addendum:

In correspondence dated October 15, 2001, GlaxoSmithKline stated the following:

"Reference is made to a teleconference on October 10, 2001, with Dr. Moo Jhong Rhee regarding dutasteride Trade Name. We acknowledge that if the above referenced dutasteride NDA 21-319 is approved by FDA without a trade name, GlaxoSmithKline will submit a trade name for the Agency's review and approval either as a labeling supplement or as part of a supplemental NDA containing 2-Year efficacy and safety data."

Teleconference Minutes

Date: October 11, 2001 **Time:** 11:30-1:00 PM, EST **Location:** PKLN; 13B45

NDA 21-319 **Drug:** dutasteride **Indication:** BPH

Sponsor: GlaxoSmithKline

Type of Meeting: Guidance

Meeting Chair: Daniel Shames, M.D., Acting Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs, GlaxoSmithKline (GSK)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Daniel Shames, M.D. – Acting Director, DRUDP (HFD-580)
Mark Hirsch, M.D. – Medical Team Leader, DRUDP (HFD-580)
George Benson, M.D. – Medical Officer, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. – Pharmacokinetics Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Henry Malinowski, Ph.D. – Director, OCPB, Division of Pharmaceutical Evaluation II (DPE II; HFD-870)
Sayed Al-Habet, Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)
Laurie McLeod, Ph.D. – Toxicology Reviewer, DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees:
Dr. David Wheadon – Regulatory Affairs
Dr. Charles Depew – Regulatory Affairs
Dr. Jane Harrelson – Biometabolism
Dr. Frank Hoke – Clinical Pharmacology
Dr. Dipak Patel – Biometabolism
Dr. Richard Clark – Clinical Pharmacology
Dr. Paul Strumph – Medical Affairs
Mr. Russ Yeager – Biometabolism
Ms. Jackie Greene – Safety Assessment
Dr. Lynda Haberer – Clinical Pharmacology
Mr. Tim Wilson – MDS-Clinical Statistics
Dr. Paula Rogenes – Regulatory Operations
Ms. Jayne Dukes – Regulatory Operations
Dr. Munir Abdullah - Product Director, Regulatory Affairs

Meeting Objective: To address the impact of missing metabolism data.

Background: The sponsor submitted NDA 21-319 on December 21, 2000, for dutasteride soft-gelatin capsules to be used for the treatment of symptomatic BPH in men with an enlarged prostate gland. During the review of this application, the sponsor has been contacted several times to clarify or provide additional metabolism data.

Discussion:

- in response to a request for comments on the completeness of the metabolism evaluation for dutasteride, the sponsor stated that:
  - radiolabeled studies in humans were not possible for this compound due to its long half life, however, single-dose mass balance studies at steady state were conducted
  - dutasteride had a short half life after a single dose, but that single-dose studies do not yield adequate information; data collected from single-dose studies is not clinically relevant; similar studies have been conducted in animals
  - clearance of dutasteride varies according to the dose; clearance is faster at lower doses
  - data should be collected so that adequate information is obtained for drug metabolism under conditions similar to drug use
  - qualitatievely, dutasteride, and its metabolite, are very similar across subjects, despite the variability in recovery
- in response to a request for comments on the metabolic characterization of dutasteride, the sponsor stated that:
  - five metabolites have been identified in humans, of which three are major metabolites
  - the majority of the data has been collected for the 4-hydroxy metabolite; this metabolite has been tested for activity and mutagenicity; this has one tenth the activity of the parent for five-alpha-reductase inhibition
  - the 6-hydroxymetabolite is as active as the parent compound
  - the 1-2 dihydro metabolite is also a major human metabolite; it has been studied in rats and dogs, and has been found to be non-mutagenic and less potent than the parent compound; this metabolite is under study
  - the 6-beta-hydroxy metabolite has not been synthesized yet; it is under study
- in response to a request for comments on why the data from a single-dose study was offered to support use in the elderly, if single-dose does not reflect conditions similar to drug use, the sponsor stated that:
  - single dose study will address clearance differences with age
  - the original single-dose study used to support the geriatric statement in the label is now considered insufficient; subsequent Phase 3 studies provided more information, which adds support to the original data
- DRUDP stated the following comments and concerns:
  - further discussion is needed to determine which additional studies are necessary to fully characterize the metabolism of dutasteride
  - the large variability in the drug recovery is of concern, since it does not allow for a clear identification of the drug's metabolic disposition
  - the large percentage of metabolites which remain uncharacterized, and whether these metabolites are active, remains a concern
  - a less frequent dosing regimen may be possible, due to the long half life of dutasteride
  - the potential risk to patients with hepatic insufficiency is a concern

- the mechanism by which other drugs interact with dutasteride should be clarified
- that the lack of metabolic characterization could potentially lead to an overdose, and potential adverse effects on different organ systems, is also a concern
- additional issues of concern are: potential teratogenic effects through blood donations; monkey studies showed effects on the fetus at the highest dose, indicating that there might be a risk to human fetuses through blood transfusion; the calculations from the monkey studies were based on maternal blood exposure levels; the sponsor does not agree with DRUDP that there is the potential for toxic effects to fetal organs resulting from blood donation transmission and will provide data and reasoning to support their position
- the feasibility of an *in vitro* metabolic study at therapeutic concentrations using radiolabeled dutasteride should be considered
- the data regarding drug interactions with calcium channel blockers cannot be located in the application

- in response to a request for comments on the following clinical issues, the sponsor stated:
  - drug interactions, particularly interactions with ketoconazole and other CYP 3A4 inhibitors, should be addressed in the **Precautions** section of the label, because of limited knowledge
  - the elimination of dutasteride in patients with hepatic insufficiency should be addressed in the **Precautions** section of the label, because there is no information on hepatically impaired subjects
  - the breast cancer reported in one patient was a pre-existing condition, and was not thought to be drug related
  - there were no true differences between the drug arm and the placebo arm in number of cardiovascular related deaths; the mild elevation of testosterone levels in patients receiving dutasteride is not significant, and will not lead to changes associated with androgenic effects; even the highest levels of testosterone observed in outliers were still below the range leading to severe adverse events from high anabolic exposure
  - monkey studies did not show effect on the fetus, indicating that there should not be a risk to women or human fetuses through seminal transmission of dutasteride; the calculations from the robust monkey studies were derived from daily exposure predicated upon complete drug absorption through the semen
  - the transmission of dutasteride via a blood donation to a pregnant female is trivial; the levels of dutasteride were below those seen in the monkey study at the no effect level; the sponsor does not agree with DRUDP that there is the potential for toxic effects to fetal organs resulting from blood donation transmission; data from the monkey study will be provided to DRUDP to support lack of effect in fetuses from dutasteride exposure through blood donations

Decisions made:

- OCPB will contact GSK for additional discussion and clarification regarding dutasteride metabolism and distribution, and assess the need for additional studies
- DRUDP will send a revised label to the sponsor for review and comments in the near future
- The sponsor will resubmit data on population PK modeling studies, which was submitted as a manuscript on March 1, 2001, and is located in Vol. 9, page 280
- GSK will provide data in support of the absence of toxic fetal effects arising from dutasteride exposure through blood donations
- An extension of the 10-month PDUFA clock is being considered (*it was verified that the PDUFA goal date was postponed to November 20, 2001)*

Action Items:

- DRUDP to schedule a teleconference between OCPB and GSK (*teleconference between Drs. Parekh and Malinowski and GSK was held Monday, October 15, 2001*)
- FDA's revised label will be sent to the sponsor for comments prior to the action date
- Population PK modeling studies will be resubmitted by the sponsor for OCPB's review (*it was verified that the manuscript pages were missing from Vol. 9; GSK faxed the manuscript on October 12, 2001and indicated that there was no additional formal report)*
- data from monkey studies showing lack of fetal effect will be submitted by GSK in the near future
- minutes of this teleconference will be sent to the sponsor within 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Meeting Minutes

Date: 10/15/01 Time: 9:30 a.m. Location: 17B45, PKLN

NDA: 21319 **Drug:** Dutasteride **Indication**: Benign Prostatic Hyperplasia

Sponsor: Glaxo SmithKline

Type of Meeting: Request for information

Meeting Recorder: Ameeta Parekh, Ph.D., Team Leader, Division of Pharmaceutical Evaluation II (DPEII), Office of Clinical Pharmacology and Biopharmaceutics (OCPB)

FDA Attendees: Henry Malinowski, Ph.D., Director, DPEII, OCPB, HFD-870
Ameeta Parekh, Ph.D., Team Leader, DPEII, OCPB, HFD-870

External Attendees:
Dr. Munir Abdullah - Product Director, Regulatory Affairs
Mr. Russ Yeager – Biometabolism
Dr. Frank Hoke – Clinical Pharmacology
Dr. Lynda Haberer – Clinical Pharmacology
Dr. Dipak Patel – Biometabolism
Dr. Keith Muir – Clinical Pharmacology

This was a telephone conference with Glaxo SmithKline (GSK) initiated by OCPB and DPEII, to discuss the deficiencies listed in the Discipline Review Letter (DRL) sent to the sponsor dated 10/4/01. These issues were discussed with the sponsor to determine resolution either as Phase IV commitments or scientific discussion to bring issues to a closure. The following lists the five issues discussed, and their respective conclusions:

1. Consider conducting a study to investigate the effect of hepatic impairment on the PK of dutasteride.

   GSK agreed that this study has not been conducted and also indicated that this is not in their investigation plans. In absence of this study, it was agreed that this information could be addressed in the label and an additional study in hepatically impaired patients will not be a requirement and will be left to the sponsor's discretion.

2. We remind you that the Division has not received the population PK analysis to verify certain drug-drug interaction claims. For example, data regarding increase in dutasteride exposure by 37 % to 44 % with calcium channel antagonists should be submitted.

   Following this, GSK re-submitted this report (note that this was submitted in the original NDA but was not available to the reviewer in the desk copy). This report has been reviewed and appropriate information regarding the drug interaction potential with calcium channel antagonists has been included in the label.

3. Submit a mass balance study and characterization of parent and metabolites profiles in serum, urine, and feces following oral administration.

   GSK stated that a steady state mass balance study is more appropriate for this drug since the single dose is not reflective of the long t1/2 (about 5 weeks) that contributes to achievement of steady state. With this nonlinearity in perspective, the sponsor had conducted the mass balance study at multiple dosing which was submitted in July, 2001 and reviewed by OCPB/DPEII. Due to the long t1/2, radiolabeled drug was not considered ethical and 19F-NMR technique was used to assess mass balance. This study showed that in 2 of 8 subjects less than 20% of the dose was recovered. However in three subjects. about 60-97% of the dose has been recovered. Since qualitatively the contents of recovery were similar, the sponsor stated that this discrepancy in recovery might be due to the technique used to quantitate the recovery. GSK stated that:
   a) a single dose study (e.g. with radiolabel) will not be reflective of multiple dose
   b) repeating a multiple dose study is not warranted and may not be feasible with radiolabel
   c) adequate safety has been established for the drug (10 fold higher dose than that recommended for approval, over 6 months).
   Upon discussing this deficiency with GSK it was agreed that although mass balance information lends itself to a better understanding of the drug disposition, a study to address this has been attempted by the sponsor. An additional, well designed study, may have feasibility issues, however, GSK was urged to consider such a study if possible. The sponsor agreed to send a concept protocol as a proposal to the Agency, with the caveat that such a study may not be feasible and that IRBs may not approve of this study. In conclusion it was agreed at this point that GSK would propose a mass balance study addressing all limitations for conducting such a study. Rather than a commitment for Phase IV, it was agreed that OCPB/DPEII would evaluate the proposal and discuss its feasibility with the sponsor.

4. Submit an *in vitro* metabolism study using therapeutically relevant dutasteride concentration to characterize the metabolic pathways.

   GSK agreed to conduct this in-vitro metabolism study and would submit this protocol with appropriate timelines for Phase IV commitment.

5. Submit a drug interaction study with ketoconazole in humans.

   The sponsor explained that since the drug has a long t1/2, a single dose drug interaction study with ketoconazole would not be therapeutically relevant. Rather than conducting a study that is not relevant, it was agreed that this concern related to drug interactions with chronic potent CYP3A4 inhibitors would be address appropriately in the label

Action Items:

- Deficiencies # 1, 2 and 5 have been resolved. Deficiencies 1 and 5 will be appropriately addressed in the label.
- The sponsor has agreed to conduct a Phase IV study to investigate *in vitro* metabolism using therapeutically relevant dutasteride concentration to characterize the metabolic pathways; a protocol with timelines will be submitted before the action date
- The sponsor will propose a concept protocol to address the mass balance information on dutasteride; the feasibility of such a study is in question and will be further discussed with the Agency

Teleconference Minutes

Date: October 17, 2001 **Time:** 1:30-1:45 **Location:** PKLN; 13B45

NDA 21-319 **Drug:** dutasteride **Indication:** BPH

Sponsor: Glaxo SmithKline

Type of Meeting: Clarification

Meeting Chair: Ameeta Parekh, Ph.D., Pharmacokinetics Team Leader, Clinical Pharmacology and Biopharmaceutics (OCPB)@ Division of Reproductive and Urologic Drug Products (DRUDP; HFD 580)

External Lead: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs, Glaxo Smith Kline (GSK)

Meeting Recorder: Evelyn R. Farinas, R.Ph., M.G.A., Regulatory Project Manager, DRUDP (HFD-580)

FDA Attendees:
Ameeta Parekh, Ph.D. - Pharmacokinetics Team Leader, OCPB @ DRUDP (HFD-580)
Evelyn R. Farinas, R.Ph., M.G.A. – Regulatory Project Manager, DRUDP (HFD-580)

External Attendees: Munir Abdullah, Ph.D., Product Director, Regulatory Affairs

Meeting Objective: To follow-up on previous requests for additional information.

Background: The sponsor submitted NDA 21-319 on December 21, 2000, for dutasteride soft-gelatin capsules to be used for the treatment of symptomatic BPH in men with an enlarged prostate gland. In support of this NDA, the sponsor submitted three Phase III trials, ARIA 3001, ARIA 3002 and ARIB 3003. In a teleconference held on October 15, 2001, between Dr. Abdullah (GSK) and Drs. Parekh and Malinowski, (OCPB) outstanding dutasteride metabolite and drug interaction issues were discussed.

Discussion:

- the sponsor indicated that the response to whether AMIDASES are involved in cleaving the amide bond in the dutasteride molecule was faxed to DRUDP on October 17, 2001 *(facsimile received on October 17, 2 001)*
- DRUDP requested that the sponsor also provide the basis for including ciprofloxacin in the **Drug Interactions** section of the dutasteride draft labeling

Decisions made:

- the sponsor agreed to provide the basis for the inclusion of ciprofloxacin in the **Drug Interactions** section of the dutasteride draft labeling

Action Items:

- the sponsor will submit the basis for the inclusion of ciprofloxacin in the **Drug Interactions** section of the dutasteride draft labeling, as soon as possible (*facsimile received October 18, 2001)*
- minutes of this teleconference will be sent to the sponsor within 30 days

Note to sponsor: These minutes are the official minutes of the meeting. You are responsible for notifying us of any significant differences in understanding you may have regarding the meeting outcomes.