CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-812

MEDICAL REVIEW

MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center for Drug Evaluation and Research
Division of Nonprescription Clinical Evaluation

Date: **January 18, 2006**

From: **Andrea Leonard-Segal, M.D.**
Acting Director

Subject: **NDA 21-812**
Minoxidil
Men's Rogaine Extra Strength 5% Topical Foam

Sponsor: **Pfizer Consumer Healthcare**

Recommendation:
This NDA should be approved if:

- Before the PDUFA date, the sponsor makes the changes to their proposed labeling that the Division recommended in a FAX sent to Pfizer on January 9.
- If the chemistry review does not raise new issues.

Otherwise the NDA should be approvable.
There is no need for Phase IV clinical studies.

Background
Pfizer Consumer Healthcare submitted this new NDA for a 5% minoxidil topical foam (MTF) aerosol formulation for the nonprescription treatment of androgenic alopecia of the vertex region of the scalp. The product is targeted for use in men at least 18 years of age. Minoxidil was first developed as an orally administered vasodilator for the treatment of hypertension. Eighty percent of treated subjects developed hypertrichosis and this led to the development of a topical solution for the treatment of androgenic alopecia. Men's Rogaine Regular Strength (2% minoxidil topical solution) was first marketed by prescription in the United States in 1987. This product was switched from prescription to over-the-counter (OTC) status in 1996. Rogaine Extra Strength for Men (5% Minoxidil Topical Solution) was approved as an OTC product in 1997. The dosing regimen for both strengths is 1 ml of solution applied topically twice daily. (A 2% minoxidil solution is approved OTC for women.)

The development program for the minoxidil 5% topical foam aerosol consisted of:

- Chemistry data
- Pharmacology/Toxicology Data
- One dermal sensitization study (MINOB-9140-004)
- Two pharmacokinetic studies (MINOB-9140-001 and MINOB-9140-005)
- One vehicle-controlled safety and efficacy trial (MINOB-9140-006)
- 3 studies assessing the ability of consumers to accurately dispense 1 gram of 5% MFT without a metered device.

Pfizer also submitted postmarketing safety data for the 2% and 5% minoxidil topical solutions (MTS). The sources for this postmarketing safety data were:

- Pfizer's own postmarketing safety database

- World Health organization database
- FDA AERs database
- American Association of Poison Control Centers
- Medical literature

Discussion:

Chemistry:

The chemistry review has not yet been completed.

Pharmacology/Toxicology:

Refer to review by Dr. Kumar Mainigi.

During the IND stage two studies were performed; one measured the penetration of minoxidil into human cadaver skin in vitro and the other measured the penetration of minoxidil into the hair follicles of hamster ears. These studies suggested that the penetration of minoxidil across skin might be slightly greater with the foam than with the solution. No new animal toxicology studies were conducted for this NDA submission. Relevant studies were reviewed by Dr. Javier Avalos under NDA 20-834 (Rogaine Extra Strength for Men (5% MTS) in May, 1997. The Pharmacology/Toxicology reviewer recommended that the NDA be approved. He stated that there were no unresolved toxicology issues, and that the draft label submitted by the sponsor included appropriate information for the safe use of this new formulation.

Microbiology: Not applicable.

Clinical Pharmacology/Biopharmaceutics:

Refer to review by Tapash Ghosh

The serum minoxidil levels for this new formulation, when used in the 50 mg minoxidil (1 gram of foam) dose, were significantly lower than the currently approved 5% MTS. The systemic exposure increased linearly with increasing dose. However, exaggerated use of the foam preparation up to three times the recommended dose (3 grams of foam) produced blood levels of 11.5 ng/ml which is far below the level associated with any systemic effects (approximately, 20 ng/ml). The reviewer recommended approval of this product with no suggested labeling changes.

Statistics:

Refer to Review by Dr. Steve Thompson.

The two primary endpoints in the efficacy study were:

- The change from baseline in hair count in a small area of the vertex of the scalp
- A subject self-assessment rating of overall treatment benefit scored on a seven point ordinal scale

For both endpoints, differences in favor of the 5% foam were very highly statistically significant ($p < 0.0001$) for both the intent-to-treat and the per protocol populations. There was little relation between the actual hair count and the level of the "Subject Hair Condition Rating." However, in the January 16, 2003 end of phase 2 meeting minutes, although the sponsor was told to use hair count and subject self-assessment to assess efficacy, they were not told that the results of these two assessments had to correlate well.

Results for both primary endpoints were highly statistically significant for men < 40 years of age and for men aged 40 – 49 years ($p = 0.0001$). Most patients were Caucasian and among them all differences were highly statistically significant in favor of Minoxidil ($p = 0.0001$). The non Caucasian population consisted of only 44 men and treatment differences were only barely significant in favor of Minoxidil ($p = 0.0475$) for change in baseline for hair counts and non-significant for the subject self-assessment rating ($p = 0.2109$).

Clinical:

Efficacy:

Refer to reviews by Dr. Phyllis Huene and by Dr. Markham Luke. Dr. Huene recommended not approving this application and stated four reasons for this recommendation. After considering her four reasons, Dr.

Luke recommended that this application be approved. I agree with Dr. Luke's recommendation and the rationale he provided.

In the January 16, 2003 meeting, the Agency told the sponsor that a single, adequate, and well-controlled 16-week study in which the new product is compared to its vehicle might be acceptable in the study of androgenic alopecia. The use of a single study to support efficacy was reaffirmed in an Agency communication to the sponsor at a teleconference on July 26, 2004, where the Agency stated that a single study submission for this indication would be acceptable with the following recommendations:

- Very small p-values
- Consistency of efficacy results across study subgroups
- Consistency of efficacy across study centers

The study met these criteria.

The p-values in this study were robust. There was no correlation between the two primary endpoints, but, as Dr. Luke states in his review, this was not deemed to be essential for the approval of this product. Although the magnification methodology for hair count in the target area used by Pfizer in this study was called into question by the dermatology and statistical reviewers, Dr. Luke and Dr. Thompson note that this method has been used for prior approvals for other hair regrowth products.

The sponsor did not study men over the age of 49 and the population of non-Caucasians who enrolled was small so the data for this latter group may not be so meaningful. These issues can be addressed in product labeling (see below).

Safety:

Refer to review by Dr. Daiva Shetty.

The safety data suggests that the safety profile of the 5% minoxidil topical foam is consistent with that of the 2% and 5% MTS. There were 694 subjects in the safety data base. The adverse events for skin rash were uncommon and none were deemed to be serious. (See page 42 of Dr. Shetty's review.) This would not be surprising because, unlike the MTS, the MTF does not contain alcohol as an inactive ingredient. A review of the post marketing data for the 2% and 5% MTS was submitted for this NDA and did not reveal any new safety signals.

One of the concerns raised by FDA during the drug development phase was the ability of consumers to accurately dispense 1 gram of the 5% MTF without a metered device. On several occasions, FDA encouraged the sponsor to develop a quantitative measurement device for this product. The sponsor did not do this and the efficacy/safety study was not conducted with a metered device. The sponsor did conduct three studies designed to measure the amount of foam study participants dispensed after reading the directions for use. The bioavailability data, the exaggerated use pharmacokinetic study, and the results of the three studies that tested the ability of consumers to dispense the correct amount of foam bolster confidence in the safety profile of this new formulation and its use without a metered device.

Dermal Sensitization Study (MINOB-9140-004)

Refer to the review by Dr. Phyllis Huene

The topical treatment of vertex scalp with minoxidil is well-studied and available as 2% and 5% solutions for OTC use.

The results of a provocative sensitization study were submitted to address dermal safety. In general, a cumulative irritation and a contact sensitization study are required as a part of the dermal safety evaluations. In this case, the applicant has conducted a sensitization study. The initial two applications were made under occlusive patches, but because of high level of irritancy applications were changed to semi-occlusive patches. During the induction phase with semi-occlusive patches moderate irritation in one or two subjects with each test formulation was noted. On challenge two subjects had reaction of sensitization; however, upon re-challenge reactions were considered to be very mild and transient. This study appears to be a modified maximization study, capturing sensitization and irritancy potential o f minoxidil foam with a single population. The primary reviewer's concern regarding financial interest of the prinicipal investigator

for this study is noted. However, the study did suggest that there is some irritation and possibly some sensitization from the minoxidil foam aeorsol.

The safety data base of 5% minoxidil foam included 694 subjects. Two non-serious possibly or probably drug-related rashes and three non-serious cases of pruritis occurred. One subject with a rash discontinued treatment as did one subject with itching. Reported local skin reaction included pruritus, rash, tingling of the scalp and at the test site in a small number of subjects.

The Agency discussed the safety data regarding local irritation with the applicant on January 13, 2006. It was noted that three subjects exhibited rash related to use of 5% minoxidil foam. Two of the subjects required super potent to midpotent topical corticosteroid to treat the resulting irritation. Overall, the incidence of scalp related irritation for 5% MTF was 1.7% and for the vehicle was 0.6%.

The results of the safety data from the clinical study 006 and the irritation seen in the provocative sensitization study, obviate the need for additional dermal safety testing. The labeling for minoxidil foam includes cautionary wording with regard to potential for irritation in that it directs subjects to see a physician if irritation occurs.

Pediatrics:
In accordance with recommendations from Dr. Lisa Mathis, Acting Director, Division of Pediatric Drug Development the sponsor was granted a full waiver for pediatric studies for this NDA for the indication of androgenic alopecia.

Labeling:
See review by Dr. Matthew Holman.
I agree with his recommendations that:

- The sponsor change the dosage form name to "topical aerosol" because "foam" is not a recognized dosage form name.
- The statement of identity should appear in boldface type.
- The sponsor should remove the statement "extra strength" because there is no
- data demonstrating that this formulation is at least as effective as MTS 5%.
- The label read [redacted] to be consistent with MTS labels.
- The statement "easy-to-use foam" should be removed because it is not supported by data.
- The sponsor should include a prominent instruction to peel-back label for more information.
- The sponsor should include instructions to wash hands after use under the Directions heading.
- Under Other Information, to reflect the study results, the sponsor should include the statement "hair growth has been shown in a clinical study of men (mostly white) aged 18-49 years who used it for 4 months." This statement would be consistent with MTS labeling.
- The sponsor should include the directions on how to dispense the correct amount of foam with illustrations in the area on the inside of the fold-out flap.

With regard to the package insert, the sponsor should revise the directions so that the text and illustration are consistent.

All labeling changes need to be made before this NDA is approved.

Conclusion:
The study data suggests that 5% MTF is safe and effective when used as a hair regrowth product for androgenic alopecia of the vertex of the scalp in men. Data from the exaggerated pharmacokinetics study suggests that there is a reasonable therapeutic safety margin. Thus, it appears that this product would offer a favorable benefit/risk ratio for nonprescription consumers who would self-select to use it. In the future, it would be reasonable to request that sponsors of hair regrowth products provide data to correlate the objective hair count findings with the findings of subject self-assessment.

Because of the sought indication, there is no apparent reason to request that this sponsor study 5% MTF in the pediatric population.

The chemistry review is not complete as of the time of this review, so it is uncertain if there are outstanding chemistry issues.

There are outstanding labeling issues that the sponsor must address in their proposed labeling prior to the PDUFA date.

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/s/

Andrea Segal
1/18/2006 10:08:48 AM
MEDICAL OFFICER

Clinical (Efficacy) Team Leader Secondary Review
Rogaine (minoxidil) 5% Aerosol Foam NDA 21-812 N000

December 22, 2005

NDA 21-812 is an application for Rogaine (minoxidil) 5% Aerosol Foam for the OTC indication of "Hair Regrowth" with specific use described as "to regrow hair on the top of the scalp (vertex only, see pictures inside label)."

The clinical review of this product was divided between two Divisions, with the Division of Non-Prescription Clinical Evaluation (DNPCE) reviewing the overall safety and the Division of Dermatology and Dental Products (DDDP) reviewing the overall efficacy, as well as the safety derived from the dermal safety battery studies. The Dermatology Clinical Team Leader, while agreeing that there is some merit to the concerns described by Dr. Phyllis Huene, the primary DDDP reviewer, recommends that Rogaine (minoxidil) 5% Aerosol Foam be approved by the Agency from an efficacy perspective.

Effectiveness for the "Hair Regrowth" Indication

The applicant, Pfizer, has demonstrated in one adequate and well-controlled study that Rogaine 5% Aerosol Foam is superior to the Aerosol Foam vehicle with regard to the two chosen co-primary endpoints of

1) change from baseline in magnified hair counts in a 1 square cm target area at the vertex of the scalp at week 16 and,
2) subject rating of overall treatment benefit scored on a seven point ordinal scale.

No final agreement had been reached with the applicant at the EOP2 meeting with regard to study design. However, it was discussed at that January 16, 2003 meeting that "a single, adequate and well-controlled study in which the new product is compared to its vehicle might be acceptable in the study of androgenetic alopecia on the vertex." The topical treatment of vertex scalp with minoxidil in various formulations is well-studied and available in the OTC marketplace in 2% and 5% concentrations. Both concentrations are available as Rogaine (Reference Listed Drug Products – NDA 20-834 Rogaine Extra Strength for Men, 5%, NDA 19-501 Rogaine for Men and Women, 2%) and numerous generic formulations.

The use of a single study to support efficacy was reaffirmed in Agency communication to the sponsor (teleconference of July 26, 2004) where the Agency stated that a single study submission for this indication would be acceptable with the following recommendations:

1) Very small p-values, as one would be looking for a much smaller p-value than the 0.05 required for 2 studies
2) Consistency in efficacy results across study subgroups

3) Consistency of efficacy across study centers, as efficacy results driven by a few centers would not provide reassurance of robustness in a single multi-center trial.

As noted by the Agency statistician, the following statistical findings were evident:

For both mean change from Baseline in visualized hair counts in the target region and the subject rating of treatment benefit, treatment differences in favor the 5% Foam were highly statistically significant ($p < 0.0001$). This was true both in the intent to treat (ITT) population using ANOVA, van Elteren, or Cochran-Mantel Haenszel tests, and in the per protocol population. However, as detailed in Appendix 4, the association between the primary endpoints was generally low. Grouping ITT patients into two roughly equally sized groups of those aged less than 40 and those 40-49, for both primary endpoints treatment differences in each group were still highly statistically significant in favor of minoxidil foam (all $p \leq 0.0001$). Most patients were Caucasian, and among them all differences were still highly statistically significant in favor of Minoxidil (both $p \leq 0.0001$). Although actual success proportions among the non-Caucasian patients were similar to those among the Caucasian, there were only a relatively small number of patients in this subgroup (44) and treatment differences were only barely statistically significant for change from baseline in hair counts ($p \leq 0.0475$) and non-significant for the subject rating ($p \leq 0.2109$). For the Norwood Baseline Hair Loss Patterns IIIv, IV and V treatment differences in the change from baseline were all statistically significant ($p \leq 0.0001$, $p \leq 0.0184$, and $p \leq 0.0020$, respectively). Results for the subject rating were similar ($p \leq 0.0001$, $p \leq 0.0110$, and $p \leq 0.0002$, respectively). An expert panel review found consistent results.

Thus, the p-values were robust. There was concern that that the p-values for hair count did not correlate well with the other co-primary endpoint of patient self-assessment. Future studies for this indication should attempt to more carefully evaluate this correlation and be designed to correlate better (e.g. more areas for hair counting than just a single cm square area and use of a better validated self assessment scoring system for hair growth). Of note the delta for hair count was about 16 hairs per square cm between the 5% foam vs. placebo.

Of note, the review of photographs by an expert review panel is less useful as evidence of effectiveness than a clinical trial where patients scalps are actually examined using a static global assessment for vertex hair growth conducted by investigators looking for clinical effectiveness. The photographs reviewed by the expert panel were not time blinded so this secondary endpoint is not factored into our approval decision.

The primary reviewer stated that despite the effectiveness being demonstrated in the one pivotal study, there were caveats that may mitigate the robustness of the demonstration of effectiveness. The first point was that there was no correlation between the two co-primary endpoints. While the lack of correlation was observed, it was not deemed to be essential for approval of this product. However, again, this should be examined more carefully for future studies and evaluated as a possible requirement to allow for more meaningful endpoints, especially with regard to the patient reported outcome.

The second point was that a study endpoint review conducted by Jane Scott and Laurie Burke as requested by the Office of Non-Prescription Drug Products found that the results suggest that only a subset of patients experienced a noticeable improvement, and that these improvements tended to be modest. This secondary reviewer is in

agreement with that conclusion. However, such a concern should not preclude approval. Other products previously approved also show only modest improvement. Please see also the Biostatistics review by Steve Thomson regarding subgroup analysis.

The third point was that the study excluded men over the age of 49, whereas the indication is common in patients over 49 years of age. The sponsor was advised previously that the inclusion criteria should include subjects over the age of 49. This should be adequately described in the labeling. The Non-Prescription Drug review division should carefully examine the data at hand with regard to safety of use of topical minoxidil in this age group to determine the extend of age restriction for labeling purposes. It is also noted that no women were studied. This product should be labeled for use in men only.

The primary DDDP reviewer's fourth consideration is regarding the methodology used, in particular the level of magnification of the hair count target area, may have caused vellus hairs to be counted as non-vellus hairs. This has been discussed in detail with the applicant. The applicant stated that this methodology with a similar magnification was used for prior approvals for hair regrowth. The unknown clinical relevance of vellus hairs somewhat confound the efficacy result of the objective endpoint. Future studies should be encouraged to more carefully discriminate between these two hair types.

An additional concern by both the statistician and the clinical review team was the short timing of the hair evaluation (16 weeks). Hair loss is a progressive condition. This drug may only affect the hair loss briefly in the setting of clinical use. The study submitted was not a typical longer term study that is presented for hair growth (see studies for Propecia and for previous Rogaine products). We would not be able to extrapolate this short term growth to longer term maintenance of hair growth except for the use of the same active ingredient in a product that might be characterized as having bioavailability somewhere between the 2% and 5% solution products (see Biopharmaceutics review).

This recommendation for approval with regard to effectiveness, on the basis of one study has limited applicability (see Agency guidances with regard to evidence of effectiveness). The following information was relevant to making this decision:

1) The efficacy was robust for both co-primary endpoints in the pivotal study with very small p-values.
2) The minoxidil active ingredient has broad use in the OTC environment with other Rogaine products and with generic formulations found to be safe and effective.

While not directly addressing the efficacy it is also reassuring that the bioavailability appears to be bracketed for the upper bound by the other 5% product and a lower concentration 2% solution product is available. This may also have implications for overall clinical safety, which is not in the scope of this Team Leader review.

Dermal Safety Studies

The primary clinical reviewer states the following with regard to the dermal safety studies:

In regard to Phase 1 studies, the sponsor has provided only a sensitization study. They need to provide a cumulative irritation study, which is in accord with our current requirements.

The sensitization study was performed by an investigator with a substantial financial investment in Pfizer. This study should be repeated by an independent investigator, because there was a potential bias in the study, the results were somewhat ambiguous in two subjects, and challenge patch readings were not done at 72 hours.

Thus, the potential of irritation and sensitization as per provocative testing is not known. Please refer to Non-Prescription Drug clinical safety review with regard to topical safety from the pivotal clinical study. The excipients used in this drug product are novel to this indication.

This reviewer recommends that the provocative irritation and sensitization studies be requested from the applicant as post-marketing commitments for study for this product unless there is concern from the pivotal study.

Conclusions

In summary, the following actions are recommended for this product from the clinical evaluation of efficacy and the dermal safety studies submitted:

1) The product may be approved on the basis of efficacy, albeit limited, that was observed in the one clinical study submitted.
2) Provocative irritation (at least 35 evaluable subjects) and sensitization (at least 200 evaluable subjects) should be conducted by the applicant as a post-marketing commitment.
3) Labeling should address that the product is for use in men younger than 50 years of age. This restriction can be removed when the applicant conducts studies to evaluate the clinical use of this product in older men.

Final decision for approval should be based on both the efficacy and the safety (see also Review by the clinical safety reviewer, Dr. Daiva Shetty) of the product.

Markham C. Luke, M.D., Ph.D.
Lead Medical Officer, Dermatology

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-812
Submission Code	N-000
Letter Date	March 23, 2005
Stamp Date	March 25, 2005
PDUFA Goal Date	January 24, 2006
Reviewer Name	Phyllis A. Huene, M.D.
Review Completion Date	November 28, 2005
Established Name	Minoxidil
(Proposed) Trade Name	Rogaine
Therapeutic Class	Hair growth agent
Applicant	Pfizer
Priority Designation	S
Formulation	Minoxidil 5% topical foam
Dosing Regimen	Applications twice daily
Indication	Male androgenetic alopecia
Intended Population	Males with alopecia of the vertex area of the scalp

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1. Executive Summary

Recommendation on Regulatory Actions: From an efficacy standpoint, the application is not approvable. Effectiveness for the proposed indication has been demonstrated in one clinical study, but this needs to be replicated in a second study. For a line extension product, the requirement historically for a demonstration of effectiveness has been that either one three arm study which compares the product, the product vehicle, and the reference listed product (in this case, 5% Rogaine solution) or two two arm studies which compare the product with the product vehicle should be performed.

However, the sponsor was advised by the Agency that a single study submission for this indication would be acceptable if the results of the study had the following properties: a) very small p-values, as one would be looking for a much smaller p-value than the 0.05 required for two studies, b) consistency in results across study subgroups, and c) consistency of efficacy across study centers. The biostatistician has found that the study has fulfilled these criteria.

Although the effectiveness has been demonstrated in the one pivotal study, Study 006, there are certain caveats regarding the results, and concerns in regard to the methodology, which may mitigate the robustness of the demonstration of effectiveness. These are:

1) There was no correlation between the two co-primary endpoints, which were counts of non-vellus hairs, and the subject's assessment of improvement scored on a seven point scale.

2) A Study Endpoint Review by the Office of Non-Prescription Products found that the results suggest that only a subset of patients experienced a noticeable improvement, and that these improvements tended to be modest.

3) The study excluded males over the age of 49, whereas the indication is common in patients over 49 years. The sponsor was advised at the End of Phase 2 meeting that the inclusion criteria needed to be revised to include subjects over the age of 49.

4) The methodology used, in particular the level of magnification of the hair count target area, may have caused vellus hairs to be counted as non-vellus hairs.

The sponsor plans to market the product in [redacted] formulations: unscented, [redacted] Study 006 was done only on the [redacted]

Except for Phase 1 studies, the safety of the product for the proposed usage has been reviewed and evaluated by the Division of OTC Drug Products, in accordance with agreements between the Divisions at the time of the initial submission.

In regard to Phase 1 studies, the sponsor has provided only a sensitization study. They need to provide a cumulative irritation study which is in accord with our current requirements.

The sensitization study was performed by an investigator with a substantial financial investment in Pfizer. This study should be repeated by an independent investigator, because there was a potential bias in the study, the results were somewhat ambiguous in two subjects, and challenge patch readings were not done at 72 hours.

Phototoxicity and photosensitization studies are not required, as the ultraviolet absorption spectra for the —— foam formulations are similar to that for 5% minoxidil solution, without significant absorption in the —— range.

Summary of Clinical Findings

1) Brief Overview of Clinical Program

The clinical program consisted of the following studies:

a. Study MINOB-9140-001: The systemic bioavailability of two 5% foam formulations of minoxidil vs 5% minoxidil topical solution in males and 2% topical solution in females.

b. Study MINOB-9140-005: The systemic absorption of minoxidil after the application of increasing doses of 5% minoxidil foam in males.

c. Study MINOB-9140-004: Contact sensitization.

d. Study MINOB-9140-006: A double blind, randomized, placebo-controlled trial of the efficacy and safety of 5% minoxidil foam in the treatment of androgenetic alopecia in males.

Only Study 004 and the portions of Study 006 which are related to efficacy have been reviewed by this reviewer, in accordance with an agreement between this Division and the Division of OTC Drug Products. The safety data in Study 006, and Studies 001 and 005 have been reviewed by the Division of OTC Drug Products.

2) Efficacy

Study 006 was a multicenter, double-blind, randomized, placebo-

controlled trial of the efficacy and safety of 5% minoxidil foam in the treatment of androgenetic alopecia of the vertex region of the scalp in males. Applications of 5% minoxidil foam or the foam vehicle were made twice daily for 16 weeks. The co-primary efficacy variables were a) the mean change in hair counts in a target area of the scalp as determined by a computer assisted dot mapping technique, and b) a subject rating of treatment benefit on a seven point scale of change from baseline, using global photographs of the vertex region.

A total of 315 subjects completed the 16 weeks of treatment. The results of the primary efficacy variables were as follows.

a) Mean change in hair counts.

Mean change in hair counts		
	Minoxidil	Vehicle
Baseline \# subjects Hair count	 180 170.8	 172 168.9
Week 16 \# subjects Hair count Change	 167 191.5 **20.9**	 156 173.6 **4.7**
Adjusted mean change	**21.0**	**4.3**
Difference	**16.7**	
p value	< 0.0001	

b) Subject rating of treatment benefit.

Subject rating of treatment benefit		
	Minoxidil	Vehicle
Mean rating	**1.4**	**0.5**
Difference	**0.9**	
p value	< 0.0001	

3) Safety

The safety data in Study 006 have been reviewed by the Division of OTC Drug Products. Information relevant to Phase 1 cutaneous safety studies have been reviewed by this reviewer; this consists of a) the results of Study 004 on contact sensitization, and b) ultraviolet and visible light absorption spectra for the foam formulations.

a) Study 004: Contact sensitization

The primary objective of this study was to evaluate the potential to induce contact sensitization following repeated application to the skin of human subjects. The secondary objective was to evaluate the safety of the test materials as evidenced by cumulative irritation during the induction phase and adverse events during the study. A total of 240 subjects were included in the irritancy assessment; of these, 198 subjects were evaluated for contact sensitization.

The test materials were the following: Minoxidil 5% Foam unscented, Minoxidil 5% Foam [redacted] Minoxidil 5% Foam [redacted] and Foam Placebo (the vehicle) unscented.

During the induction phase, applications of each of the undiluted test materials were made to the same, randomly assigned skin sites on the back in each subject, three times weekly for nine applications. The initial two applications were made under occlusive patches; these were subsequently changed to semi-occlusive patches due to the high level of irritancy. After a rest period of 10 to 17 days, challenge patches were applied to new skin sites for 48 hours. The sites were evaluated for reactions at 15 minutes and 48 hours after patch removal.

Subjects who exhibited questionable responses, possibly indicative of sensitization, were re-challenged, and the test articles were also openly applied to opposite forearms twice daily for four days.

During the induction phase with semi-occlusive patches, moderate irritation, denoted as moderate erythema, occurred in one or two subjects with each test formulation, while severe irritation, denoted by strong erythema, occurred in one subject with Minoxidil Foam [redacted]

At challenge two subjects had reactions indicative of sensitization. These subjects were re-challenged with Minoxidil Foam [redacted] and Vehicle Foam unscented, and open

applications of these two test products were made twice daily for four days to the volar forearms. The responses to the re-challenge patches were very mild and transient, and no responses were elicited to the open applications on the forearms.

b) Absorption spectra

Absorption spectra in the [redacted] range for the foam products and 5% minoxidil solution have been provided. The spectra for the unscented foam, the [redacted] foam, and the [redacted] foam show some slight absorption in the [redacted] to about [redacted] range, with no significant absorption from [redacted]. The absorption characteristics of the three foam formulations are similar to that of 5% minoxidil solution.

4) Dosing Regimen and Administration

The dosing regimen consists of topical applications of Rogaine Foam twice daily for an indefinite period.

2. Introduction and Background

Product Information

The product name is Men's Rogaine Extra Strength (5% minoxidil) Topical Foam. The foam formulation is a new dosage form of Rogaine for male androgenetic alopecia. The product is to be available OTC in three formulations which vary by fragrance; these are unscented, with a [redacted] fragrance, or with a [redacted] fragrance.

The indication statements on the product label are "Hair Regrowth Treatment" and [redacted]

Currently Available Treatment for Indications

Currently available topical products for androgenetic alopecia in males are Rogaine Regular Strength (2% minoxidil) Topical Solution and Men's Rogaine Extra Strength (5% minoxidil) Topical Solution. Rogaine (2% minoxidil) Topical Solution is available for androgenetic alopecia in women.

Availability of Proposed Active Ingredient in the United States

Topical minoxidil is available in Rogaine Regular Strength (2% minoxidil) Topical Solution and Men's Rogaine Extra Strength (5% minoxidil) Topical Solution.

Important Issues With Pharmacologically Related Products

Systemic minoxidil is marketed as an antihypertensive agent.

Presubmission Regulatory Activity

The most pertinent points conveyed to the sponsor at pre-submission meetings and communications are summarized here. A more complete summary of pre- and post-submission regulatory activity is provided in the appendix to this review.

End of Phase 2 meeting - January 16, 2003

The Agency advised the sponsor of the following points:

a) The recommended co-primary efficacy endpoints are nonvellus hair counts and subject assessment of treatment benefit.

b) Generally, line extensions are based on either two clinical trials in which the new product is compared to vehicle, or a single, three-armed study in which the new product is compared to the currently-marketed product and the new vehicle. However, a single, adequate and well-controlled study in which the new product is compared to its vehicle might be acceptable in the study of androgenetic alopecia on the vertex.

c) A trial of 16 weeks duration is acceptable in the study of androgenetic alopecia on the vertex, if the Sponsor were to agree to include in the label a discussion of the diminution of treatment effect seen in the clinical trials with their currently-marketed 5% MTS.

d) The clinical trials should be conducted with the to-be-marketed formulations. Topical safety studies would be required for each to-be-marketed formulation; however, separate clinical studies for each of the to-be-marketed products may not be required (if the studies are of an appropriate design).

e) As to whether topical safety studies with the fragranced formulations would support marketing of an unfragranced formula, the Agency advised that the studies with the fragranced formulas would have to reveal no irritation or sensitization potential, in order to support marketing of an unfragranced formula.

Telecon of 7/26/04

The Agency's comments strongly encouraged a 3-arm Phase 3 trial in order to ensure robustness of study findings and consequently study interpretability, as an alternative approach to replication of study findings based on 2 trials. The Agency stated that it should be noted however, that a single study submission for this indication would be acceptable to provide such assurances if results from this single study had the following properties:

(i) Very small p-values, as one would be looking for a much smaller p-value than the 0.05 required for 2 studies.

(ii) Consistency in efficacy results across study subgroups.

(iii) Consistency of efficacy across study centers, as efficacy results driven by a few centers would not provide assurance of robustness in a single multi-center trial.

3. Significant Findings from Other Review Disciplines

Biostatistical final review is pending at the time of completion of the clinical review; however, there have been continuing discussions between the biostatistical and clinical reviewers, and there is concurrence on the direction and the significance of the efficacy results of Study 006.

A study endpoint review has been done by the Study Endpoints and Label Development (SEALD) Team in response to a request for consultation by the Office of Non-prescription Products and the Division of Dermatologic and Dental Drug Products regarding the adequacy of the endpoint measures used to document change in hair growth patterns. In the review of the co-primary measures (hair counts and subject assessment of treatment benefit), the key finding of the SEALD team was that there is a weak association between the co-primary endpoint measures, which is likely to be due to these problems noted with the assessment of perceived hair growth:

a) Technical terminology and complex sentence structure may have made it difficult for patients to understand the evaluation task.

b) Use of suboptimal photographs and the lack of rigorous standardization of visual evidence of hair growth patterns in the photographs may not have provided adequate before and after documentation of hair growth patterns.

c) The instructions do not preclude patients from incorporating information about how their scalps feel in their evaluation of the photographic evidence of change in hair growth patterns. This could explain some of the variability between clinician and patient assessments of photographs.

d) Due to the known side effects of minoxidil that are easy to learn about from published information for patients, the patients who received minoxidil and experienced contact dermatitis may have been unblinded to treatment assignment. If so, their perceptions should not be the basis of efficacy decisions. This also could explain some of the variability between clinician and patient assessments of photographs.

The conclusions of the SEALD team review were:

a) The sponsor used a poor measure to evaluate the patient's perception of hair growth.

b) The data do not provide a strong case for the validity of the patient reports, e.g., results from this study show limited agreement between the co-primary endpoints or between patient and expert review of photographic evidence of hair growth patterns.

c) The magnitude of differences observed between treatments was small.

d) Potential unblinding of patients who receive minoxidil and who experience common side effects such as contact dermatitis makes it difficult to rely on patient perceptions.

On review of the secondary endpoints, the overall endpoint conclusions were that:

1) There was little association between hair counts and patient or clinician perceived change in hair growth patterns. Whatever the source of variability in these different endpoints, the results suggest only a subset of patients experienced a noticeable improvement, and those improvements tended to be modest improvement with 16 weeks of twice daily 5% minoxidil therapy.

2) The data based on the patient assessment may not be valid because the question they were asked to answer to evaluate hair loss patterns may not have been adequately understood by all patients. It also may not have been worded in a way that makes clear that the patients were supposed to consider only the photographs to evaluate the change in their hair growth.

3) If the patient experienced contact dermatitis (scalp irritation, dryness, itching, scaling and redness) he and his clinician may no

longer be blinded to the treatment received. This raises significant concerns about reliance on findings from the patient assessments to evaluate the efficacy of this treatment.

4) Weak association between patient and clinician panel evaluation of change in the hair growth patterns based on the same photographs reflect the tendency for clinician review of the same photographs to be evaluated as showing no change. Due to the other questions raised in the review of the patient assessment, the poor correspondence between clinician assessment and hair counts indicates very limited clinical benefit can be expected from this therapy.

5) Any description of the results based on this study should reflect the poor correspondence between perceived and measured hair growth.

Biopharmaceutical, Pharmacology/Toxicology, and CMC reviews are pending.

4. Data Sources and Financial Disclosure

a) Data sources: The sole study provided in the NDA submission for a determination of effectiveness is Study 006.

b) Financial Disclosures

Study [redacted]: The sponsor disclosed that [redacted], M.D., the investigator for Study [redacted] holds Pharmacia & Upjohn stock with a value of $ 321,267.

Study [redacted] The sponsor has provided the following statement: "As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f)."

Listed are all clinical investigators except [redacted] had $ 92,000 in Pharmacia stock, which became Pfizer stock. He was at Center [redacted] which was one of five centers having fewer than 10 subjects per treatment arm who were pooled into new centers. Center [redacted] had [redacted] subjects [redacted] active and [redacted] placebo, and their results were pooled with the results of two other centers.

was one of three dermatologists who constituted the 'Expert Panel', which reviewed the hair growth of each subject by comparison of baseline and week 16 photographs, as a secondary efficacy variable.

5. Integrated Review of Efficacy

Indication: The product is for OTC use in men for balding of the vertex portion of the scalp (male androgenetic alopecia). The precise wording on the product label is as follows.

The front panel of the outer carton bears the following message.

MEN'S

Rogaine

EXTRA STRENGTH

5% MINOXIDIL TOPICAL FOAM
HAIR REGROWTH TREATMENT

FOAM

Not for use by women

On the back panel of the outer carton is stated:

"**Use**: to regrow hair on the top of the scalp (vertex only, see pictures inside label)"

Methods: The efficacy evaluation of Men's Rogaine Extra Strength Minoxidil 5% Foam is based on the single pivotal study MINOB-9140-006.

General discussion of endpoints: The co-primary endpoints are nonvellus hair counts and the subject's evaluation of treatment benefit. These were recommended by the Agency at the End of Phase 2 meeting, and were used in previous Rogaine NDA submissions.

Secondary efficacy variables were 1) an Expert Panel review of non-vellus hair growth, and 2) the mean percent change from baseline in non-vellus hair counts in the target area.

The procedure for counting non-vellus hairs consisted of photographing the clipped hairs within a target area on the vertex of the scalp, magnification of the photograph and placement of a transparency over the photograph, placement of dots on the transparency over each non-vellus hair by a trained observer, and counts of the dots by computer.

The subject rating of treatment benefit was based on the viewing of photographs of the vertex area of the scalp, and was scored on a seven point scale which ranged from 'significantly improved' to 'significantly worse'.

The Expert Panel consisted of three dermatologists who were also study investigators. On the basis of photographs of the vertex area, each panel member rated the amount of improvement or worsening on the same seven point scale as was used for the subject rating of treatment benefit.

The percent change in non-vellus hair counts was not designated as an efficacy variable, secondary or otherwise, in the study protocol or protocol amendments.

Study design

The investigators for the study were as follows.

Wilma Bergfeld, M.D. Cleveland, OH	Dan Piacquadio, M.D. LaJolla, CA
Karl Beutner, M.D. Vallejo, CA	James Swinehart, M.D. Denver, CO
Toni Funicella, M.D. Austin, TX	Janet Roberts, M.D. Portland, OR
Maria Hordinsky, M.D. Minneapolis, MN	Ronald Savin, M.D. New Haven, CT
Anne Lucky, M.D. Cincinnati, OH	David Whiting, M.D. Dallas, TX
Jeffrey Miller, M.D. Hershey, PA	Leonard Swinyer, M.D. Salt Lake City, UT
Elise Olsen, M.D. Durham, NC	Steven Kempers, M.D. Fridley, MN

1) Study title: A Double-Blind, Randomized, Placebo-Controlled Trial of the Efficacy and Safety of 5% Minoxidil Foam in the Treatment of Androgenetic Alopecia in Males.

2) Study objectives: The primary objective was to evaluate the efficacy of a topical 5% minoxidil formulation for the treatment of androgenetic alopecia in males.

   The secondary objective was to evaluate the safety of a topical 5% minoxidil foam formulation in males when used twice daily to the vertex of he scalp for up to one year.

3) Study population: 352 males were enrolled at 14 study centers.

4) Dates of study: The first subject was enrolled in October 2003, and the last subject completed the study in July 2004.

5) Study design: This was a double blind, randomized, multicenter comparison of 5% minoxidil foam with the foam vehicle, with treatment twice daily for 16 weeks.

   Subsequent to the double blind study, an open label extension was performed to obtain further safety data on a total of 12 months treatment with 5% minoxidil foam.

6) Inclusion criteria: Subjects who met the following criteria were enrolled into the study.

   a. Males aged 15 to 49 years, in good health.

   b. Androgenetic alopecia with vertex pattern IIIv, IV, or V on the Norwood-Hamilton scale.

7) Exclusion criteria: Subjects with the following conditions or history were excluded from enrollment in the study.

   a. Known hypersensitivity to minoxidil.

   b. History of hypotension (blood pressure less than 90/60).

   c. Untreated or uncontrolled hypertension (not stable on current medication for the past three months). Hypertension was defined as blood pressure greater than 150/90.

   d. 'Buzz' cut hairstyle, defined as hair cut to less than one inch in length.

   e. A chronic dermatological condition (eczema, psoriasis, infection, etc.) of the scalp other than male pattern hair loss.

f. Use of vitamin A supplements or a vitamin A dietary intake exceeding 10,000 IU/day.

g. Known underlying medical problems that could adversely affect hair growth, such as HIV infection, connective tissue disease, and inflammatory bowel disease.

h. Current or prior use of oral hair re-growth medications (finasteride, other 5-alpha-reductase inhibitors) within one year or neutraceuticals/botanicals for three months before enrollment.

i. Application of a topical minoxidil preparation, or any other topical OTC or prescription medication for hair re-growth, to the scalp for two weeks or more during the six months before enrollment.

j. Current or prior use (within the previous six months) of any immunosuppressive drugs (e.g., cyclosporin), anti-seizure drugs, beta blockers, diuretics, or anti-androgens (e.g., spironolactone, flutamide), diazoxide, or systemic minoxidil.

k. Use of cimetidine or ketoconazole for more than two weeks in the three months before enrollment.

l. Use of systemic steroids (more than 14 consecutive days in the two months before enrollment).

m. Use of isotretinoin in the 12 months before enrollment.

n. Presence of hair transplants, scalp reductions, or hair weaves.

o. Radiation therapy on the scalp or chemotherapy within the year before enrollment.

p. Active, untreated cancer, excluding basal cell or squamous cell cancer of non-scalp areas.

8) Study procedures: At the baseline visit and at weeks 8, 12, and 16 global photographs were taken prior to hair clipping, and 'macro' photographs of the target site were taken for hair count evaluation.

The procedure as described in the protocol and study report was as follows.

To enable consistency and uniformity, the investigators were provided photographic equipment with predetermined settings, which was to be used exclusively for this study. In the photographs the only feature allowed to change was the condition of the subject's hair within the target area. The elements involved in taking the photographs, e.g., film emulsion, lighting, framing, exposure, lens focus, and magnification, were held constant. For each subject the photographs were standardized for lighting, camera angle, and position of subject's head to achieve similar camera angle and relative image size. The magnification threshold for both the camera lens and the color transparency printing were predetermined to optimize the visualization of only the non-vellus hair.

All films were processed and monitored by _____ for compliance with the photographic procedures, and all approved films were mapped and imaged for total visualized hair. Trained and validated mapping technicians mapped all visualized hairs. Hair counts were determined by a validated computer assisted dot mapping technique.

Because many details of the procedures were omitted in the protocol and study report, the sponsor was requested by the Agency on 6/21/05 to provide further information. Our request stated as follows:

"Neither the protocol nor the study report describes how the hairs were actually counted. A description is needed of the procedure which was followed after the 'macro' photographs of the target area were taken. This should be a step-by-step description of how the photographs were treated, whether and how they were enhanced, the nature of the 'dot mapping', and how this ensured that only non-vellus hairs were visualized, the precise role of the computers, the qualifications and training of hair count evaluators, instructional material provided, methods of validation, and any other relevant issues."

The sponsor replied that the use of the term 'visualized' hairs in this protocol, versus the term 'non-vellus' hairs does not represent any change in the hair counting method being used, but only a change in terminology. The procedures used in this study to assess hair count are the same procedures used in previous pivotal trials for hair regrowth products (Rogaine Extra Strength 5% Solution and Propecia), and utilizes the standardized, published, and Agency accepted technique using macro photography. The definition of 'visualized' hairs in this methodology are those hairs seen at the

magnification used in this photographic procedure. Fine unpigmented hair (vellus hair) is not typically visualized in this method.

At a teleconference on 8/25/05, the sponsor provided additional information on the methodology. They stated that the photography technology was designed to measure the regrowth of hair that is equal to or greater than 0.03 mm in diameter. Pfizer is unable to rule out the possibility that hair less than 0.03 mm was included in the regrowth count as well as the possibility that vellus hairs were inadvertently included in the hair count. The camera technology used in the study cannot distinguish between pigmented (non-vellus) and non-pigmented (vellus) hair. Counts were conducted using magnified (at least 5X normal magnification) photographs of the treatment area.

The Agency stated that there appeared to be many sources of variability in the measurement techniques used to assess hair

regrowth and that there was concern regarding the use of magnification to assess the hair growth endpoint.

Pfizer stated that both the dot-mapping technique used for counting hair and the photographic magnification used for visualized hair counts were valid based on internal quality checks that they had conducted and were previously used for other applications for hair growth assessments. In response, the Agency requested the sponsor to submit any information which the sponsor could access, including publications and results of their early work which they referenced to during the meeting, in support of their assertions.

In response to our questions on the methodology raised in the teleconference, the sponsor provided the following information on 9/2/05.

1) What is the support for 0.03 mm (30 microns) as the appropriate diameter threshold for identifying non-vellus hairs?

   The sponsor stated that 0.03 mm is accepted as the upper limit diameter for vellus hairs. A reference cited is Atlas of Hair and Nails, 2000, by Hordinsky, Sawaja, and Scher, in which it is stated "Small hairs, with no pigment or medullary cavity, a diameter of less than 0.03 mm, and a length of less than 1 cm, are classified as vellus (downy) hairs. Another reference is The structure of the Human Hair Follicle, 2004, by Whiting, in which it is stated "Vellus hairs are inconspicuous and are 0.03 mm or less in diameter and often less than 1 cm in length and lack melanin and medulla."

2) How was the 5.7 fold final magnification determined to be the appropriate magnification at which only non-vellus would be visualized and thereby counted in the hair counting methodology used?

   The following is the sponsor's response, paraphrased in part. The sponsor states that over the past 20 years, hair re-growth has been evaluated by counting visualized hairs, at first by direct observation and then with the use of photographs magnified to a sufficient extent to exclude the visualization of vellus hairs. The technology used in Study 006 has been the basis of regulatory approvals, and is the current technology of photographic magnification. Without a diameter measurement of each individual hair, insignificant numbers of vellus and miniaturized vellus hairs may be counted. The technology to measure the diameter of each hair is being explored for future use.

   _____, the technical/medical imaging service provider, has confirmed that a final magnification of 5.7 fold was used both in Study 006 and in the Merck studies on

Finasteride. It is Pfizer's belief that this study was one of the pivotal studies used to approve Finasteride as noted in the Summary Basis of Approval. Pfizer also received assurances from that the photographic equipment and hair counting technique used in Study 006 was the same as those used in the Finasteride trial, and therefore initiated the 006 trial with the understanding that this methodology is currently accepted by the regulatory authorities to support the approval of hair regrowth products.

Pfizer participated in research on hair count methodology by comparing hair counts by the technique used in Study 006 with counts by newer technology which determines actual hair diameter measurements, and believes, while the results are preliminary, that they are supportive of the magnification used in Study 006 and of the accuracy of the non-vellus hair counts. The research compared the number of non-vellus hairs equal to or greater than 0.03 mm counted with the magnification technique to the actual numbers of hairs with a diameter equal to or greater than 0.03 mm as measured by the newer technology. The results showed that the mean target area hair count using the 5.7 fold magnification technique was 169.1 and the number of hairs in the same target area with a measured diameter of >/= 0.03 mm was 166.6.

Pfizer believes that there is further support for the appropriateness of this magnification level from a comparison of the number of non-vellus hairs per cm^2 in target areas on the leading anterior edge of the vertex area in subjects with androgenetic alopecia in different studies, specifically, in Study 006, in the Finasteride study, and in a biopsy study in the literature.

9) Treatment: The test products were 5% minoxidil foam with fragrance and the foam vehicle with fragrance. The subjects were randomized to receive either the active foam or the foam vehicle. Applications were made twice daily for 16 weeks to the scalp in the hair loss area of the vertex, using an amount of no more than half a capful (approximately 1 gm of product). The subjects spread the foam over the area of thinning, gently massaged it into the scalp, and then let the area dry before using styling aids. The subjects were instructed to wash their hands thoroughly with soap and water after applications.

The investigator provided verbal instructions for application and dosage, and written instructions were also provided. The first application was made under supervision at the study site.

The subjects were required to maintain their normal shampooing habits and products during the study, and to maintain the same hairstyle, approximate hair length, and hair color. Normally

prescribed medications and OTC medications were continued, unless already excluded.

Subjects who participated in the open label extension beyond week 16 were provided with 5% minoxidil foam for BID use.

10) Blinding: The investigators, study personnel, monitors, and subjects were blinded as to treatment with the active foam or the vehicle. Neither the protocol nor the study report states that the hair count evaluators were blinded as to timepoint, but the sponsor in subsequent discussions stated that they were blinded to timepoint.

11) Efficacy assessments: Return visits were made at weeks 1, 4, 8, and 12. Efficacy parameters included hair counts, a subject rating of treatment benefit on a questionnaire, and an expert panel review of global photographs.

a) Hair counts: These were done at weeks 8, 12, and 16, as described under 'Treatment procedures' above.

b) Subject rating of treatment benefit: At week 16 the patient received a questionnaire, on which the subject was asked to compare the current hair loss condition with that at baseline by reference to Polaroid photographs. The following scale was used.

3	Significantly improved
2	Moderately improved
1	Slightly improved
0	No change
-1	Slightly worse
-2	Moderately worse
-3	Significantly worse

c) Expert panel review: At week 16 an independent photographic assessment of the global photographs was made by a panel of three investigators; these were Drs. The panel was blinded as to treatment, but was not blinded to timepoint. The expert panel review was conducted under the guidance of After viewing a subject's projected slides, the reviewer recorded an evaluation on the subject's Photographic Evaluation Form. A numeric scale was used which is not provided; from the data analyses it appears to be the

same scale as that for the subject rating of treatment benefit. The Photographic Evaluation Form was not included in the sample Case Report Form provided; the results of this evaluation were apparently recorded separately in the database.

12) Primary efficacy variables: These were as follows.

a) The mean change in visualized hair count in the target area between baseline and week 16, as determined by a computer assisted dot mapping technique.

b) The subject rating of treatment benefit via use of global photographs of the vertex region, assessed as an overall change from baseline.

The secondary efficacy variables designated in the study report were a) the expert panel review of hair re-growth, in a comparison of global photographs taken at baseline to those at week 16, and b) the percent change from baseline in non-vellus hair counts within the target area. However, the latter was not designated as a secondary (or other) variable in the protocol or protocol amendments.

13) Safety assessments: This consisted of the following.

a) Vital signs, including blood pressure, pulse, and weight, taken at screening, baseline, and every four weeks thereafter.

b) Laboratory tests at screening, week 8 and week 16 or discontinuation. These included:

Hemograms: CBC with differential.

Clinical chemistries: albumin, alkaline phosphatase, SGOT, SGPT, calcium, chloride, creatinine, GGT, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, total protein, BUN, uric acid.

Urinalyses: complete urinalyses.

c) Minoxidil serum levels. These were determined as needed if an adverse event of a cardiac nature occurred, namely, a clinically significant change in pulse, blood pressure, or body weight, or if abnormal hair growth (hypertrichosis) were reported or observed.

d) Assessment of the treatment site at each return visit for irritation, particularly erythema, dryness/scaling,

stinging/burning, folliculitis, and itching, with rating as mild, moderate or severe.

e) Recording of adverse events which initiated during the treatment period or within two weeks post-treatment, including the duration, severity, outcome, and the investigator's opinion on a possible drug relationship.

13) Open label extension study. Following completion of the double blind study, approximately 125 subjects were to continue on the active foam for an additional 8 to 12 months. Those who used the active product during the first 16 weeks were to continue its use for an additional 8 months, and those who had used the vehicle were to use the active product for 12 months. Applications were to be made BID as in the double blind study.

The subjects were to return every 4 to 8 weeks, at which times they were to be queried as to adverse events, and vital signs were to be taken, including blood pressure, pulse, and body weight. Laboratory tests, including CBC, chemistries, and urinalysis were to be done at the final visit. Minoxidil serum levels were to be determined as needed if an adverse event of a cardiac nature occurred, namely, a clinically significant change in pulse, blood pressure, or body weight, or if abnormal hair growth (hypertrichosis) were reported or observed. The scalp was to be evaluated for dermatitis at the final visit.

Efficacy findings

Study results:

a) Primary efficacy endpoints: Minoxidil foam was superior to the vehicle in the change in mean non-vellus hair counts from baseline to week 16, and in the subject rating of treatment benefit, with statistically highly significant results. These are summarized as follows.

Mean non-vellus hair counts		
	Minoxidil	Vehicle
Baseline hair count	171	169
Week 16 hair count	192	174
Adjusted mean change	21.0	4.3
Difference	16.7	
p value	< 0.0001	

Subject rating of treatment benefit		
	Minoxidil	Vehicle
Mean rating	1.4	0.5
Difference	0.9	
p value	< 0.0001	

b) Secondary efficacy endpoints: Minoxidil foam was superior to the vehicle in the change in the Expert Panel review and in the mean percent change in non-vellus hair counts, with statistically highly significant results. These are summarized as follows.

Expert Panel Review		
	Minoxidil	Vehicle
Mean rating	0.5	0.0
Difference	0.5	
p value	< 0.0001	

Mean percent change in non-vellus hair counts		
	Minoxidil	Vehicle
Adjusted mean % change	13.7	3.3
Difference	**10.3**	
p value	< 0.0001	

The following additional tabulations were submitted by the sponsor in September 2005, in response to the Agency's request.

a) The correlation between the hair counts and the subject assessment.

The mean hair count change for subjects in each category of the subject assessment is as follows.

Subject assessment	Placebo		5% foam	
	N	Mean count	N	Mean count
-3 = significantly worse				
-2 = moderately worse	7	- 6.3	1	29.0
-1 = slightly worse	22	3.2	9	15.3
0 = no change	53	5.2	29	18.3
1 = slightly improved	34	4.6	39	17.2
2 = moderately improved	24	12.2	45	20.4
3 = significantly improved	8	- 5.0	38	26.6

b) The correlation between the subject assessment and the median score of the Expert Panel review.

In the tabulations that follow, the percentages have been added by this reviewer. Also, it is noted that the scale used was the same for the subject self assessment and for the expert panel review; this was not stated in the study report.

The number of subjects in each category of the subject self assessment rating, and the number of subjects in the same category according to the median score of the expert panel rating is as follows.

Subject self assessment and median score of expert panel review				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	Expert panel review	Subject assessment	Expert panel review
-3 = significantly worse				
-2 = moderately worse	8 (5%)		1 (0.5%)	
-1 = slightly worse	25 (15%)	4 (2%)	10 (6%)	
0 = no change	56 (33%)	134 (78%)	32 (18%)	94 (52%)
1 = slightly improved	36 (21%)	8 (5%)	41 (23%)	55 (31%)
2 = moderately improved	28 (16%)	1 (0.6%)	47 (26%)	14 (8%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

c) The correlation between the subject assessment and the assessment of the individual members of the Expert Panel.

The distribution of the scores in the subject assessment, and the distribution of the scores of each Panel member, were as follows.

Correlation between subject self assessment and rating by [illegible]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	[illegible]	Subject assessment	[illegible]
-3 = significantly worse				
-2 = moderately worse	8 (5%)	1 (0.5%)	1 (0.5%)	
-1 = slightly worse	25 (15%)	11 (6%)	10 (6%)	7 (4%)
0 = no change	56 (33%)	127 (74%)	32 (18%)	112 (62%)
1 = slightly improved	36 (21%)	7 (4%)	41 (23%)	39 (22%)
2 = moderately improved	28 (16%)	1 (0.5%)	47 (26%)	5 (3%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

Correlation between subject self assessment and rating by [illegible]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	[illegible]	Subject assessment	[illegible]
-3 = significantly worse				
-2 = moderately worse	8 (5%)		1 (0.5%)	
-1 = slightly worse	25 (15%)	7 (4%)	10 (6%)	
0 = no change	56 (33%)	118 (69%)	32 (18%)	73 (41%)
1 = slightly improved	36 (21%)	22 (13%)	41 (23%)	65 (36%)
2 = moderately improved	28 (16%)		47 (26%)	25 (14%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

Correlation between subject self assessment and rating by [illegible]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	[illegible]	Subject assessment	[illegible]
-3 = significantly worse				
-2 = moderately worse	8 (5%)	1 (0.5%)	1 (0.5%)	
-1 = slightly worse	25 (15%)	4 (2%)	10 (6%)	
0 = no change	56 (33%)	124 (72%)	32 (18%)	93 (52%)
1 = slightly improved	36 (21%)	17 (10%)	41 (23%)	50 (28%)
2 = moderately improved	28 (16%)	1 (0.5%)	47 (26%)	20 (11%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

d) The individual scores fo each member of the Expert Panel.

The frequency distribution of the individual Panel member scores is as follows.

Frequency distribution of scores of expert panel reviewers						
Rating scale	Placebo n=172			5% foam n=180		
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
-3 = significantly worse						
-2 = moderately worse	1 (0.5%)		1 (0.5%)			
-1 = slightly worse	11 (6%)	7 (4%)	4 (2%)	7 (4%)		
0 = no change	127 (74%)	118 (69%)	124 (72%)	112 (62%)	73 (41%)	93 (52%)
1 = slightly improved	7 (4%)	22 (13%)	17 (10%)	39 (22%)	65 (36%)	50 (28%)
2 = moderately improved	1 (0.5%)		1 (0.5%)	5 (3%)	25 (14%)	20 (11%)
3 = significantly improved						
Missing	10 (6%)		25 (15%)	17 (9%)	17 (9%)	17 (9%)

Discussion of study results: In summary, the results of Study 006 showed minoxidil foam to be statistically highly superior to its vehicle in the co-primary endpoints, namely, increase in non-vellus hair counts and subject rating of treatment benefit. Minoxidil foam was also highly superior to the vehicle in the secondary efficacy variables, namely, in the Expert Panel review and in the mean percent change in non-vellus hair counts.

There are, however, certain caveats in the interpretation of, and conclusions to be drawn from, these results. These are as follows.

1) The age of the subjects in the study. The inclusion criteria limited the age to 49 years and below, whereas the condition is common in males over the age of 49 years. The sponsor was advised in the clinical comments of 3/19/04 on the protocol for study 006 that there should be no upper limit for age in the inclusion criteria.

2) Use of hair dye. The sponsor was also advised in the clinical comments of 3/19/04 on the protocol for study 006 that subjects using hair dye should be excluded, but this was not included in the exclusion criteria.

3) Lack of blinding to timepoint in the Expert Panel review. This may have introduced bias into the study if the evaluator sensed a lack of change or a trend. The sponsor was so advised prior to initiation of the study in the clinical comments of 3/19/04. The Agency also recommended that the evaluator assessment for the Expert Panel review be based on direct clinical evaluation during treatment visits rather than on photographs.

4) Post hoc designation of the mean percent change in non-vellus hair counts as a secondary efficacy variable. This was not designated as an efficacy variable in the protocol or protocol amendments.

5) The lack of correlation between the mean hair counts and the subject's assessment of treatment benefit, and between the assessment of change in hair growth by the Expert Panel and by the subjects.

Certain considerations arose during the clinical and statistical reviews of study 006, which after further discussion with the sponsor and submission of additional information by the sponsor are felt by this reviewer to have been resolved. These are:

a) The study methodology. The original submission of the NDA did not adequately describe the methodology for hair counts, and the sponsor was requested to provide additional information. The sponsor subsequently provided greater detail on the study procedures, with substantiation for certain features such as the

minimum hair diameter cutoff for non-vellus hairs and the standardized magnification level of the photographs that were used for hair counts. The technicians who performed the dot mapping procedure were blinded as to timepoint; this had not been stated in the study protocol or study report.

The sponsor stated that this methodology was the same as that used in previous pivotal trials for Rogaine Extra Strength 5% solution and Propecia.

It appears that, while it is possible that some borderline vellus hairs might have been included in hair counts, a substantial effort was made to ensure that only non-vellus hairs were counted, and the technology used is the current state-of-the-art, having been used in pivotal studies on other approved hair regrowth products. The methodology is considered to be satisfactory.

b) The question of bias in the Expert Panel review. [redacted] had a substantial financial interest in Pfizer and was one of the three members of the Expert Panel. The sponsor was requested to compare the scores of the individual Panel members, and provided this comparison. It was found that in the distribution of scores, [redacted] actually rated the subjects in the minoxidil group lower, (i.e., showing less improvement), with less difference between the active and vehicle groups, than did the other two Panel members.

Efficacy conclusions: The results of Study 006 demonstrate that Rogaine 5% Foam is effective in producing hair regrowth in male androgenetic alopecia of the vertex region of the scalp, although there are certain caveats in the interpretation of the study results, as have been listed above. These results need to be replicated in a second study.

It is noted that the sponsor was advised by the Agency that a single study submission for this indication would be acceptable if the results of the study had the following properties: a) very small p-values, as one would be looking for a much smaller p-value than the 0.05 required for 2 studies, b) consistency in results across study subgroups, and c) consistency of efficacy across study centers. The biostatistician has found that the study has fulfilled these criteria.

However, for a line extension, the requirement historically for a demonstration of effectiveness has been that either one three-arm study which compares the product, the product vehicle, and the reference listed product (in this case, 5% Rogaine solution), or two two-arm studies which compare the product with the product vehicle, should be performed. The abrogation of this precedent may be problematic in our evaluation of other line extension products. In consideration of this, and the fact that several of the salient recommendations made by the

Agency were not followed in the design of the study, a second study should be performed.

6. Integrated Review of Safety

The only safety data reviewed by the Division of Dermatologic and Dental Drug Products are the Phase 1 studies, in accordance with an agreement between this Division and the Division of OTC Drug Products at the filing meeting for NDA 21-812.

A Phase 1 sensitization study (Study 004) has been provided, which is also intended to provide information on cumulative irritation through the repeated exposure in the induction phase. This is as follows.

Study MINOB-9140-004: Contact sensitization

This was performed by

1) Study title: Evaluation of the Potential for Contact Sensitization with 5% Minoxidil Foams in Human Adults under Repeated Insult Patch Conditions.

2) Study objectives: The primary objective was to evaluate the potential to induce contact sensitization following repeated application to the skin of human subjects. The secondary objective was to evaluate the safety of the test materials as evidenced by cumulative irritation during the induction phase and the report of adverse events during the study.

3) Test population: 240 subjects were included in the irritancy assessment; of these, 198 subjects were evaluated for contact sensitization.

4) Test materials: These were the following:

   A. Minoxidil 5% Foam Unscented

   B. Minoxidil 5% Foam

   C. Minoxidil 5% Foam

   D. Foam Placebo Unscented

5) Test procedures:

A score was given to a patch site when at least 25% of the patch area demonstrated a clinically significant skin response. The scores consisted of a numeric grade, which was appended with a letter grade as appropriate; these were as follows.

Numerical grades	
0	No visible reaction
plus	Slight, confluent or patchy erythema
1	Mild erythema (pink)
2	Moderate erythema (definite redness)
3	Strong erythema (very intense redness)

Letter grades	
E	Edema - swelling, spongy feeling when palpated
P	Papule - red, solid, pinpoint elevation
V	Vesicle - small elevation containing fluid
B	Bulla reaction - fluid filled lesion (blister)
S	Spreading - evidence of the reaction beyond the pad area
W	Weeping - result of a vesicular or bulla reaction - serous exudate
I	Induration - solid, elevated, hardened, thickened skin
star	Residual reaction to earlier application
-	Response occurs on 25% or less of test site

Superficial effects	
g	glazing
y	peeling
c	scab, dried film of serous exudate of vesicular or bulla reaction
d	hyperpigmentation (reddish-brown discoloration of test site)
h	hypopigmentation (loss of visible pigmentation at test site)
f	fissuring - grooves in the superficial layers of the skin
additional comments as appropriate were noted	

Applications were terminated or moved to new adjacent sites if an accumulated score of 2 or greater were observed. For this purpose the letter grades appended to the numerical grades, except for edema, were considered to be equal to a score of 1, and the superficial effects fissuring or scabbing were equal to 1.

Results were as follows.

1) Subject enrollment and disposition: 240 subjects were enrolled in the study, of which 41 subjects did not complete the study. The reasons for non-completion were as follows.

Reason	# subjects
Withdrew consent	27
Lost to followup	10
Other, specified	2
Adverse event	2

One of the adverse events was a skin ulcer unrelated to the study products. The other adverse event which resulted in discontinuation was not specified, but the only other adverse event of the skin reported was pruritus, which was possibly related to the study medications.

2) Reactions during the induction phase: With the inital two applications of the test materials under occlusive patches, moderate to strong irritation was found in the majority of subjects. After the study procedures were changed to semi-occlusive patches for the remainder of the study, irritation levels subsided substantially. All four test materials showed similar results, with 52% to 78% showing no irritation, 22% to 48% showing slight to mild irritation, and 1% or less showing moderate irritation over the course of the induction period. The highest frequencies of moderate or severe irritation with semi-occlusive applications at any visit during the induction phase were:

Incidence of moderate and severe reactions Induction phase		
Irritation score	2	3
Minoxidil foam unscented	1 (0.5%)	0
Minoxidil foam [redacted]	1 (0.5%)	0
Minoxidil foam [redacted]	2 (1.0%)	1 (0.5%)
Placebo foam unscented	1 (0.5%)	0

3) Reactions at challenge: Two subjects had reactions that were considered to be indicative of sensitization. The first subject had a very mild reaction at 15 minutes and a strong reaction, with a score of 3E, at 48 hours to minoxidil foam [redacted], and a very mild reaction at 15 minutes and a moderate reaction, with a score of 2Ey, at 48 hours to the vehicle foam unscented. The second subject had a mild to moderate reaction (1E) at 15 minutes and a moderate reaction (2E) at 48 hours to minoxidil foam [redacted] and a very mild reaction (+) at 15 minutes and a mild to

moderate reaction (1E) at 48 hours to vehicle foam unscented.

Both subjects were re-challenged with minoxidil foam —— and vehicle foam unscented, and open applications of these two test products were made twice daily for four days to the volar forearms. The responses to the re-challenge patches were very mild and transient, and no responses were elicited to the open applications on the forearms.

A third subject showed at the 15 minute evaluation a mild reaction (1) to minoxidil foam —— and placebo foam unscented, and a mild to moderate reaction (1E) to minoxidil foam —— and minoxidil foam unscented. At the 48 hour evaluation this subject showed a mild reaction (1 or 1y) with minoxidil foam —— , —— , and vehicle foam unscented, and a mild to moderate reaction (2c) with minoxidil foam unscented. This subject was not re-challenged due to the similar responses to all four test materials. It was felt that these were likely to be irritant responses related to the alcohol component of the vehicle.

Other Phase 1 studies

On May 25, 2005, at an Agency request the sponsor submitted absorption spectra in the —— range for the foam products and 5% minoxidil solution. (This information had previously been submitted in December 2002 in the briefing package for the End-of-Phase-2 meeting). The spectra for the unscented foam, the —— scented foam, and the —— scented foam show some absorption in the —— to about —— range, with no significant absorption from —— —— The absorption characteristics for the three foams are the same as for 5% minoxidil solution.

Discussion of results - Phase 1 studies

1) Study 004: Contact sensitization.

In view of the following concerns, the study should be repeated by an independent investigator.

a) The investigator for this study had a substantial investment in Pfizer stock and must be considered to be potentially biased.

b) Reactions to the challenge patch should have been read at 72 hours after patch removal, as was advised by the Agency.

c) The reactions at challenge were ambiguous in two subjects, although the subjects were re-challenged and did not show sensitization reactions at 48 hours after patch removal.

d) A third subject also showed a reaction indicative of

sensitization (designated as 'c', which is described as a scab, dried film of serous exudate of vesicular or bullous reaction), but was not re-challenged.

The sponsor has intended that the induction phase of the sensitization study serve as an irritation study. During the induction phase it was found that moderate to severe irritation occurred with occlusive patches, and that the level of irritation diminished with semi-occlusive patches.

The frequency and duration of patching in the induction phase was not in accord with our requirements for an irritation study. A cumulative irritation study which entails daily applications for 21 days to the same skin site in a minimum of 30 subjects should be performed; this should preferably include a positive and a negative control, the vehicle, and 5% minoxidil solution. The sponsor was advised of the requirement for a cumulative irritation study in pre-submission communications.

The absorption spectra provided for the three foam formulations are adequate to obviate the need for phototoxicity and photosensitization studies.

7. Overall Assessment

a) Conclusions

Study 006 has demonstrated the effectiveness of Rogaine 5% Foam in producing hair regrowth in male androgenetic alopecia of the vertex region of the scalp. These results need to be replicated in a second study.

An additional sensitization study by an independent investigator, and a cumulative irritation study should be performed.

b) Recommendation on Regulatory Action: The application is not approvable.

c) Recommendation on Postmarketing Actions: None

d) Labeling Review: Not applicable.

8. Appendices

Presubmission Regulatory Activity

The following is a summary of the meetings and communications with the sponsor which are relevant to the review of NDA 21-812.

a) End of Phase 2 meeting - January 16, 2003

The following is the portion of the clinical discussion at the End of Phase 2 meeting which is considered by this reviewer to be relevant to the current NDA submission; the discussion of other issues has been omitted.

Sponsor's Question 1:

While the current dosing of our Rogaine topical minoxidil solutions is metered with a calibrated dropper, we propose to direct consumers to apply the foam product to "the Affected hair loss area," without quantitative measurement but with semi-quantitative guidance on the amount of foam applied, as [is] the practice with other Rx foams applied to the scalp. Based on the rationale and proposed dosing directions, is this acceptable?

Agency Response:

Unlike some other foam products, the sponsor's product is intended for daily application(s) of a specified dose (approximately 50 mg of minoxidil) for an indefinite period; both safety and efficacy could be impacted by misapplication. The sponsor is requested to address how the amount of foam dispensed would be controlled in the absence of a meter. Also, the sponsor is requested to clarify the application procedures to the vertex i.e., how subjects would estimate the golf-ball sized amount to directly apply given that the vertex might be difficult to visualize during application.

Sponsor's Question 2:

Is a single study of this men's protocol design acceptable to support an indication for use on the vertex and/or frontal hair loss area with twice daily dosing?

Agency Response:

A) The recommended co-primary efficacy endpoints are nonvellus hair counts and subject assessment of treatment benefit. B) Generally, line extensions are based on either two clinical trials in which the new product is compared to vehicle, or a single, three-armed study in which the new product is compared to the currently-marketed product and the new vehicle. However, a single, adequate and well-

controlled study in which the new product is compared to its vehicle might be acceptable in the study of androgenetic alopecia on the vertex..... If the Sponsor plans to make any comparative claims to the currently-marketed product, two three-armed studies would be needed, i.e. the new product vs the currently-marketed product vs the foam vehicle (a solution vehicle arm could be included). C) A trial of 16 weeks duration is acceptable in the study of androgenetic alopecia on the vertex, if the Sponsor were to agree to include in the label a discussion of the diminution of treatment effect seen in the clinical trials with their currently-marketed 5% MTS.

Additional comments:

1) No commitments can be made in the absence of sufficient information, e.g., the methodologies for the Global Panel Review, hair counts and photographic procedures were not included in the draft protocols.

2) The sponsor proposes to use different fragrances in the product planned for marketing to males and that proposed for females. The clinical trials should be conducted with the to-be-marketed formulations. Topical safety studies would be required for each to-be-marketed formulation; however, separate clinical studies for each of the to-be-marketed products may not be required (if the studies are of an appropriate design).

3) Minoxidil levels should be obtained in the face of any cardiovascular events and with hypertrichosis on sites distant from the hairline.

The Sponsor inquired whether topical safety studies with the fragranced formulations would support marketing of an unfragranced formula. Agency advises that the studies with the fragranced formulas would have to reveal no irritation or sensitization potential, in order to support marketing of an unfragranced formula. Inclusion of the unfragranced formula in a clinical study may be useful to tease out whether the fragrance was a contributing factor in any irritation or sensitization seen.

All photographs should be maintained so that they are available to the reviewer (on request).

Since the product is for cosmetic use, it is important that subject assessment of treatment benefit be assessed.

b) Clinical comments on the protocol for Study 006 - March 19, 2004

A large number of clinical deficiencies were relayed to the sponsor in

this communication. This summary includes only those deficiencies deemed relevant to the current submission, omitting those that have been satisfied by the sponsor.

1. The sponsor was advised at the End-of-Phase 2 meeting that the Agency recommends co-efficacy endpoints of non-vellus hair counts and subject assessment of treatment benefit. However, hair counts in this study include all hairs that are visualized in photographs (i.e., both vellus and non-vellus). The sponsor states that at the magnification used in the photographs for hair counts, 'fine pigmented hair (vellus hair) is not typically visualized." Nonetheless, vellus hairs which are visible in photographs should not be included in hair counts. Increased numbers of vellus hairs may not result in a clinically meaningful improvement for this cosmetic indication.

2. As indicated at the End-of-Phase-2 meeting, to evaluate the relative efficacy of this product compared to 5% minoxidil topical solution, the sponsor should consider a three arm safety and efficacy trial comparing the new formulation to the already approved 5% minoxidil topical solution and placebo in men. If such a three-armed study is not conducted, it is strongly recommended that two clinical trials be performed.

3. The inclusion criteria for age need to be revised. The sponsor has not justified the exclusion of males over the age of 49 with androgenetic alopecia who otherwise meet eligibility criteria. This indication is common in men over age 49. It is recommended that there be no upper age limit.

4. In this study, panel review is based on the assessment of photographs. However, it is recommended that evaluator assessment be performed by investigators based on direct clinical evaluation during treatment visits.

5. In the current proposed study, evaluators in the panel review are non-blinded with respect to the time point when photographs are taken; no rationale has been provided for non-blinding of evaluators, which may introduce bias.

6. As was discussed at the End of Phase 2 meeting, the sponsor has provided a rationale for non-metered dosing of 5% minoxidil topical foam. They have provided information from two systemic bioavailability studies in human subjects and conclude that these studies support the contention that it is unnecessary to meter the dose. They also state that "historically, with very few exceptions, dermatologic drugs have not required precise dosing for reasons of either safety or efficacy." The submitted information will be reviewed and taken under consideration. However, unlike some other foam products, the sponsor's product is

intended for daily application for an indefinite period; both safety as well as efficacy could be impacted by misapplication. In addition, adverse effects reported for marketed minoxidil solution products have included syncopal episodes and hypotension. Therefore, the safety of non-metered dosing remains an important concern.

7. Patients using hair dye should be excluded from the study.

c) Clinical comments on Phase 1 studies - March 31, 2004

The deficiencies noted by the Agency in the sponsor's protocol for a contact sensitization study were relayed to the sponsor in this communication. This summary includes only those deficiencies deemed relevant to the current submission, omitting those that have been satisfied by the sponsor.

1. Following removal of the challenge patch, readings should be performed by a trained and blinded observer at 30 minutes, 24, 48, and 72 hours; under the current protocol readings are performed only at 15 minutes and 48 hours.

2. For patients who are being re-challenged to 'suspected components of the clinical test material", this should include sports fragrance and floral fragrance in all cases. Re-challenge is not necessary after a positive challenge result; it should be reserved for responses that are ambiguous.

3. A narrative description of each reaction in the challenge phase should be provided, together with the opinion of the investigator as to whether such reactions are felt to be indicative of contact sensitization. Data analysis should also include daily observations as well as a tabulation of the percentage of subjects with each grade of skin reaction and degree of patch adherence on each study day. The mean cumulative irritation score and the total cumulative irritation score for all the study subjects should be calculated for each test product, and a statistical analysis of the comparative results should be performed.

4. Dermal safety studies should include both a skin sensitization study and a cumulative skin irritation study. A cumulative skin irritation study needs to incorporate daily patch application and evaluation for a minimum of 21 days. The sponsor may combine these studies by modifying the current protocol to include daily patch application. Otherwise, the sponsor needs to conduct a separate cumulative skin irritation study. If the sponsor chooses to conduct a separate cumulative skin irritation study, the number of patients enrolled should ensure a minimum of 30 evaluable subjects. A randomized, controlled repeat patch test should be performed in which patches are applied for 23 hours (plus or minus

one hour) daily for 21 days to the same skin site. At each patch removal the site should be evaluated for irritation reaction and the patch reapplied.

5. If any components of the new formulations absorb light in the UVA, UVB or visible spectrum, then photosafety testing should also be performed.

6. Dermal safety studies should be performed using the final to-be-marketed formulation.

d) Clinical comments on Study 006 - June 9, 2004

The information conveyed to the sponsor that is relevant to the current NDA submission is as follows.

1. In this submission, the sponsor requested a response to the following question: "Does the Agency agree that the information provided herein adequately addresses all the deficiencies noted?"

   The Agency replied that it does not agree that the information provided here adequately addresses all of the clinical deficiencies noted in our review of this protocol. The sponsor is strongly encouraged to follow the recommendations made regarding this protocol at the End-of-Phase 2 meeting and our communications of March 19, 2004 and March 25, 2004. These clinical recommendations remain unchanged.

2. The Agency is receptive to reviewing additional Phase 3, open label and other studies to support this indication prior to their start.

e) Telecon of 7/26/04

The following are the verbatim minutes of the telecon.

"A teleconference was held between the Division and the Sponsor on July 26, 2004, in response to the Sponsor's submission (IND 50,063/SN 23) dated July 16, 2004, to clarify the requirements for the number of pivotal trials expected for the 5% Minoxidil topical foam for men as outlined at the End of Phase 2 meeting.

Dr. Wilkin started the meeting with a brief introduction related to the sponsor's submission of July 16, 2004, and indicated that the meeting will focus on the following two points related to Sponsor's submission:

1. In your submission you have stated that your protocol for the proposed study was submitted to the Agency for

comments on September 24, 2003, and that the study was initiated shortly thereafter in October of 2003. This indicates that you were not looking for the Division's comments prior to study initiation. Also, you made reference that the Division's comments were faxed to you on March 19, 2004. The Division reminds you that you could have submitted a request for Special Protocol Assessment, and you would have received the Division's comments on your protocol within 45 days of the date of your submission.

In response, the Sponsor indicated that they thought that all aspects of the study were acceptable to the Division and consequently they proceeded with the study shortly after the submission of the protocol to the Division.

The Division reminded the Sponsor that unresolved issues related to primary endpoints of the study were raised at the End of Phase 2 meeting but were not resolved prior to protocol submission and study initiation.

2. The Division's comments strongly encouraged a 3-arm Phase 3 trial in order to ensure robustness of study findings and consequently study interpretability, as an alternative approach to replication of study findings based on 2 trials. It should be noted however, that a single study submission for this indication would be acceptable to provide such assurances if results from this single study had the following properties:

   (i) Very small p-values, as one would be looking for a much smaller p-value than the 0.05 required for 2 studies.

   (ii) Consistency in efficacy results across study subgroups.

   (iii) Consistency of efficacy across study centers, as efficacy results driven by a few centers would not provide assurance of robustness in a single multi-center trial.

The Sponsor acknowledged the Divisions's comments concerning the requirements expected for a single study submission and the teleconference ended."

f) Meeting minutes on protocol for female androgenetic alopecia - February 2, 2005

This meeting was held to discuss the sponsor's questions and comments on the Agency's Special Protocol Assessment of a protocol for the treatment of female androgenetic alopecia. Some of the clinical points made by the Agency at this meeting are relevant to the review of the current submission for the indication male androgenetic alopecia, and are repeated here by this reviewer.

1. The Agency emphasizes the need for patients to be blinded to time point for subject self-assessment if photographs are used (refer to July 7, 2004 Meeting Minutes). The Agency considers this very important. Patients should be presented with two photographs in which the chronological sequence is randomized and coded so that it is unknown to both the patient and the investigator administering the assessment. It is important that photographs exclude any features such as clothing or jewelry that might indicate the time the photograph was taken. As noted, photographs should be maintained and available upon request by the Agency.

2. The Agency also continues to believe that a static scale would be preferable for use in patient self-assessment. Thus, patients (blinded to the time point of the photographs) would rate each photograph independently during patient self-assessment instead of rating one relative to the other. The Agency would consider a static scale to be a cleaner and more convincing comparison than the current dynamic scale proposed by the sponsor. A static scale would avoid complications related to asymmetry in departure from 0 in rating positive and negative effects.

3. A 7-point integer scale will be used for patient self-assessment in this study. As noted at the SPA meeting, you should rely on clinically meaningful differences between the active and vehicle groups. The scale should be dichotomized with success defined as a score of 2 or 3. See also Biostatistics comments.

   The Agency would consider success to be defined as at least a 2 on the integer scale proposed by the sponsor, where 0 is "no change," 3 is "greatly increased," and -3 is "greatly decreased" scalp coverage as assessed by the patient (based on comparing two photographs while blinded to time point). A change of only one unit might indicate a minor change that is not clinically meaningful. Patients may have difficulty distinguishing between no change and a "slight increase" or "slight decrease" (i.e. a 1 unit change) of scalp coverage. See also Biostatistics comments.

4. The use of "macro" photography for measuring hair counts needs to be substantiated and validated. The procedure for hair counting by this method should be detailed, including information about whether it will be computer-assisted, and how vellus hairs will be excluded from counts. It is unclear who is performing the hair counts and their qualifications. Investigators calculating hair counts should be blinded (including to treatment and time point in the study).

Sponsor's response: The sponsor responded that [redacted] has been widely published and used as co-primary endpoints in past minoxidil and finasteride submissions. The sponsor further stated that more recently developed digital photographic methodology provides hair counts based on the selective detection of hairs with a width >30 microns, which are non-vellus or terminal hairs. As with the previous 35 mm film based method, the new method relies on a technician to identify individual hairs for the system to count and measure. Imaging technicians are trained on performing hair identification and measurement processes that allows them to make decisions on complex conditions such as clipped hairs in the target area or identifying when multiple shafts are originating from a single follicle. In addition, these individuals are trained on the analysis software and in ICH GCP and FDA guidance for electronic records (21 CFR Part 11).

[redacted] acting as the central imaging laboratory for this study, will remain blinded to treatment. In order to blind technicians to time during analysis, individual images will only be identified with a image number and not with corresponding study site, subject, or visit information.

Agency response: The Agency requests that the sponsor submit detailed information (which may include publications) regarding the methodology to be used for hair counting. This information should validate the specific method to be used for this purpose in the proposed study (i.e., the digital photographic method for hair counting).

The proposed cut off of > 30um width to define non-vellus hairs does not appear acceptable (see Dawber R, Van Neste, D. Hair and Scalp Disorders. Philadelphia: J.B. Lippincott; 1995, p. 33). Also, you should address if variation of hair width is expected based on factors such as race, ethnicity, or age, and how such variation will be taken into account in the proposed study. The methodology to be used for measuring hair width should be carefully defined.

Key considerations discussed are as follows:

1) When evaluating the literature for a cut-off width for non-vellus hairs, copies of all such references should be forwarded to the Agency.

2) In addition, the minimum width selected should not be the absolute minimum, but [should] allow for some degree of assurance that the hairs are mostly non-vellus. The 30um width is not adequate.

3) The sponsor was asked to address the race and age issues with regard to hair width, (e.g., do different races have different cut-off widths for non-vellus hairs?)

4) What is the gold standard for comparison for hair width?

5) What is the precision that is achievable using the method that is proposed by the sponsor?

5. The Agency commented that the safety of non-metered dosing remains an important concern. The product is intended for daily application for an indefinite period; both safety and efficacy could be impacted by misapplication. In addition, adverse effects reported for marketed minoxidil solution products have included syncopal episodes and hypotension.

The sponsor replied that an appropriate foam metering device remains unavailable at this time, but that it has been demonstrated in the recently completed Phase 3 study with 5% minoxidil topical foam in males that the subjects were able to accurately dispense the labeled amount of product.

The Agency responded that we consider the reliability of non-metered dosing to remain an important safety concern. As discussed in the comments of March 17, 2004, it is important that the patient's reliability in not exceeding the amount of foam per use be evaluated based on weights of clinical test material during and at the completion of the study.

Conformance with Agency recommendations

The following are the points and recommendations discussed by the Agency in various communications and meetings prior to the NDA submission which the sponsor did not appear to address in the NDA submission. These are denoted under headings which describe the particular issue, as follows.

1) Duration of clinical study: In the End-of Phase 2 meeting, the Agency said that a trial of 16 weeks duration is acceptable in the study of androgenetic alopecia of the vertex, if the Sponsor were to agree to include in the label a discussion of the diminution of treatment effect seen in the clinical trials with their currently-marketed 5% minoxidil topical solution. It does not appear that this was addressed.

2) Phase 1 studies

Sensitization study: In reviewing the protocol for the sensitization study, the Agency said in the fax of 3/31/04 that following removal of the challenge patch, readings should be performed at 30 minutes and at 24, 48, and 72 hours. In the sensitization study which was performed, readings were taken only at 15 minutes and 48 hours after patch removal.

Need for cumulative irritation: In the fax of 3/31/04, the Agency said that they would need a cumulative skin irritation study as well as a sensitization study. The sponsor was told that this should entail daily patch application to the same skin site for a minimum of 21 days in a minimum of 30 subjects. The sponsor has not provided this.

3) Inclusion and exclusion criteria: In clinical comments on the protocol for study 006 of 3/19/04, the Agency said that the inclusion criteria for age need to be revised, and that the sponsor had not justified the exclusion of males over the age of 49 with androgenetic alopecia who otherwise meet eligibility criteria. It was noted that this indication is common in men over age 49, and it was recommended that there be no upper age limit. The sponsor did not comply with this.

The Agency also said that subjects using hair dye should be excluded from the study. This was not done.

6) Panel review: In the clinical comments of 3/19/04 on the protocol for Study 006, the Agency said that Panel review is to be based on the assessment of photographs, but the Agency recommended that evaluator assessment be performed by investigators based on direct clinical evaluation during treatment visits. The Agency also said that evaluators in the Panel review are to be non-blinded with respect to the time point when photographs are taken, and that no rationale has been provided for this, which may introduce bias. The sponsor did not revise this, and in the study the Panel was not blinded to timepoint.

Post-Submission Communications

a) Agency facsimile of 6/21/05

The following requests for information were made on 6/21/05, to which the sponsor responded on 7/19/05. These were as follows.

1. (Agency) The sensitization study does not appear to have been performed with the minoxidil foam formulations or the vehicle formulation that were used in Study 006, as the formula numbers provided in the separate study reports are not the same. Please clarify.

   The sponsor replied that the formulations used in the two studies were the same; an error in the formulation codes occurred in the study report for 006, and the sponsor will provide corrected pages in this regard.

2. (Agency) Neither the protocol nor the study report describes how the hairs were actually counted. A description is needed of the procedure which was followed after the 'macro' photographs of the target area were taken. This should be a step-by-step description of how the photographs were treated, whether and how they were enhanced, the nature of the 'dot mapping', and how this ensured that only non-vellus hairs were visualized, the precise role of the computers, the qualifications and training of hair count evaluators, instructional material provided, methods of validation, and any other relevant issues.

   The sponsor replied that the use of the term 'visualized' hairs in this protocol, versus the term 'non-vellus' hairs does not represent any change in the hair counting method being used, but only a change in terminology. The procedures used in this study to assess hair count are the same procedures used in previous pivotal trials for hair regrowth products (Rogaine Extra Strength 5% Solution and Propecia), and utilizes the standardized, published, and Agency accepted technique using macro photography. The definition of 'visualized' hairs in this methodology are those hairs seen at the magnification used in this photographic procedure. Fine unpigmented hair (vellus hair) is not typically visualized in this method.

3. (Agency) A report on the progress of the long term safety extension study (Study 006) should be provided, with the anticipated date of submission of the final study report.

   The sponsor replied that a Safety Update Report that will include interim information from the safety extension study is planned for submission by August 1, 2005. The final report will be submitted by October 14, 2005.

b) Agency e-mail of August 12, 2005

This communication, and the sponsor's reply of 8/23/05 to each point, was as follows.

"The review team has the following questions and requests for information concerning the information you submitted on July 19, 2005."

1. "What is the cutoff of diameter for hair measurement using dot mapping technique (smallest hair diameter measured)?"

   The sponsor replied that the cutoff diameter is 0.03 mm for the dot mapping technique used.

2. "Could you please provide a reanalyses of the data using a hair

counting technique that excludes hair with a diameter of less than 0.03 mm and an additional analysis excluding hair of less than 0.05 mm diameter?"

The sponsor replied that reanalysis of the data using diameter of hair as cut points is not possible using the photographs taken in the trial (Study 006). While the hair counting technique used permits the establishment of a lower threshold (0.03 mm), it does not permit direct measurement of individual hair diameter.

3. "Provide a graphic plot showing the distribution of hair diameters vs counts for their given study population with a comparison between the different arms?"

   The sponsor replied that graphic plots showing distribution of hair diameters can not be provided since individual hair diameters can not be measured. Reference is made to the response to question 2.

4. "Provide a graphic plot showing the distribution of hair diameters vs counts for the study population with a comparison between the different arms."

   The sponsor replied that graphic plots showing distribution of hair diameters can not be provided since individual hair diameters can not be measured. Reference is made to the response to question 2.

This request for information was reiterated in the teleconference of 8/25/05.

c) Agency e-mail of August 22, 2005

This communication was a request for additional information, as follows.

"As hair count measurements were not carried out as visualized hair counts, as specified in the study protocol, the Agency is requesting that you submit the results of the following analyses to help us in interpreting efficacy findings of your drug men's Rogaine Extra Strength Minoxidil 5% Topical Foam for androgenetic alopecia.

1. Using the primary analysis method specified in the protocol, carry out the efficacy evaluation based on hair count using progressively increasing thresholds for hair diameter to define the subset of data included in the analysis. Specifically, include counts for hair diameter of >/= 0.01 mm; >/=0.02 mm; >/= 0.03 mm; ..... >/= 0.08 mm.

2. Investigate the association between the subject self assessment and hair counts using the different threshold considered in (1)

including fitting statistical models, using ranks and box plots.

3. Investigate agreement between subject self assessment and median score of the expert panel review.

4. Provide individual score for each member of the expert panel review and investigate agreement between expert's scores with and without [redacted] score."

This request for information was further discussed in the teleconference of 8/25/05, and the sponsor responded on 9/2/05 to request items 2, 3, and 4 above.

d) Teleconference of 8/25/05

This teleconference was initiated by the FDA to discuss the clinical endpoints and the hair count methodology in Study 006, as follows.

"BACKGROUND

At the end-of-Phase 2 meeting on January 16, 2003, FDA recommended co-efficacy endpoints of non-vellus hair counts and subject assessment of treatment benefit. The sponsor chose to use endpoints that differed from those previously recommended in one pivotal study submitted with their pending NDA 21-812. In general, two pivotal studies are needed for a new product. FDA had also recommended that the sponsor compare the relative efficacy of the proposed product with that of 5% minoxidil solution, in addition to comparing the proposed product to its vehicle (which could be one study instead of two): but the submitted study did not include a 5% minoxidil solution arm and only a comparison of the proposed product against its vehicle.

MEETING OBJECTIVES:

FDA called this meeting to discuss the clinical endpoints and hair counting methodology used by the sponsor in the pivotal clinical study submitted to support the proposed product, a Minoxidil 5% topical aerosol for androgenic alopecia. Specifically, FDA required clarification on Pfizer's responses to the following clinical information requests sent to the sponsor on August 12, 2005:

1. What is the cutoff of diameter for hair measurement using dot mapping technique (smallest hair diameter measured)?

2. Provide a reanalysis of the data using a hair counting technique that excludes hair with a diameter of less than 0.03 mm and an additional analysis excluding hair of less than 0.05 mm diameter?

3. Provide a graphic plot showing the distribution of hair diameters vs counts for their given study population with a comparison

between the different arms?

DISCUSSION POINTS:

Pfizer provided the following information about the methodology used to evaluate hair regrowth in the pivotal study submitted to support this NDA:

- Photographs were taken before and after treatment with 5% minoxidil topical aerosol or vehicle. No control using the currently marketed minoxidil solution was used.
- The photography technology is designed to measure the regrowth of hair that is equal to or greater than 0.03 mm in diameter.
- Pfizer is unable to rule out the possibility that hair less than 0.03 mm was included in the regrowth count as well as the possibility of whether vellus hairs were inadvertently included in the hair count.
- The camera technology used in the study cannot distinguish between pigmented (non-vellus) and non-pigmented (vellus) hair.
- Counts were conducted using magnified (at least 5X normal magnification) photographs of the treatment area.
- Counts were based on a dot-mapping technique.
- The visualized hair counts were conducted by a single trained technician blinded to treatment arm and time point.
- The technician used dot-mapping to measure new hair growth. The dot maps were then counted using a modern scanning technology.
- A relationship exists between the hair counted by the dot mapping technique and the regrowth of pigmented hair.

FDA explained its position that vellus hair should not be included in counts of hair regrowth because vellus hair has historically not been used in a regulatory manner as a demonstration of providing a clinically meaningful benefit to persons affected by androgenic alopecia. FDA asserted their position that there appeared to be many sources of variability in the measurement techniques used to assess hair regrowth and that there was concern regarding the use of magnification to assess the hair growth endpoint.

Pfizer asserted their position that both the dot-mapping technique used for counting hair and the photographic magnification used for

visualized hair counts were valid based on internal quality checks that they had conducted and was previously used for other applications for hair growth assessments. In response, the Agency requested the sponsor to submit any information which the sponsor could access, including publications and results of their early work which they referenced to during the meeting, in support of their assertions.

ACTION ITEMS:

Pfizer agreed to submit the following data and information:

1. Evidence that the hair counting techniques that they used excluded counts of vellus hair.

2. Data supporting the existence of a correlation between the diameter of vellus hair and the cut-off hair diameter selected for this study (0.03 mm).

3. Data supporting a correlation between subject self-assessment and hair counts stratified by treatment group.

Pfizer also agreed to respond to the following questions and information requests that FDA sent by electronic mail to the sponsor on August 22, 2005 by September 6, 2005:

1. Investigate the association between the subject self assessment and hair counts using the different threshold considered in (1) including fitting statistical models, using ranks and box plots.

2. Investigate agreement between subject self assessment and median score of the expert panel review; and agreement between the subject self assessment and the score of each member of the expert panel review.

3. Provide individual score for each member of the expert panel review and investigate agreement between expert's scores with and without Dr. ——— score."

The agency requested all requested analyses to address the FDA request of August 22, be carried out by treatment group (active, placebo) in addition to the overall analyses."

d) Sponsor e-mail of September 2, 2005

In this submission the sponsor provided a response to the requests for information in the teleconference of 8/25/05. In addition, a response to the following two questions related to the clinical endpoint were provided, as follows.

1) What is the support for 0.03 mm (30 microns) as the appropriate

diameter threshold for identifying non-vellus hairs?

The sponsor states that 0.03 mm is accepted as the upper limit diameter for vellus hairs. A reference cited is Atlas of Hair and Nails, 2000, by Hordinsky, Sawaja, and Scher, in which it is stated "Small hairs, with no pigment or medullary cavity, a diameter of less than 0.03 mm, and a length of less than 1 cm, are classified as vellus (downy) hairs. Another reference is The structure of the Human Hair Follicle, 2004, by Whiting, in which it is stated "Vellus hairs are inconspicuous and are 0.03 mm or less in diameter and often less than 1 cm in length and lack melanin and medulla."

2) How was the 5.7 fold final magnification determined to be the appropriate magnification at which only non-vellus would be visualized and thereby counted in the hair counting methodology used?

The following is the sponsor's response, paraphrased in part. The sponsor states that over the past 20 years, hair re-growth has been evaluated by counting visualized hairs, at first by direct observation and then with the use of photographs magnified to a sufficient extent to exclude the visualization of vellus hairs. The technology used in Study 006 has been the basis of regulatory approvals and is the current technology of photographic magnification. Without a diameter measurement of each individual hair, insignificant numbers of vellus and miniaturized vellus hairs may be counted. The technology to measure the diameter of each hair is being explored for future use.

the technical/medical imaging service provider, has confirmed that a final magnification of 5.7 fold was used both in Study 006 and in the Merck studies on Finasteride. It is Pfizer's belief that this study was one of the pivotal studies used to approve Finasteride as noted in the Summary Basis of Approval. Pfizer also received assurances from that the photographic equipment and hair counting technique used in Study 006 was the same as those used in the Finasteride trial, and therefore initiated the 006 trial with the understanding that this methodology is currently accepted by the regulatory authorities to support the approval of hair regrowth products.

Pfizer participated in research on hair count methodology by comparing hair counts by the technique used in Study 006 with counts by newer technology which determines actual hair diameter measurements, and believes, while the results are preliminary, that they are supportive of the magnification used in Study 006 and of the accuracy of the non-vellus hair counts. The research compared the number of non-vellus hairs equal to or greater than 0.03 mm counted with the magnification technique to the actual numbers of hairs with a diameter equal to or greater than 0.03 mm as measured

by the newer technology. The results showed that the mean target area hair count using the 5.7 fold magnification technique was 169.1 and the number of hairs in the same target area with a measured diameter of >/= 0.03 mm was 166.6.

Pfizer believes that there is further support for the appropriateness of this magnification level from a comparison of the number of non-vellus hairs per cm^2 in target areas on the leading anterior edge of the vertex area in subjects with androgenetic alopecia in different studies, specifically Study 006, the Finasteride study, and a biopsy study in the literature.

The information requested in the teleconference of 8/22/05 and the sponsor's response, were as follows.

1) An investigation of the association between the subject self assessment and hair counts, including fitting statistical models, using ranks and box plots.

The sponsor notes that hair count is an objective measurement, and subject assessment is a subjective measurement with relatively lower reproducibilty and larger variation in relation to hair count. Hair count was also measured in the 1 cm^2 target area of the scalp while the subject assessment was based on photographs of the entire vertex area.

The tabulated summary of the mean hair count change for subjects in each category of the subject assessment is as follows.

Subject assessment	Placebo		5% foam	
	N	Mean count	N	Mean count
-3 = significantly worse				
-2 = moderately worse	7	- 6.3	1	29.0
-1 = slightly worse	22	3.2	9	15.3
0 = no change	53	5.2	29	18.3
1 = slightly improved	34	4.6	39	17.2
2 = moderately improved	24	12.2	45	20.4
3 = significantly improved	8	- 5.0	38	26.6

The sponsor has also provided additional statistical analyses of the correlation between the hair counts and the subject assessment.

2) An investigation of the agreement between the subject self

assessment and the median score of the expert panel review, and the agreement between the subject self assessment and the score of each member of the expert panel review.

In the tabulations that follow, the percentages have been added by this reviewer. Also, it is noted that the scale used was the same for the subject self assessment and for the expert panel review; this was not stated in the study report.

A summary tabulation of the number of subjects in each category of the subject self assessment rating, and the number of subjects in the same category according to the median score of the expert panel rating, has been provided by the sponsor, as follows.

Subject self assessment and median score of expert panel review				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	Expert panel review	Subject assessment	Expert panel review
-3 = significantly worse				
-2 = moderately worse	8 (5%)		1 (0.5%)	
-1 = slightly worse	25 (15%)	4 (2%)	10 (6%)	
0 = no change	56 (33%)	134 (78%)	32 (18%)	94 (52%)
1 = slightly improved	36 (21%)	8 (5%)	41 (23%)	55 (31%)
2 = moderately improved	28 (16%)	1 (0.6%)	47 (26%)	14 (8%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

Summary tabulations of the number of subjects in each category of the subject self assessment rating, and the number of subjects in the same category according to the rating of each individual member of the expert panel has been provided by the sponsor, as follows.

Correlation between subject self assessment and rating by Dr. [illegible]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	Dr. [illegible]	Subject assessment	Dr. [illegible]
-3 = significantly worse				
-2 = moderately worse	8 (5%)	1 (0.5%)	1 (0.5%)	
-1 = slightly worse	25 (15%)	11 (6%)	10 (6%)	7 (4%)
0 = no change	56 (33%)	127 (74%)	32 (18%)	112 (62%)
1 = slightly improved	36 (21%)	7 (4%)	41 (23%)	39 (22%)
2 = moderately improved	28 (16%)	1 (0.5%)	47 (26%)	5 (3%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

Correlation between subject self assessment and rating by Dr. [illegible]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	Dr. [illegible]	Subject assessment	Dr. [illegible]
-3 = significantly worse				
-2 = moderately worse	8 (5%)		1 (0.5%)	
-1 = slightly worse	25 (15%)	7 (4%)	10 (6%)	
0 = no change	56 (33%)	118 (69%)	32 (18%)	73 (41%)
1 = slightly improved	36 (21%)	22 (13%)	41 (23%)	65 (36%)
2 = moderately improved	28 (16%)		47 (26%)	25 (14%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

Correlation between subject self assessment and rating by Dr. [redacted]				
Rating scale	Placebo n=172		5% foam n=180	
	Subject assessment	Dr. [redacted]	Subject assessment	Dr. [redacted]
-3 = significantly worse				
-2 = moderately worse	8 (5%)	1 (0.5%)	1 (0.5%)	
-1 = slightly worse	25 (15%)	4 (2%)	10 (6%)	
0 = no change	56 (33%)	124 (72%)	32 (18%)	93 (52%)
1 = slightly improved	36 (21%)	17 (10%)	41 (23%)	50 (28%)
2 = moderately improved	28 (16%)	1 (0.5%)	47 (26%)	20 (11%)
3 = significantly improved	9 (5%)		39 (22%)	
Missing	10 (6%)	25 (15%)	10 (6%)	17 (9%)

3) The individual scores for each member of the expert panel review and an investigation of the agreement between the expert's scores with and without Dr. [redacted]s scores.

The sponsor has provided the individual scores for each member of the expert panel. The frequency distribution of each panel member's scores are provided, as follows.

Frequency distribution of scores of expert panel reviewers						
Rating scale	Placebo n=172			5% foam n=180		
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
-3 = significantly worse						
-2 = moderately worse	1 (0.5%)		1 (0.5%)			
-1 = slightly worse	11 (6%)	7 (4%)	4 (2%)	7 (4%)		
0 = no change	127 (74%)	118 (69%)	124 (72%)	112 (62%)	73 (41%)	93 (52%)
1 = slightly improved	7 (4%)	22 (13%)	17 (10%)	39 (22%)	65 (36%)	50 (28%)
2 = moderately improved	1 (0.5%)		1 (0.5%)	5 (3%)	25 (14%)	20 (11%)
3 = significantly improved						
Missing	10 (6%)		25 (15%)	17 (9%)	17 (9%)	17 (9%)

N21812.wpd

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-812 (IND 50,063)
Submission Code	N 000
Letter Date	March 23, 2005
Stamp Date	March 24, 2005
PDUFA Goal Date	January 24, 2006
Reviewer Name	Daiva Shetty, MD
Review Completion Date	December 12, 2005
Established Name	Minoxidil
(Proposed) Trade Name	Men's Rogaine® Extra Strength
Therapeutic Class	Hair regrowth
Applicant	Pfizer Consumer Healthcare
Priority Designation	S
Formulation	5% Topical Foam
Dosing Regimen	Apply half a capful 2 times a day
Indication	Androgenic alopecia
Intended Population	Men over 18 years of age

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based on the overall safety data review, the proposed 5% minoxidil topical foam should be approved for OTC treatment of androgenetic alopecia in men. A final approvability decision depends upon the outcome of the clinical efficacy, chemistry, biopharm, and pharmtox data analyses.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No special post-marketing risk management activities are recommended.

1.2.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

1.2.3 Other Phase 4 Requests

None.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Pfizer Consumer Healthcare is seeking approval to market a new minoxidil formulation, 5% topical foam, for OTC treatment of androgenetic alopecia of the vertex region in men.

The clinical development program for the 5% minoxidil topical foam consists of four clinical studies:

- One vehicle-controlled safety and efficacy trial (MINOB-9140-006)
- Two pharmacokinetic studies (MINOB-9140-001 and MINOB-9140-005)
- One dermal sensitization study (MINOB-9140-004)

In addition, in support of this NDA, the sponsor submitted postmarketing safety data for minoxidil 2% and 5% topical solutions (MTS) from the following sources:

- Pfizer's own postmarketing safety database,
- World Health Organization database,

- FDA database,
- American Association of Poison Control Centers, and
- Medical literature.

1.3.2 Efficacy

Results of the efficacy trial MINOB-9140-006 and dermal sensitization study MINOB-9140-001 are being reviewed by the reviewers in the Division of Dermatological and Dental Drug Products.

1.3.3 Safety

Safety data collected from one Phase 3 controlled efficacy and safety study, two PK studies, and one dermal sensitization study with 5% minoxidil foam form the basis of the clinical safety database for this NDA. The safety database comprises a total of 694 subjects, of whom 522 were treated with one or more formulations of 5% minoxidil foam.

In all, approximately 28% (194/694) of the subjects experienced at least one treatment-emergent adverse event (AE). This includes two subjects in the 5% Minoxidil Topical Foam (MTF) group who developed serious adverse events; both of the events were considered by the investigator to be unlikely related to study treatment. Infection NOS was the most commonly reported treatment-emergent AE, affecting 5.0% of the subjects (35/694). Headache (3.5%, 24/694 subjects) and injury NOS (2.3%, 16/694 subjects) were the only other treatment-emergent AEs reported in more than 2% of the subjects. All drug-related treatment-emergent AEs occurred in less than 1% of the subjects, with the most common being headache (5/694 subjects).

No deaths occurred in any of the 4 clinical studies.

A total of six subjects withdrew from the 4 clinical studies due to AEs possibly related to study drug; none of them were assessed as serious.

Analysis of clinical laboratory test results, vital signs, and physical examination findings revealed no new or unexpected safety issues relevant to the intended use of 5% minoxidil foam.

A total of 143 subjects enrolled into the extension phase of the clinical study, and 114 completed it. Results from the extension phase of the study did not reveal any new unexpected adverse events associated with the use of the 5% minoxidil foam formulation up to one year. The most common AEs reported during the extension phase were related to a local irritation at the site of application. Most of the reported AEs were nonserious in nature.

Overall safety analyses in the 4 clinical trials have shown 5% minoxidil foam to be well tolerated in healthy subjects and in subjects with androgenetic alopecia who were treated for up to 1 year. The safety profile of the 5% minoxidil topical foam is consistent with that of 2% and 5% minoxidil topical solution (MTS). Post marketing data for 2% and 5% MTS gathered by the sponsor, and supplemented by reports from the World Health Organization, FDA, the American

Association of Poison Control Centers, and medical literature, did not reveal any new safety signals.

1.3.4 Dosing Regimen and Administration

Dosing regimen is identical to that of other topical OTC minoxidil formulations except that the foam formulation does not have a metered device to accurately dispense 1 gram of the foam. The sponsor proposed the following dosing instructions: "Apply half a capful 2 times a day to the hair loss area."

These instructions were supported by three actual use (dispensation) studies in a total of 111 subjects, which showed that the mean quantities dispensed ranged from 0.97 to 1.14 grams, with standard deviations ranging from 0.37 to 1.00.

The sponsor also conducted an exaggerated use pharmacokinetic study, which showed that there was an increase in serum minoxidil level from the foam when applied in 2 or 3 times higher amounts (2 g and 3 g) than the recommended on the label (1 g). The highest concentration of minoxidil after twice-daily application of 3 g of 5% MTF was 11.5 ng/mL. The sponsor states that from oral dosing data, it is known that the concentration of minoxidil associated with systemic effects is approximately 20 ng/mL. What kind of safety issues are associated with the 11.5 ng/mL serum level of minoxidil is unclear. However, knowing that the minoxidil foam formulation is less bioavailable than minoxidil solution, and that people, when tested in actual use, did not make significant measurement errors, marketing of the 5% topical minoxidil foam without a quantitative measurement device does not appear to present safety concerns in the targeted population.

1.3.5 Drug-Drug Interactions

No special drug interaction studies were requested by FDA or performed by the sponsor.

1.3.6 Special Populations

No studies were performed in any special populations.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

This is a clinical safety review for the Men's Rogaine Extra Strength (minoxidil) Topical Foam (MTF), 5%, submitted under the New Drug Application (NDA) 21-812. This NDA seeks marketing approval for a new foam formulation of 5% topical minoxidil for OTC treatment of androgenetic alopecia of the vertex region in men over 18 years of age. The proposed dosing directions are:

- apply half a capful 2 times a day to the scalp in the hair loss area
- see enclosed booklet for complete directions on how to use
- using more or more often will not improve results
- continued use is necessary to increase and keep your hair regrowth or hair loss will begin again

Minoxidil was first developed as an orally administered vasodilator for the treatment of hypertension. It was observed that approximately 80% of the treated subjects developed hypertrichosis as a side-effect. This led to the development of a topical solution for the treatment of androgenetic alopecia.

The detailed mechanism by which topical minoxidil exerts its effect on the stimulation of hair growth has not been clearly identified. Research suggests that minoxidil sulfate acts on the hair follicle, possibly by a mechanism involving the non-enzymatic transfer of the sulfate moiety to a regulatory protein in the hair follicle. This activity also appears to involve the ATP-sensitive K+ channel agonist activity of endogenously-formed minoxidil sulfate. It is therefore hypothesized that in balding areas where miniaturized follicles are still present, the continuous application of minoxidil results in a reversal of the miniaturization process of the hair follicle, gradually leading to the conversion of miniaturized follicles to larger, terminal follicles supporting the growth of a pigmented hair shaft.

2.2 Currently Available Treatment for Indications

Currently minoxidil is available for OTC consumers as Minoxidil Topical Solution (MTS) in two different strengths (2% and 5%) for men and one strength (2%) for women. The dosing regimen for both strengths is 1 mL of solution applied topically twice a day.

Rogaine (2% Minoxidil Topical Solution) was first approved for prescription sale in the US in August 1988. In 1996 it was approved for OTC availability and in November 1997 Rogaine Extra Strength for Men (5% Minoxidil Topical Solution) was approved for OTC sale.

In addition to minoxidil, there are other topical and oral therapies available to the US consumers. However, those options are not readily accessible to consumers because they need either a prescription, or a direct health care professional intervention.

2.3 Availability of Proposed Active Ingredient in the United States

See section 2.1.

2.4 Important Issues With Pharmacologically Related Products

Use of minoxidil is associated with an increased risk mainly for local effects. The most common postmarketing reports with already approved minoxidil products are: no response, pruritus, dry skin, skin exfoliation, and headache. The sponsor states that the new foam formulation of the product will be less locally irritating and therefore will decrease the incidence of local reactions.

2.5 Presubmission Regulatory Activity

The sponsor sought the regulatory guidance and advice from FDA on several occasions during the development phase of the product. The pre-IND meeting for this product took place on March 25, 2002 where the stability program, preclinical program, and Phase 1 clinical protocols were discussed. The End-of-Phase 2 meeting was held on January 16, 2003 where the preliminary results of pharmacokinetic studies and the proposed clinical study protocols were discussed. There were several written communications between FDA and the sponsor after this meeting concerning the design of clinical studies.

The following issues were raised by FDA:

- FDA stated that the safety of non-metered dosing for 5% minoxidil foam is an important concern but agreed that they would assess the totality of the data supporting the use of nonmetered dosing when the NDA was filed.
- FDA strongly encouraged a 3-arm Phase 3 trial to ensure the robustness of study findings and consequently study interpretability, as an alternative approach to replication of study findings based on 2 trials. During the July 26, 2004 teleconference, however, FDA noted that a single study submission for this indication would be acceptable to provide such assurances if results from this single study had very small p-values, consistency in efficacy results across study subgroups, and consistency of efficacy across study centers.
- For previously conducted studies in men with androgenetic alopecia of the vertex, FDA required study duration to be greater than 32 weeks. On the basis of previous clinical experience in such studies, the sponsor proposed efficacy at 16 weeks to be predictive of efficacy at longer time points and provided FDA with justification to this effect. During the End-of-Phase 2 Meeting on January 16, 2003, FDA agreed that a trial of 16-week duration is acceptable in the study of androgenetic alopecia of the vertex in men if the sponsor were to agree to include in the label a discussion of the diminution of treatment effect seen in the clinical trials with currently marketed 5% MTS labeling.

- FDA stated that the duration of the proposed study seemed too short considering the long-term use of the product and encouraged the sponsor to follow the E1A document guidelines for safety assessment.

2.6 Other Relevant Background Information

Not applicable.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Chemistry section of this NDA is being reviewed by chemistry reviewers.

One chemistry issue related to the safety of the product is its potential for flammability. In order to determine its flammability, the Minoxidil 5% Topical Foam (— fragrance) has been tested in accordance with 16 CFR 1500.45 and 16 CFR 1500.46. Based on this testing, the drug product is being labeled as "extremely flammable".

3.2 Animal Pharmacology/Toxicology

Numerous nonclinical pharmacology, safety and toxicology studies have been conducted with minoxidil using various animal species (rat, mouse, rabbit, dog, monkey, and miniature pig) during the last four decades with very large doses of the active ingredient.

Two animal studies were conducted to support the minoxidil foam formulation as part of this NDA application and are being reviewed by pharmtox reviewers.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The clinical development program for 5% minoxidil foam consists of 4 clinical studies: 2 pharmacokinetic studies, 1 special study for dermal sensitization, and 1 Phase 3 vehicle-controlled study of the efficacy and safety of 5% minoxidil foam in the treatment of androgenetic alopecia of the vertex in men. The Phase 3 study included an extension phase to collect additional safety data during a full year of continued treatment which were submitted at the end of the review cycle, and therefore, are being discussed separately, in Section 7.2.9 of this review.

4.2 Tables of Clinical Studies

Table 1. List of Clinical Studies

Study No.	Study Type/Design	Treatment Type & Duration	No. of Subjects
MINOB-9140-001	Bioavailability, RA, OL, CO	5% minoxidil foam 5% minoxidil solution 2% minoxidil solution	67
MINOB-9140-005	Bioavailability, RA, OL, CO	5% minoxidil foam, 1 g 5% minoxidil foam, 2 g 5% minoxidil foam, 3 g	35
MINOB-9140-004	Dermal Sensitization, RA, IB	Three 5% minoxidil foams Placebo foam	240
MINOB-9140-006	Clinical Safety and Efficacy, RA, DB, PC	5% minoxidil foam Vehicle	352

RA: randomized; OL: open label; CO: cross-over; IB: investigator blind; PC: placebo controlled.

4.3 Review Strategy

This review covers safety data only. The clinical efficacy and dermal sensitization studies are being reviewed by the reviewers in the Division of Dermatologic and Dental Drug Products. In addition, bioavailability studies will be reviewed by the biopharmacology reviewers.

4.4 Data Quality and Integrity

Data quality and integrity are being addressed by the reviewers of clinical studies. There were no DSI audits conducted for the study sites or data analyses.

4.5 Compliance with Good Clinical Practices

Compliance with good clinical practices is being addressed by the reviewers of clinical studies.

4.6 Financial Disclosures

The sponsor conducted four new clinical studies in support of this application. These studies and the financial disclosure of the investigators will be addressed by the reviewers in the Division of Dermatological and Dental drug products.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

Clinical pharmacology studies conducted in support of 5% MTF include two pharmacokinetic (PK) studies and one dermal sensitization study. To investigate potential differences in systemic bioavailability due to the change in dosage form, pharmacokinetic study, MINOB-9140-001

(Study 001), was conducted. Because the currently marketed 5% MTS and 2% MTS products were approved with metered devices, an additional pharmacokinetic study, MINOB-9140-005 (Study 005), was conducted to investigate the effect of exaggerated doses in the event that an amount up to three times the labeled dose was inadvertently applied.

Since safety data from all PK studies are being discussed in this review, brief outline of these studies is presented below.

Both PK studies were randomized, crossover, open-label clinical investigations of 5% minoxidil foam formulations and were conducted at the same study site in the United States, in populations of subjects with androgenetic alopecia and who were in good health. The studies used a crossover design that ensured that each subject received all the treatments being assessed.

MINOB-9140-001 (Study 001) had two arms, a male treatment arm and a female treatment arm. Subjects received 3 treatments, in randomized order, within their respective arm of the study. Two 5% minoxidil foam formulations were compared with minoxidil topical solution (MTS) (i.e., 5% MTS in men and 2% MTS in females) in this study. MINOB-9140-005 (Study 005) included men only, and subjects received each of 3 treatments (1.0, 2.0, or 3.0 grams of 5% minoxidil foam, BID) in randomized order.

In Study 001, the 5% minoxidil foam formulations were identical in composition with the exception of one component. While Foam #1 contained glycerin as a component in the vehicle, Foam #2 contained propylene glycol instead. The results of this study showed that in men, the systemic absorption of each of the 5% minoxidil foam formulations with twice daily application was about half of that observed with 5% MTS with twice-daily application, as evidenced by the area under the curve (AUC) of serum minoxidil concentration and maximum serum minoxidil concentration (C_{max}).

Study 005 showed that mean serum minoxidil concentrations after twice-daily application of 1, 2, or 3 g of 5% minoxidil foam increase by statistically significant amounts with increasing minoxidil dose. The highest blood level of 5% minoxidil foam at the highest exaggerated dose of 3 gram used twice daily was 11.5 ng/mL. Pharmacokinetic profile of 5% MTS was not directly compared to the three doses of 5% MTF in the study. However, we know from Study 001 that the highest blood level of 5% MTS when used twice a day, was 7.23 ng/mL. The sponsor states that from oral dosing data, it is known that the concentration of minoxidil associated with systemic effects is approximately 20 ng/mL. What kind of safety issues are associated with the 11.5 ng/mL serum level of minoxidil is unclear. However, the minoxidil foam formulation is less bioavailable than minoxidil solution, and men, when tested in actual use, did not make significant measurement errors that cause safety concern (see section 8.1 of the review). Thus, data suggests that marketing of the 5% topical minoxidil foam without a quantitative measurement device will not be less safe than already marketed topical minoxidil formulations.

5.2 Pharmacodynamics

No new pharmacodynamics data were submitted to this application.

5.3 Exposure-Response Relationships

No new exposure-response relationship data were submitted to this application because 5% minoxidil was previously established and is currently marketed as a safe and effective dose for OTC, twice-a-day treatment for androgenetic alopecia of the vertex in men.

6 INTEGRATED REVIEW OF EFFICACY

The efficacy database for 5% minoxidil foam consists of data from a single Phase 3 study, MINOB-9140-006 (Study 006). This study had the primary objective of evaluating the efficacy of a topical 5% minoxidil foam formulation in men for the treatment of androgenetic alopecia. The primary efficacy endpoint was the mean change in non-vellus hair count in the target region between Baseline and Week 16, as determined by a computer-assisted dot-mapping technique and subjects' rating of treatment benefit. Secondary efficacy measures were scores from the review of hair regrowth by a panel of experts and the percent change from Baseline in non-vellus hair counts within a pre-specified area of clipped hair.

The results of the efficacy study MINOB-9140-006 are being reviewed by the reviewers in the Division of Dermatological and Dental Drug products. Safety data gathered during this study will be discussed in the safety portion of this review.

6.1 Indication

The proposed indication for the Men's Rogaine Extra Strength (minoxidil 5%) Topical Foam is for the treatment of androgenic alopecia of the vertex region in men.

7 INTEGRATED REVIEW OF SAFETY

Safety database to support this NDA consists of the following:

- One Phase 3 controlled clinical safety and efficacy study,
- Two pharmacokinetic studies,
- Dermal sensitization study,
- Adverse Events (AEs) associated with the use of 2% and 5% minoxidil MTS, reported to Pfizer safety database for the time period beginning March 1, 1999 through July 31, 2004,
- Adverse Event Reporting Data gathered from the World Health Organization (WHO) International Drug Monitoring Program for the time period from January 1984 to August 2004,

- FDA Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) data for the time period from January 1, 1969 through September 30, 2003,
- Data from the American Association of Poison Control Centers (AAPCC) for 1994-2003, and
- Medical literature (MEDLINE and EMBASE) for minoxidil from January 1, 1999 through January 31, 2005.

7.1 Methods and Findings

Safety data collected from one Phase 3, controlled efficacy and safety study, two PK studies, and one dermal sensitization study with 5% minoxidil foam form the basis of the clinical safety database for this NDA. The safety database comprises a total of 694 subjects, of whom 522 were treated with one or more formulations of 5% minoxidil foam. Specific safety aspects of the individual clinical studies are summarized as follows:

Study 001: The safety objective in this study was the comparative incidence, severity and duration of any adverse events as well as the comparative incidence, severity and duration of any clinical laboratory value abnormalities that were observed during the study. Adverse events were collected through regular questioning at each visit. Each subject was asked if they had experienced any health problems since the previous visit. Additionally, any adverse events that were spontaneously reported were collected. Hematology, blood chemistry, and urinalysis were performed at baseline and at the end of each phase.

Study 004: The primary objective of this study was to evaluate the safety of the test materials as evidenced by the potential to induce contact sensitization following repeated application to the skin of human subjects. The secondary objective of this study was to evaluate the safety of the test materials as evidenced by irritation during the induction phase. Irritation was assessed via visual assessments throughout the induction and challenge phase. Sensitization potential was assessed for subjects that received nine induction applications with at least eight evaluations and one challenge application with two subsequent evaluations. Adverse events were reported for all subjects that received at least one application of test material.

Study 005: This study was designed to evaluate three basic safety considerations. The first consideration was whether either of the exaggerated dosages influenced the systemic absorption of the topically applied minoxidil and therefore could pose a potential safety hazard to the target population. The second consideration was the comparative incidence, severity and duration of any adverse events that occurred during the study. The final consideration was the comparative incidence, severity and duration of any clinical laboratory value abnormalities that were observed during the study. The study consisted of three six-day (11 application) phases with a 7-day washout period between each phase. Each subject was randomized to one of three dosing regimens (1gm, 2gm, or 3gm) in the first phase and crossed over to a different regimen in each subsequent phase, to ensure treatment with each of the three dosing regimens. Systemic minoxidil bioavailability was measured in serum levels drawn on Day 1, 2, 4, 6 and 7 of each phase of the study. Prior to the first dose of each phase, serum samples were taken to measure baseline values. The incidence, severity and duration of all adverse events was collected through

the use of spontaneous reporting and regular questioning of subjects at each study visit regarding health problems that may have occurred since the previous study visit. The incidence, severity and duration of potential clinical laboratory abnormalities were determined by ongoing analysis of hematology, chemistry and urinalysis results.

Study 006: This efficacy and safety study was a randomized, double-blind, vehicle-controlled, parallel-group study (Study 006) conducted at 14 centers in the U.S. A total of 352 men with androgenetic alopecia were enrolled and randomized in the ratio of 1:1 to receive either 5% minoxidil foam twice daily (BID) or vehicle foam BID for 16 weeks. Subjects were considered evaluable for safety if they received at least one dose of double-blind study medication. All subjects met this criterion and were included in the safety evaluation. Safety assessments were based on standard safety measures (adverse events, clinical laboratory tests, vital signs determinations, and assessments of skin irritation).

The safety objective of this study was to evaluate the safety of a topical 5% minoxidil foam formulation in males when used daily for the treatment of androgenetic alopecia. A subset of subjects continued in an extension phase of this study for a total treatment duration of up to 1 year. Safety results from the extension phase were submitted late into the review process, and therefore, are analyzed in Section 7.2.9 of this review.

7.1.1 Deaths

No deaths occurred in any of the 4 clinical studies.

7.1.2 Other Serious Adverse Events

No serious adverse events occurred in Studies 001, 004, or 005.

In Study 006, two 5% minoxidil foam subjects and three placebo subjects developed a total of 6 serious adverse events. In the 5% minoxidil foam group the serious adverse events were severe cholelithiasis and pancreatitis in 1 subject and severe pneumonia in another subject. In the placebo group the events were 1 episode each of severe accidental injury, severe grand mal convulsion, and self reported acute kidney failure which could not be substantiated after review of subject's medical records. All the serious adverse events were considered by the investigator to be unlikely related to study treatment; none of the serious adverse events resulted in discontinuation of study drug; and, except for the acute kidney failure, all had resolved by the end of the study. The serious adverse events in Study 006 are summarized in Table 2.

Table 2. Serious Adverse Events Reported During the Trial Period (Study 006)

Treatment Group Subject Number	Serious Adverse Event	Causality	Outcome
5% Minoxidil Foam Scented			
197	Cholelitiasis and pancreatitis	Unlikely	Resolved
366	Pneumonia NOS	Unlikely	Resolved
Foam vehicle			
298	Injury (automobile accident) NOS	Unlikely	Resolved
380	Grand mal convulsions	Unlikely	Resolved
393	Renal failure acute	Unlikely	Unresolved

7.1.3 Dropouts and Other Significant Adverse Events

The incidence of adverse events leading to study withdrawal was low overall.

- Two subjects withdrew from Study 001 because of non-serious AEs, 1 female, when using 2% MTS, because of moderate to severe abrasions and lacerations not related to study drug and 1 female, when using 5% MTF because of constant moderate toothache not related to study drug.
- Three subjects withdrew from Study 004. One woman subject withdrew because of a positive pregnancy test (not an AE) at Visit 11 and subsequently gave birth to a normal, healthy baby with no congenital anomalies. Complications from her cesarean section were not related to the test materials, and all resolved. One subject withdrew because of a skin ulcer unrelated to study drug, and one subject withdrew because of pruritus that was possibly related to one or more of the test products.
- In Study 006, five subjects withdrew from the study because of non-serious AEs, 2 placebo subjects (1 subject for moderate nausea probably related to study drug; and 1 subject for mild, intermittent rapid respiration and rapid heartbeat possibly related to study drug) and three 5% minoxidil foam subjects (1 subject for mild intermittent increased hair shedding possibly related to study drug; 1 subject for mild scalp irritation probably related to study drug; and 1 subject for moderate intermittent headaches possibly related to study drug). AEs that led to withdrawal in Study 006 are summarized in Table 3.

Table 3. Discontinuation Due to Adverse Events (Study 006)

Treatment Group Subject Number	Adverse Event	Causality	Outcome
5% Minoxidil Foam Scented			
159	Alopecia	Possibly	Resolved
247	Rash NOS	Possibly	Resolved
326	Headache	Possibly	Resolved
Foam Vehicle			
148	Nausea	Possibly	Resolved
516	Hyperventilation and tachycardia NOS	Possibly	Resolved

7.1.3.1 Overall profile of dropouts

See section 7.1.3.

7.1.3.2 Adverse events associated with dropouts

See section 7.1.3.

7.1.3.3 Other significant adverse events

Not applicable.

7.1.4 Other Search Strategies

Not applicable.

7.1.5 Common Adverse Events

Historically, the most common adverse events (>2%) associated with the use of topical minoxidil (2% or 5%) include the following reactions:

- Pruritus
- Alopecia
- Skin desquamation
- Dry skin
- Drug ineffective
- Skin irritation
- Dandruff
- Hypertrichosis
- Rash
- Hair texture abnormal
- Hair color changes
- Headache

Common adverse events seen during 5% minoxidil topical foam development program are discussed by study in the following paragraphs.

7.1.5.1 Eliciting adverse events data in the development program

Participating subjects were queried by the study personnel at each visit about changes in medical condition, new medications, or changes in concomitant medication doses. The question asked was: "Since your last clinic visit, have you experienced any health problem(s)?" Investigators participating in the clinical studies reported all directly observed events and adverse events spontaneously reported by the trial subjects. All observed or reported adverse events were recorded on the case report form.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

To analyze adverse events by organ system or syndrome in the total study population, all adverse events reported in Study 001, 004, 005 and 006 were converted to a common adverse event coding dictionary (MedDRA 7.0).

Adverse events from Protocols 001 and 005 were originally coded in MedDRA 4.1, and adverse events from Protocols 004 and 006 were originally coded in COSTART. All adverse events for presentation in the Integrated Summary of Safety (ISS) of this NDA have been recoded by the sponsor using the current dictionary, MedDRA 7.0.

7.1.5.3 Incidence of common adverse events

Incidence of adverse events was presented as the number and percentage of subjects with AEs. Some subjects may have had more than one AE.

In Studies 001 and 005, adverse events were reported in 29 (28.4%) of 102 subjects. The most commonly reported AEs were colds (5.9%), headache (3.9%), diarrhea (2.9%) and toothache (2.9%). Adverse events for Studies 001 and 005 are presented in Table 4.

Adverse events for the intent to treat population were reported in 18 (8%) of 240 subjects in Study 004. All AEs occurred in less than or equal to 1% of the subjects, and only 3 AEs occurred in more than 1 subject, including bacterial infection (2 subjects), infection (3 subjects) and bronchitis (2 subjects). Adverse events for Study 004 are presented in Table 5.

Adverse events for the intent to treat population were reported in 82 (45.6%) of 180 subjects in the 5% minoxidil foam scented group and 80 (46.5%) of 172 subjects in the foam vehicle group in Study 006. Adverse events in the intent to treat population that occurred in at least 1% of subjects in either the 5% minoxidil foam scented or foam vehicle group are summarized in Table 6.

The most common AEs in Study 006 were infection (similar incidence between treatment groups), headache, which occurred in 7.2% of the subjects in the 5% minoxidil foam scented group and 3.5% of the subjects in the foam vehicle group, and rash, which occurred in 3.9% of the subjects in the 5% minoxidil foam scented group and < 1% of the subjects in the foam vehicle group. Adverse events that differed in incidence of more than 1% in the 5% minoxidil foam scented group relative to the vehicle foam group included abdominal pain, allergic reaction, fever, headache, viral infection, hypertension, SGOT increased, arthralgia, myalgia, pharyngitis, acne and rash.

7.1.5.4 Common adverse event tables

Table 4. Summary of Adverse Events (Studies 001 and 005)

Verbatim Term	Number (%) of Subjects (N=102)
Cold	6 (5.9)
Headache	4 (3.9)
Diarrhea	3 (2.9)
Toothache	3 (2.9)
Sore Throat	2 (2.0)
Abrasion left arm	1 (1.0)
Abrasion right wrist	1 (1.0)
Arthritis flare up left knee	1 (1.0)
Depression - increased	1 (1.0)
Flu	1 (1.0)
Headache(more painful than usual)	1 (1.0)
Head cold	1 (1.0)
Heartburn	1 (1.0)
Heat rash on forehead	1 (1.0)
Itching on test site	1 (1.0)
Laceration right knee	1 (1.0)
Nasal congestion	1 (1.0)
Post nasal discharge	1 (1.0)
Pulled muscle	1 (1.0)
Rash on test site	1 (1.0)
Rash on both arms	1 (1.0)
Tingling scalp	1 (1.0)
Tooth Pain	1 (1.0)
Upper respiratory infection	1 (1.0)
Vaginal infection	1 (1.0)
Yeast infection	1 (1.0)

Table 5. Summary of Adverse Events (Study 004)

Preferred Term	Number (%) of Subjects (N=240)
Infection	3 (1.0)
Infection bacterial	2 (<1.0)
Bronchitis	2 (<1.0)
Headache	1 (<1.0)
Pain	1 (<1.0)
Pharyngitis	1 (<1.0)
Rhinitis	1 (<1.0)
Colitis	1 (<1.0)
Nausea	1 (<1.0)
Pruritus	1 (<1.0)
Skin ulcer	1 (<1.0)
Conjunctivitis	1 (<1.0)
Tinnitus	1 (<1.0)
Kidney pain	1 (<1.0)
Ovarian disorder	1 (<1.0)
Migraine	1 (<1.0)

Table 6. Adverse Events (Occurring >1%) in ITT Population (Study 006)

Body System	Preferred Term	5% Foam (N=180) N (%)	Foam Vehicle (N=172) N (%)
Body as a Whole	Abdominal pain	2 (1.1)	1 (<1.0)
	Accidental injury	5 (2.8)	13 (7.6)
	Allergic reaction	3 (1.7)	0
	Fever	2 (1.1)	0
	Flu syndrome	4 (2.2)	3 (1.7)
	Headache	13 (7.2)	6 (3.5)
	Hernia	2 (1.1)	2 (1.2)
	Infection	20 (11.1)	22 (12.8)
	Infection bacterial	1 (<1.0)	2 (1.2)
	Pain	4 (2.2)	2 (1.2)
	Photosensitivity reaction	1 (<1.0)	4 (2.3)
	Viral infection	2 (1.1)	1 (<1.0)
Cardiovascular System	Hypertension	2 (1.1)	1 (<1.0)
Digestive System	Diarrhea	2 (1.1)	3 (1.7)
	Gastrointestinal disorder	1 (<1.0)	3 (1.7)
	Nausea	2 (1.1)	2 (1.2)
	Periodontal abscess	1 (<1.0)	2 (1.2)
Metabolic and Nutritional Disorders	GGT increased	3 (1.7)	2 (1.2)
	Hyperglycemia	1 (<1.0)	5 (2.9)
	Hyperuricemia	0	2 (1.2)
	SGOT increased	2 (1.1)	0
	SGPT increased	3 (1.7)	2 (1.2)
Musculoskeletal System	Arthralgia	2 (1.1)	1 (<1.0)
	Myalgia	2 (1.1)	0
Nervous System	Depression	1 (<1.0)	2 (1.2)
	Dizziness	1 (<1.0)	3 (1.7)
Respiratory System	Bronchitis	4 (2.2)	2 (1.2)
	Pharyngitis	4 (2.2)	0
	Pneumonia	1 (<1.0)	3 (1.7)
	Rhinitis	1 (<1.0)	4 (2.3)
Skin and Subcutaneous Tissue Disorders	Acne	5 (2.8)	3 (1.7)
	Dry skin	0	2 (1.2)
	Pruritus	4 (2.2)	2 (1.2)
	Rash	7 (3.9)	1 (<1.0)
Urogenital System	Albuminuria	0	2 (1.2)
	Glycosuria	0	4 (2.3)
	Hematuria	3 (1.7)	7 (4.1)
	Urine abnormality	4 (2.2)	6 (3.5)

7.1.5.5 Identifying common and drug-related adverse events

In Studies 001, 004, and 005, five subjects experienced mild, non-serious AEs that were considered related to test material, for which no action was taken with respect to study drug and all of which resolved without residual effects. In Study 001, one male subject experienced rash

at the application site; in Study 004, one subject had pruritus; and in Study 005, one subject each had tingling scalp, itching on the test site, and heat rash on the head.

In Study 006, the incidence of drug-related AEs was low overall. Twelve vehicle subjects (7.0%) and 12 subjects (6.7%) in the 5% minoxidil foam group experienced drug-related AEs. Of these, the only events that occurred in more than 1% of subjects in either treatment group were headache (2 vehicle subjects [1.2%], 3 minoxidil subjects [1.7%]); Pruritus (no vehicle subjects [0%], 2 minoxidil subjects [1.1%]); rash (no vehicle subjects [0%], 2 minoxidil subjects [1.1%]); and pain (2 vehicle subjects [1.2%], 1 minoxidil subject [<1%]). No drug-related AE occurred in more than 5 subjects overall.

The drug-related AEs occurring in more than 1% of subjects in either treatment group were minor conditions related to pain or to application of study drug to the skin.

7.1.5.6 Additional analyses and explorations

There were no additional analyses or extrapolations performed by the sponsor.

7.1.6 Less Common Adverse Events

The population and the numbers of adverse events were too small to assess the incidence of less common adverse events.

7.1.7 Laboratory Findings

No clinical laboratory tests were performed in Study 004. Studies 001, 005, and 006 performed the following laboratory tests:

- In study 001, in addition to serum minoxidil level testing, CBC, blood chemistries (glucose, BUN, uric acid, creatinine, calcium, phosphorus, alkaline phosphatase, LDH, SGOT, SGPT, bilirubin, sodium, potassium, and chloride), urinalysis, and pregnancy test if indicated, were collected at baseline and prior to each new phase of the study.
- In study 005, blood chemistry, hematology and urinalysis were performed at baseline and between treatment assignments and chemistry and hematology were performed on Day 6 of each treatment phase prior to the last dosing for that phase.
- In study 006, complete blood count, chemistries and urinalysis were performed at baseline, Week 8, and Week 16 or at the time of discontinuation from the study.

7.1.7.1 Overview of laboratory testing in the development program

No clinically relevant abnormal laboratory values occurred in Studies 001 or 005.

For Study 006, there were no more clinically significant laboratory test results (above or below the referenced normal range) in the 5% minoxidil group than in the vehicle group. The incidence of clinically significant abnormalities in vehicle and 5% MTF groups were 5.8% and 3.9% at baseline, and 4.9% and 3.5% at Week 16, respectively. None of the subjects withdrew from the

study because of the laboratory abnormalities. None of the laboratory abnormalities were assessed as drug-related.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Not applicable.

7.1.7.3 Standard analyses and explorations of laboratory data

Not performed.

7.1.7.3.1 Analyses focused on measures of central tendency
Not applicable.

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal
Not applicable.

7.1.3.3.3 Marked outliers and dropouts for laboratory abnormalities
Not applicable.

7.1.7.4 Additional analyses and explorations

There were no additional analyses or extrapolations.

7.1.7.5 Special assessments

Not applicable.

7.1.8 Vital Signs

No vital signs were recorded in Study 004.

Vital signs (HR, RR, and BP) were monitored during studies 001 and 005 at baseline, between treatment assignments and at the end of the study. In study 006, vital signs (HR, BP, and body weight) were measured at baseline and every four weeks of the study.

7.1.8.1 Overview of vital signs testing in the development program

In Studies 001 and 005, the mean pulse increased slightly from baseline to Day 6 of each treatment period, as did the mean blood pressure during treatment with 2% MTS, 5% minoxidil foam with glycerin (1 gram BID), and 5% minoxidil foam with glycerin (2 grams BID). The mean blood pressure decreased slightly from baseline to Day 6 during treatment with 5% MTS, 5% minoxidil foam with propylene glycol, and 5% minoxidil foam with glycerin (3 grams BID). In no patient was a change in pulse or blood pressure considered clinically significant in the judgment of the investigator.

In Study 006, mean blood pressure and pulse values were similar in the 5% minoxidil foam scented and foam vehicle groups at baseline and at each evaluation time point (Table 7). One subject in the foam vehicle group withdrew from the study because of a nonserious AE of mild, intermittent, rapid heart beat; this event was self-reported and could not be confirmed by the investigator. At the time of final visit, this subject's blood pressure was 118/74 mmHg and heart rate of 78 bpm. Mean body weights were similar between the 2 treatment groups at each evaluation time point and changed very little over the course of the 16-week study.

Table 7. Vital Signs (Study 006)

Time Point	5% Foam Scented				Foam Vehicle			
	Systolic/Diastolic Blood Pressure, mmHg		Pulse, bpm		Systolic/Diastolic Blood Pressure, mmHg		Pulse, bpm	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	180	121.5/79.3	180	72.1	172	122.1/79.5	172	73.8
Week 4	173	121.7/78.1	172	74.2	168	121.4/78.9	168	73.9
Week 8	164	121.3/78.7	164	73.2	155	121.5/79.6	154	73.3
Week 12	162	120.5/77.7	163	73.3	150	122.7/79.6	150	72.9
Week 16	173	120.9/78.3	173	74.3	164	120.6/78.3	164	72.6

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

See section 7.1.8.1.

7.1.8.3 Standard analyses and explorations of vital signs data

See section 7.1.8.1

7.1.8.3.1 Analyses focused on measures of central tendencies
Not applicable.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal
Not applicable.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities
Not applicable.

7.1.8.4 Additional analyses and explorations

There were no additional analyses or extrapolations.

7.1.9 Electrocardiograms (ECGs)

Electrocardiograms were not routinely done in the conducted clinical trials.

7.1.10 Immunogenicity

There are no known immunogenicity issues related to minoxidil.

7.1.11 Human Carcinogenicity

There are no known carcinogenicity issues related to minoxidil.

7.1.12 Special Safety Studies

There were no special safety studies requested or performed for this application.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Current labeling included with 5% MTS states that if hair regrowth occurs, continued use of the product is necessary or hair loss will begin again. The labeling further states that if the use of 5% MTS is stopped, newly regrown hair will be lost within 3 to 4 months. The labeling to be included with 5% minoxidil topical foam contains the same cautionary statements.

Five percent minoxidil foam contains 50 mg/g of minoxidil. This drug is not regulated under the Controlled Substances Act (21 USC 801 and 951). Minoxidil is not likely to present a substantial risk of medical abuse, to lead to addiction, or to be misused for illegal purposes.

7.1.14 Human Reproduction and Pregnancy Data

Minoxidil is a Pregnancy Category C drug. At very high exposure concentrations compared with humans, animal studies have shown signs of maternal toxicity and a risk to the fetus. As there are no adequate and well controlled studies in pregnant women, minoxidil should be used during pregnancy only if the potential benefit justifies the risk to the fetus. Systemically absorbed minoxidil is secreted in human milk. The U.S. labeling for both 2% and 5% minoxidil formulations carries the warning, "May be harmful if used when pregnant or breast-feeding". Since the marketed 5% MTS is not approved for use by women, it also includes a warning that the product should not be used by females. Proposed labeling for 5% minoxidil topical foam is consistent with these warnings.

7.1.15 Assessment of Effect on Growth

There are no new data on effects on growth. Minoxidil is not indicated for children or adolescents.

7.1.16 Overdose Experience

Accidental ingestion or the application of excessive amounts of the topical minoxidil products have the potential to produce systemic effects related to the action of the drug. Signs and symptoms of minoxidil overdosage would most likely be cardiovascular effects associated with hypotension, sudden weight gain, rapid heart beat, faintness, or dizziness.

Data on overdose with minoxidil comes from three sources:

1. The sponsor's postmarketing database,
2. Clinical Study 005, and
3. Data from the AAPCC

Overdose or Poisoning Cases from Pfizer's Post-marketing Database (ARGUS/ARISg)
In the sponsor's postmarketing database, from sources other than Pfizer sponsored androgenetic alopecia clinical trials in which "overdose" or "poisoning" was included as an adverse event term, 698 cases were reported for 5% MTS and 281 cases were reported for 2% MTS, which represent approximately 3% of all cases (5% or 2%):

- The vast majority of the 698 cases involving 5% MTS that were associated with Overdose or Poisoning were nonserious (N=668, 98%) and spontaneously reported (N=638, 91%) by patients/consumers (N=668, 96%). There were no reports of death among any of the cases. Females made up the majority of cases (N=586, 84%), and for the cases where age was reported, the mean age was 51.3 years. Among the 698 cases involving 5% MTS, those adverse event terms reported at a rate of at least 2% included medication error (579; 37%), no adverse drug effect (216; 14%), accidental exposure (77; 4.9%), alopecia (78; 4.9%), hypertrichosis (71; 4.5%), no adverse effect (64; 4.1%), pruritus (56; 3.5%), and hair texture abnormal (33; 2.1%). The 11 serious 5% MTS cases associated with Overdose or Poisoning represent 0.07% of all cases. Nine of these cases involved intentional misuse of the product and 2 cases involved accidental exposure.
- The vast majority of the 281 cases involving 2% MTS that were associated with Overdose or Poisoning were nonserious (N=276, 98%) and reported by patients/ consumers (N=267, 95%). Among the 281 cases involving 2% MTS, those adverse event terms reported at a rate of at least 2% included accidental exposure (140; 23%), no adverse effect (106; 17%), medication error (100; 16%), overdose (43; 7.0%), eye irritation (37; 6.0%), and hypertrichosis (17; 2.8%). The 5 serious cases associated with Overdose or Poisoning represent 0.03% of all cases. Three cases involved misuse of the product and 2 cases involved accidental exposure.

Serious adverse events were associated with the intentional ingestion (suicide attempt) or misuse (higher amount or higher concentration than recommended by labeling) of the product.

Among the overdose/poisoning cases, there were a total of nine (1.3%) children below 12 years of age out of a total of 698 cases involving 5% MTS and four (1.4%) out of 281 cases involving 2% MTS.

Clinical Study 005

Study 005 assessed the effects of exaggerated exposure by examining doses of 1, 2, and 3 times the recommended dosage of 5% minoxidil foam. The study demonstrated statistically significant pair wise differences in systemic absorption of minoxidil between treatment dosages. The study report concluded that use of 5% minoxidil foam at up to 3 times the recommended dose, used twice daily, does not produce blood levels of minoxidil known to be associated with systemic effects.

Data from the AAPCC

The data from the American Association of Poison Control Centers' (AAPCC) Toxic Exposure Surveillance System (TESS) database tabulates information on all cases reported to a participating poison control center in the United States involving a human exposure to topical minoxidil from January 1, 1994 to December 31, 2003. The exposures are presented in 4 route of exposure (ROE) categories: Ingestion, Dermal, Ocular and an "Other" category which includes several routes of exposure with low frequencies of reports.

Overall, there were 1302 cases of exposure to topical minoxidil reporting 688 clinical effects. Ingestions represented the majority of exposures (70.4%, 917/1302) with dermal exposures also contributing a substantial fraction (16.3%, 212/1302). Ocular exposures accounted for 9.4% (122/1302) of all reports and the Other category of exposure had 3.9% (51/1302) of all reports.

The proportion of male patients ranged from 54.4% (499/917) among ingestions to 37.3% (19/51) in the "Other" category. Overall, men comprised 50.8% (662/1302) of the reports and women 48.5% (631/1302). Only 0.7% (9/1302) of the reports had no reported gender. A total of 99.7% (1298/1302) of cases had age data. The mean age was 20.9 years and the age distribution revealed that the majority of cases with a reported age was in the < 6 age range (52.3%, 681/1302) with 42.9% (559/1302) of the reports in the > 19 age range.

There was one death reported. This was an ingestion in a 61-year-old woman in 1996 who died of a cardiac arrest complicated by a tachyarrhythmia and an unspecified conduction disturbance following an intentional ingestion which was a suspected suicide. Apart from the single death, five (0.4%, 5/1302) cases were reported with major effects. Moderate effects were reported in 2.9% (38/1302) of cases. The 5 categories of medical outcome identifying no effects, minor effects, minimal effects, or nontoxic exposures and unrelated effects accounted for 92.7% (1207/1302) of all reports. A list of the reported clinical effect terms reported at least twice for each route of exposure is presented in Table 8 in the Appendix I.

Overall, the three most frequently reported clinical effects account for 32.7% (225/688) of the total reported effects: Ocular Irritation/Pain (16.6%, 114/688), Other (8.6% 59/688) and Dizziness/Vertigo (7.6%, 52/688). For the Ingestion ROE, Vomiting (12.4%, 37/299), Tachycardia (9.7%, 29/299) and Hypotension (9.7%, 29/299) were the most frequently cited clinical effect terms.

In the Ingestion category, the large majority (66.5%, 610/917) of cases were reported in the pediatric age range (< 6). Only 28 cases were reported in the pediatric age ranges from 6-19 years. Among the < 6 age group, Unintentional reasons accounted for 606 (99.3%, 606/610) of

the cases. In the adult age range (>19) Unintentional reasons amounted to 86.6% (240/277) of the reported exposure reasons. The three terms with the highest reporting rates were: Vomiting (12.4%, 37/299), Hypotension (9.7%, 29/299), and Tachycardia (9.7%, 29/299). These accounted for 31.8% (95/299) of all reported terms.

Comments:
Based on the review of the overdose and poisoning data for minoxidil 2% and 5% topical solution, gathered from Study 005, sponsor's postmarketing and AAPCC databases, overdose with minoxidil topical products is rare considering over 17 million units of drug sold between 1999 and 2004. The majority of overdose cases were non-serious. There were a total of 16 serious cases in the sponsor's database; all of them were associated with intentional misuse or accidental exposure.

7.1.17 Postmarketing Experience

Five percent minoxidil foam has not yet been marketed anywhere in the world. Post-marketing safety data relevant to this application comes from post-marketing experience with 5% MTS and 2% MTS. The sponsor submitted postmarketing safety data from three different sources: Pfizer's corporate safety database (ARGUS/ARISg), World Health Organization's (WHO) international drug monitoring database, and FDA Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) database. Data from each of these sources will be reviewed separately.

1. Pfizer's corporate safety database ARGUS/ARISg.
Pfizer's corporate safety database for 5% MTS contains reports or cases of adverse events, both serious and non-serious, that have been spontaneously reported to Pfizer by patients/consumers, health care professionals, and health authorities or registries, as well as cases identified through review of the medical literature. The database also contains cases of serious adverse events reported from Pfizer-sponsored clinical studies, clinical studies sponsored by licensing partners, and marketing programs (solicited cases).

Available cumulative hospital and pharmacy distribution data for minoxidil 2% and 5% formulations (marketed under the trade names Regaine Maenner®, Rogaine for Men®, Regaine®, Alostil®, Rogaine Forte®, Minocalve®, and Rogaine For Men Extra Strength®) are derived from "units of volume of measurement" from IMS Global Services for the time period beginning 01 January 1999 and ending 30 June 2004. Definitive conversion of packages distributed into numbers of subjects exposed is not possible as the product is marketed over-the-counter and used without the supervision of a health care professional.

A total of 15,299 5% MTS cases and 17,514 2% MTS cases were entered into Pfizer's safety database (ARGUS/ARISg) for the time period beginning 01 March 1999 and ending 31 July 2004. Exposure information, based on available cumulative hospital and pharmacy distribution data, indicates that approximately [redacted] mL of 5% MTS and approximately [redacted] mL of 2% MTS were distributed in the U.S. and elsewhere during the time period beginning 01

January 1999 and ending 30 June 2004. The characteristics of reported cases for 2% and 5% MTS are summarized in Table 9.

Table 9. Characteristics of All Minoxidil 2% and 5% Solution Cases

		Minoxidil 2%	Minoxidil 5%
		Overall	
Total Number of case reports		17,514	15,299
Total Number of Adverse Event Terms		25,846	24,339
Age, years	N	11,927a	11,142a
	Mean (SD)	52.8 (16.28)	43.18 (15.48)
	Range	< 1 – 99	< 1 – 95
		Count (%)	
Age group, years	< 12	23 (0.13)	30 (0.2)
	12-17	35 (0.2)	50 (0.33)
	18-65	8,908 (50.86)	10,000 (65.36)
	> 65	2,961 (16.91)	1,062 (6.94)
	Unknown	5,587 (31.9)	4,157 (27.17)
Gender	Female	13,736 (78.43)	2,761 (18.05)
	Male	3,166 (18.08)	12,199 (79.74)
	Unknown	612 (3.49)	339 (2.22)
Case Seriousness	Nonserious	17,340 (99.01)	15,200 (99.35)
	Serious	173 (0.99)	98 (0.64)
	Death	1 (0.01)	1 (0.01)
Report Type	Spontaneous	17,159 (97.97)	15,119 (98.82)
	Literature	4 (0.02)	5 (0.03)
	Other	315 (1.8)	170 (1.11)
	Clinical Study	36 (0.21)	5 (0.03)
Case Outcome	Unknown	10,533 (60.14)	6,980 (45.62)
	Not recovered	3,616 (20.65)	4,227 (27.63)
	Recovering	886 (5.06)	988 (6.46)
	Recovered	2,134 (12.18)	2,184 (14.28)
	Recovered with sequelae	22 (0.13)	10 (0.07)
	Not applicable	322 (1.84)	909 (5.94)
	Death	1 (0.01)	1 (0.01)
Report Source	Patient/consumer	16,688 (95.28)	14,407 (94.17)
	Health care professional	459 (2.62)	454 (2.97)
	Unknown	321 (1.83)	427 (2.79)
	Literature	4 (0.02)	5 (0.03)
	Pfizer study	4 (0.19)	5 (0.03)
	Solicited	0 (0.00)	1 (0.01)
	Non-Pfizer Study	2 (0.01)	0 (0.00)
	Attorney	6 (0.03)	0 (0.00)

The post-marketing data indicate that 2% and 5% MTS are generally well tolerated, with serious cases making up less than 1% of all 5% MTS cases (0.64%) and less than 1% of all 2% MTS cases (0.99%). A review of all reports of death and serious cases did not identify any new safety issue or signal of an increased level of risk of either 5% MTS or 2% MTS. There were 2 deaths, one resulting from a myocardial infarction (5% MTS case), and one death resulting from a second trimester abortion (2% MTS case):

- No. 2003164836US, a consumer reported that her sister's friend, a male (reportedly in his 30s), suffered a massive heart attack and died while using Rogaine 5% (dose and therapy dates unknown) in 1995.
- Literature report. A 28-year-old, primigravid female, with a medical history of irregular menses, had used 2% Topical Minoxidil Solution to treat hair loss for the previous 4 years, as well as, during her pregnancy. Her early pregnancy course was complicated by a flu-like upper respiratory disease (cough, sore throat, and fever of 38-39^0 C) during the seventh to ninth week of pregnancy. These symptoms were treated with trimethoprim-sulfamethoxazole and erythromycin. As the patient was unaware of the pregnancy, no further evaluation was performed. The first beta-HCG blood examination, which was positive, was performed 3 weeks before the patient's admission. However, a routine ultrasound performed a few days later revealed the presence of a live fetus about 16 weeks gestational age with a severe form of caudal regression syndrome. A second trimester abortion was performed and the fetus and placenta were sent for pathologic and genetic evaluation. An autopsy revealed a male fetus with multiple deformities. No other information was provided.

Tables 10 and 11 in the Appendix II are summaries of all adverse event cases by frequency for minoxidil 2% and 5% topical solutions by MedDRA system organ classification (SOC).

As described in Table 10, 66% (17,125 of 25,846) of the adverse event terms reported within all 17,514 cases for 2% MTS coded to the skin and subcutaneous tissue disorders SOC. Among all 25,846 adverse event terms associated with all 17,514 cases under review for 2% MTS, the most commonly reported adverse event terms (those reported at a rate of at least 2% of all reported adverse event terms) were mostly related to skin and subcutaneous tissue disorders including, alopecia (4,112; 16%), pruritus (3,247; 13%), hypertrichosis (1,463; 5.7%), skin desquamation (1,214; 4.7%), dry skin (1,135; 4.4%), hair texture abnormal (1,112; 4.3%), skin irritation (914; 3.5%), hair color changes (712; 2.8%), rash (573; 2.2%), and dandruff (567; 2.2%). Other adverse event terms reported at a rate of at least 2% included drug ineffective (1,656; 6.4%), headache (616; 2.4%), and dizziness (519; 2.0%).

As described in Table 11, 71% (17,345 of 24,339) of the adverse event terms reported within all 15,299 cases for 5% MTS coded to the skin and subcutaneous tissue disorders SOC. The vast majority of cases (99%) were nonserious cases. Among all 24,339 adverse event terms associated with all 15,299 cases under review for 5% MTS, the most commonly reported adverse event terms (those reported at a rate of at least 2% of all reported adverse event terms) were mostly related to skin and subcutaneous tissue disorders including, pruritus (3,909; 16%), alopecia (3,119; 13%), skin desquamation (2,374; 9.8%), dry skin (1,546; 6.4%), skin irritation (1,173; 4.8%), dandruff (874; 3.6%), hypertrichosis (737; 3.0%), rash (705; 2.9%), and hair texture abnormal (496; 2.0%). Other adverse event terms reported at a rate of at least 2% included drug ineffective (1,135; 4.7%) and medication error (579; 2.4%).

The pattern was different for the 98 serious cases excluding deaths, with adverse event terms primarily coded across 6 SOCs: nervous system disorders, with 40 (15%) events; cardiac system disorders, with 31 (12%) events; general disorders and administration site conditions, with 26

(9.7%) events; skin and subcutaneous tissue disorders, with 24 (9.0%) events; injury, poisoning, and procedural complications, with 24 (9.0%) events; and investigations, with 24 (9.0%) events.

There were no safety issues identified among the different subgroups of individuals using 5% MTS that were evaluated in the ISS. The 5% MTS adverse event profile and reporting rates indicated no substantial differences among males, females, and all individuals, or among elderly individuals and individuals aged 18 to 65 years. The proportion of cases reported by elderly individuals was small (6.9% of all cases), and unlabeled adverse event terms reported by elderly individuals did not show any obvious pattern that might be attributed to this particular age group. Similarly, there were no safety issues identified among the different subgroups of individuals using 2% MTS that were evaluated in this report.

Comment:
Overall, reported adverse event terms associated with all 2% MTS and 5% MTS cases under review did not reveal any unusual or unexpected safety signals. Most of the reported adverse events were associated with the local application reactions and were non-serious in nature. It is difficult to interpret the causality of serious adverse events. Information (medical history, diagnosis, dose and duration of treatment, concomitant drugs) for most of the cases is incomplete. Because of the missing information, we cannot assess if the event is caused by a labeled drug use, misuse, underlying medical condition, concomitant medications, demographics or other factors. At best we can only say that the postmarketing data did not reveal new serious safety signals associated with the use of minoxidil.

2. World Health Organization's (WHO) international drug monitoring database.
The following data from the World Health Organization's (WHO) International Drug Monitoring Programme tabulates information on all cases involving topical minoxidil over the period from January 1984 to August 2004.

This database has several limitations. The data gathered in the WHO database comes from a variety of participating countries and therefore is inconsistent because in some cases the reported information does not conform to WHO requirements. The permissible outcome designations for the WHO database are different from those used by the FDA and as a result over 80% of the cases from the FDA have no outcome data in the WHO database. Over 60% of all cases actually have outcome data recorded in the FDA databases, but it has not been translated into permissible WHO outcomes. Since the FDA data comprises over 80% of the WHO data, this type of problem is a significant source of reporting error. Although the WHO Monitoring Centre has 72 participating countries, only a small number provide the vast majority of cases.

An analysis of the adverse events reported for topical minoxidil in the WHO drug safety database revealed 4036 cases involving 8043 WHO Adverse Reaction Terminology (WHOART) adverse event terms. Of these reports, 781 cases involving 1334 terms were reported from outside the United States (exUS) and were the primary focus of this document. The 3255 cases with 6709 associated adverse event terms reported by the FDA to the WHO were also tabulated for completeness. FDA US cases are reviewed in the next section of this review; therefore, they will not be discussed here.

For the exUS cases, the gender ratio of cases origin with a reported gender was 2.53 (540/213) male:female; the mean age was 39.2 years and 67.9% of the cases were in the 18-65 year age range. There was 1 death reported (0.1%, 1/781), a 37-year old man from the United Kingdom without additional listed drugs or adverse event terms. His death was not thought to be causally related to the use of topical minoxidil.

Among cases of exUS origin, 4 SOCs accounted for 68.1% (909/1334) of all reported terms. They were: Skin and appendages disorders (36.4%, 486/1334), Central and peripheral nervous system disorders (12.1%, 162/1334), Body as a whole – general disorders (11.7%, 156/1334) and Application site disorders (7.9%, 105/1334). With respect to individual terms, a total of 7 out of the 10 most frequently reported terms were from the Skin and appendage disorders SOC or the Application site disorders SOC. The 2 terms with the highest reporting rates were: Application site reaction (7.6%, 102/1334) and Pruritus (7.1%, 95/1334). A summary of the most frequent AE terms for topical minoxidil (exUS cases) is listed in Table 12 below.

Table 12. Most frequent adverse event terms for topical minoxidil (exUS cases) all reports by WHOART term and age group (frequency ≥ 1.0%) N (%)

Application site reaction	102 (7.6)
Pruritus	95 (7.1)
Headache	47 (3.5)
Rash	47 (3.5)
Dizziness	44 (3.3)
Dermatitis contact	42 (3.1)
Rash erythematous	42 (3.1)
Alopecia	36 (2.7)
Hypertrichosis	35 (2.6)
Palpitation	35 (2.6)
Dermatitis	34 (2.5)
Eczema	32 (2.4)
Paraesthesia	28 (2.1)
Chest pain	26 (1.9)
Skin exfoliation	23 (1.7)
Face oedema	22 (1.6)
Therapeutic response decreased	20 (1.5)
Oedema	19 (1.4)
Vision abnormal	18 (1.3)
Nausea	16 (1.2)
Skin dry	16 (1.2)
Urticaria	15 (1.1)
Vertigo	14 (1.0)
Oedema periorbital	13 (1.0)
Total terms	**1334 (100)**
Total Cases	**781 (100)**

Comments:
The profile of exUS adverse events for topical minoxidil gathered by WHO is consistent with safety reports in the US.

3. FDA Spontaneous Reporting System (SRS) and Adverse Event Reporting System (AERS) database.

Two FDA databases were queried for all case reports for which a topical minoxidil-containing product was recorded as a suspect agent (SRS database) or the primary or secondary suspect agent (AERS database). This report does not include cases where topical minoxidil was reported as a concomitant medication. For completeness, reports without any dose or route of administration information have been included in the tabulations.

An analysis of the adverse events reported for topical minoxidil revealed 26539 cases involving 51628 adverse event terms (see Table 13). Among the reports for topical minoxidil, there were 675 serious cases (2.5% of total reports) and 58 deaths (0.2% of total reports).

Men represented 55.9% (14831/26539) and women 41.4% (10991/26539). A total of 2.7% (717/26539) of the reports had no gender data. The mean age of the 63.1% of reports with age information was 46.1 years. A total of 53.6% (14235/26539) of the reports involved patients in the 18-65 age range.

There were 9 outcomes reported as a congenital anomaly. Overall, there were a total of 41 terms in the Congenital, familial and genetic disorders SOC. Of these, 5 had no outcome data, 13 were non-serious, 8 were serious and 15 involved a death. Examination of the individual terms did not reveal any marked case clustering. The individual terms with the highest number of reports in this SOC were: Congenital abnormality NOS (10 reports), Chondrodystrophy (6 reports), Pigmented naevus (4 reports), Facial dysmorphism (2 reports). All the remaining terms were single instances.

Across all reports irrespective of outcome, Skin and subcutaneous tissue disorders (41.1%, 21207/51628), General disorders and administration site conditions (30.6%, 15794/51628) and Nervous system disorders (8.2%, 4234/51628) accounted for 79.9% (41235/51628) of the terms used to characterize the cases. In the Skin and subcutaneous tissue disorders SOC, the 3 most frequently cited terms were: Alopecia (11.0%, 5671/51628), Pruritus NOS (8.7%, 4505/51628) and Dermatitis NOS (5.0%, 2597/51628). For General disorders and administration site conditions, the 3 most frequent terms were: Drug ineffective (9.3%, 4813/51628), Condition aggravated (7.7%, 3956/51628) and Application site reaction NOS (6.6%, 3417/51628). Lastly, for Nervous system disorders, the 3 most frequently reported terms were: Headache NOS 2.9%, 1508/51628), Balance impaired NOS (2.2%, 1156/51628) and Paraesthesia (0.8%, 432/51628).

Serious cases represented 2.5% (675/26539) of all reports. For the serious reports, the Cardiac disorders SOC (18.6%, 343/1840), General disorders and administration site conditions (16.5%, 304/1840) and Nervous system disorders (14.5%, 266/1840) were the highest ranking SOCs based on frequency of reported terms. For Cardiac disorders, the 2 most frequently cited terms were: Myocardial infarction (4.4%, 81/1840) and Palpitations (1.5%, 27/1840). In the General

disorders and administration site conditions SOC, the 3 terms with the highest reporting rate frequencies were: Chest pain (5.5%, 101/1840), Condition aggravated (1.8%, 34/1840) and Oedema peripheral (1.1%, 20/1840). For Nervous system disorders the 3 most frequent terms were: Headache NOS (1.8%, 34/1840), Dizziness (1.7%, 31/1840) and Syncope (1.5%, 27/1840).

Reports of death accounted for 0.2% (58/26539) of all cases. Among the reports of death, the 3 SOCs with the highest reporting frequencies were the same as those for the serious reports; namely, Cardiac disorders (25.2%, 39/155), General disorders and administration site conditions (11.0%, 17/155) and Nervous system disorders (11.0%, 17/155). In Cardiac disorders, Myocardial infarction (9.7%, 15/155) and Cardiac failure NOS (4.5%, 7/155) were the terms with a reporting rate over 2%. For General disorders and administration site conditions, Chest pain (3.2%, 5/155) was the single term with a reporting rate over 2%. In Nervous system disorders, Headache NOS (2.6%, 4/155) was the only term representing more than 2% of all reported terms for cases of death.

Table 13. below presents the most frequent AE terms (≥ 1.0%) for topical minoxidil sorted by frequency, based on the overall occurrence rate.

Table 13. Most Frequent AE Terms for Topical Minoxidil – All Reports by MedDRA Term and Seriousness (frequency ≥ 1.0%) N (%)

MedDRA Preferred Term	No outcome data	Not Serious	Serious	Death	Overall total
Alopecia	3866 (11.9)	1784 (10.4)	21 (1.1)	0	5671 (11.0)
Drug ineffective	3769 (11.6)	1034 (6.0)	10 (0.5)	0	4813 (9.3)
Pruritus NOS	3220 (9.9)	1269 (7.4)	15 (0.8)	1 (0.6)	4505 (8.7)
Condition aggravated	2842 (8.8)	1080 (6.3)	34 (1.8)	0	3956 (7.7)
Application site reaction NOS	2503 (7.7)	906 (5.3)	8 (0.4)	0	3417 (6.6)
Dermatitis NOS	1702 (5.2)	882 (5.1)	13 (0.7)	0	2597 (5.0)
Dermatitis exfoliative NOS	1594 (4.9)	408 (2.4)	2 (0.1)	0	2004 (3.9)
Dry skin	1237 (3.8)	458 (2.7)	2 (0.1)	0	1697 (3.3)
Headache NOS	830 (2.6)	640 (3.7)	34 (1.8)	4 (2.6)	1508 (2.9)
Hirsutism	1038 (3.2)	341 (2.0)	2 (0.1)	1 (0.6)	1382 (2.7)
Hair disorder NOS	855 (2.6)	414 (2.4)	3 (0.2)	0	1272 (2.5)
Balance impaired NOS	686 (2.1)	451 (2.6)	17 (0.9)	2 (1.3)	1156 (2.2)
Pain NOS	769 (2.4)	299 (1.7)	16 (0.9)	0	1084 (2.1)
Hair colour changes	522 (1.6)	218 (1.3)	1 (0.1)	0	741 (1.4)
Chest pain	302 (0.9)	199 (1.2)	101 (5.5)	5 (3.2)	607 (1.2)
Overdose NOS	471 (1.5)	109 (0.6)	5 (0.3)	0	585 (1.1)
Face oedema	321 (1.0)	243 (1.4)	9 (0.5)	0	573 (1.1)
Tachycardia NOS	296 (0.9)	218 (1.3)	26 (1.4)	0	540 (1.0)
Total terms	**32470 (100)**	**17163 (100)**	**1840 (100)**	**155 (100)**	**51628 (100)**
Total cases	**17455 (65.8)**	**8351 (31.5)**	**675 (2.5)**	**58 (0.2)**	**26539 (100)**

There was a modest increase in the proportion of > 65 year old patients among the serious reports (11.4% of cases) and reports of death (12.1% of cases) compared to the fraction of > 65 age group observed overall (9.1% of cases).

Comments:

Overall, for topical minoxidil, the side effect profile observed across the FDA's data primarily reflected local irritant effects. The sponsor states that the occurrence of cardiovascular-related events reported in comparison to the amount of product distributed is well below the incidence in the general population and shows no trends or signals. In the opinion of this reviewer, this assumption is probably valid. It is difficult to assess the incidence of any event based on the postmarketing reporting. Most of the events were neither medically confirmed, nor a causality was reported. Minoxidil already has an adequate labeling that directs consumers to stop using the product and consult a doctor if chest pain, rapid heartbeat, faintness, or dizziness occurs.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The safety database comprises a total of 694 subjects, of whom 522 were treated with one or more formulations of 5% minoxidil foam. A list of clinical studies conducted by the sponsor to support the 5% minoxidil foam formulation is provided in Table 14 below.

7.2.1.1 Study type and design/patient enumeration

Table 14. List of Clinical Studies

Study No.	Study Type/Design	Treatment Type & Duration	No. of Subjects
MINOB-9140-001	Bioavailability, RA, OL, CO	5% minoxidil foam 5% minoxidil solution 2% minoxidil solution	67
MINOB-9140-005	Bioavailability, RA, OL, CO	5% minoxidil foam, 1 g 5% minoxidil foam, 2 g 5% minoxidil foam, 3 g	35
MINOB-9140-004	Dermal Sensitization, RA, IB	Three 5% minoxidil foams Placebo foam	240
MINOB-9140-006	Clinical safety and Efficacy, RA, DB, PC	5% minoxidil foam Vehicle	352

RA: randomized; OL: open label; CO: cross-over; IB: investigator blind; PC: placebo controlled.

7.2.1.2 Demographics

A similar number of male and female subjects participated in Study 001, whereas only male subjects participated in Study 005 (Table 15). Mean age was 44 years for male subjects in both studies and 47 years for female subjects, and more than 80% of the subjects were white. All subjects met the protocol-specified pattern of hair loss for inclusion in the studies.

Table 15. Demographic Characteristics (Studies 001 and 005)

Variable	Study 001			Study 005
	Males (N=33)	Females (N=34)	Total (N=67)	Males (N=35)
Age (years)				
Mean (SD)	44 (11)	47 (10)	45.7 (10.45)	44.2 (9.79)
Range (min-max)	21-64	31-65	21-65	22-62
Race, n (%)				
White	26 (78.8)	29 (85.3)	55 (82.1)	29 (82.9)
Black	4 (12.1)	2 (5.9)	6 (9.0)	3 (8.6)
Hispanic	1 (3.0)	2 (5.9)	3 (4.5)	2 (5.7)
Asian/Pacific Islander	1 (3.0)	1 (2.9)	2 (3.0)	0
Other	1 (3.0)	0	1 (1.5)	1 (2.9)
Pattern of Hair Loss, n (%)				
Type IIIv	12 (36.4)	NA	NA	12 (34.3)
Type IV	9 (27.3)	NA	NA	10 (28.6)
Type V	7 (21.2)	NA	NA	8 (22.9)
Type VI	5 (15.2)	NA	NA	5 (14.3)

The 240 subjects who participated in Study 004 were normal volunteers who did not have androgenetic alopecia. The mean age of the study population was 52 years. Female subjects made up 76% of the study population, and most (83%) of the subjects were white (Table 16).

Table 16. Demographic Characteristics (Study 004)

Variable		5% Foam/Vehicle*
Age (years)	Mean (SD)	52.1 (15.55)
	Range (min-max)	18-83
Gender, n (%)	Male	58 (24.2)
	Female	182 (75.8)
Race, n (%)	White	200 (83.3)
	Black	14 (15.8)
	Hispanic	14 (15.8)
	Asian/Pacific Islander	4 (1.7)
	American Indian	4 (1.7)
	Other	4 (1.7)

* includes 5% foam [illegible] ') and foam vehicle

In Study 006 the 2 treatment groups were generally well balanced with respect to age and race; all subjects in this study were male (Table 17). All subjects met the protocol-specified pattern of hair loss for inclusion in the study, and the 2 treatment groups were generally well balanced for patterns of hair loss. The 5% minoxidil foam group had a slightly longer mean and median duration of hair loss.

Comment:
Study #006 enrolled a young population; no one was ≥ 50 years old. This may have had an impact on the safety data derived from this study.

Table 17. Subject Demographics (Study 006)

Variable		Treatment Group	
		Placebo N=172	5% MTF N=180
Age (Years)	Range (Min-Max)	20.0-49.0	21.0-49.0
	Mean (SD)	38.3 (7.34)	40.1 (6.33)
Race, N (%)	White	154 (89.5%)	151 (83.9%)
	Black	5 (2.9%)	7 (3.9%)
	Hispanic	7 (4.1%)	17 (9.4%)
	Asian/Pacific Islander	3 (1.7%)	3 (1.7%)
	American Indian/Alaskan	2 (1.2%)	2 (1.1%)
	Other	1 (<1%)	0
Duration of hair loss (months)	Mean (SD)	105.9 (67.3)	115.4 (77.03)
	Median	96.0	108.0
	Range (Min-Max)	5.0-312.0	12.0-336.0
Pattern of hair loss N (%)	Type IIIv	63 (36.6%)	77 (42.8%)
	Type IV	64 (37.2%)	53 (29.4%)
	Type V	45 (26.2%)	50 (27.8%)

7.2.1.3 Extent of exposure (dose/duration)

Studies 001 and 005 used a crossover design in which subjects were exposed to all protocol-specified treatment regimens. In Study 001, the mean number of days subjects were exposed to test material was 6.0 days when they used 5% MTS, 2% MTS, and 5% foam with propylene glycol, and 5.8 days when they used 5% foam with glycerin (Table 18). In Study 005, the mean number of days subjects were exposed to test material was 6.0 days when they used 1 or 2 grams of 5% minoxidil foam BID, and 5.9 days when they used 3 grams of 5% minoxidil foam BID.

Table 18. Drug Exposure (Studies 001 and 005)

Study No.	Gender	Treatment	Days of Exposure Mean (Range)
Study 001	Males	5% MTS (N=30)	6.0 (6-6)
		5% Foam w/GLY (N=32)	5.8 (1-6)
		5% Foam w/PG (N=30)	6.0 (6-6)
	Females	2% MTS (N=31)	6.0 (5-6)
		5% Foam w/GLY (N=30)	5.8 (3-6)
		5% Foam w/PG (N=30)	6.0 (5-6)
Study 005	Males	5% Foam 1 gram (N=34)	6.0 (6-6)
		5% Foam 2 gram (N=33)	6.0 (6-6)
		5%Foam 3 gram (N=33)	5.9 (2-6)

A block design was used in Study 004 in which the 4 test materials (5% minoxidil foam unscented, 5% minoxidil foam [illegible] scent, 5% minoxidil foam [illegible]cent, and foam vehicle [unscented]) were applied to a patch (0.2 mL) and applied to the skin of each subject according to the randomization schedule for a total of 10 applications (9 during induction, 1 during challenge) over a 6-week period of time. The total exposure to the test material was 2.0 mL.

5% minoxidil foam —— and vehicle foam (unscented) over a 1-week period.

Exposure to doses of test material in Study 006 was similar for both treatment groups, with a mean daily dose of 2.2 g of study foam (5% minoxidil or placebo) for a mean duration of approximately 108 days. The exposure of subjects to test material in Study 006, as determined from patient compliance is summarized in Table 19.

Table 19. Summary of Drug Exposure (Study 006)

Variable		Treatment group	
		Placebo	**5% MTF**
Duration	N	172	180
	Mean (SD)	107.6 (21.99)	107.9 (23.23)
	Median	113.0	113.0
	Range (Min-Max)	1.0-154.0	1.0-135.0
Actual/Estimated CTM* Use (Grams)	N	170	177
	Mean (SD)	238.7 (86.88)	241.0 (77.99)
	Median	242.4	248.1
	Range (Min-Max)	13.1-462.5	5.3-383.3
Actual/Estimates Daily CTM Use (Grams)	N	170	177
	Mean (SD)	2.2 (0.77)	2.2 (0.60)
	Median	2.2	2.2
	Range (Min-Max)	0.1-4.9	0.5-3.4

* CTM: clinical test material.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

Postmarketing safety data is discussed in Section 7.1.17 of this review. Safety data gathered from the literature is discussed in Section 8.6 of this review.

7.2.3 Adequacy of Overall Clinical Experience

Minoxidil is not a new molecular entity. It has been marketed OTC as a topical hair regrowth drug product for over 10 years. Its safety profile has been well characterized. The new foam formulation does not appear to be more irritating or toxic.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The majority of preclinical data in support of minoxidil as safe and effective active ingredient was submitted and reviewed during approval of the two topical solutions, 2% and 5%, under NDA 20-501 and 20-834. Two animal studies were conducted to support the minoxidil foam formulation as part of this NDA and are being reviewed by pharmtox reviewers.

7.2.5 Adequacy of Routine Clinical Testing

Not applicable for this application.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

The sponsor fulfilled the Agency's request for pharmacokinetic studies.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Minoxidil is not a new molecular entity. Safety profile of minoxidil is well characterized based on clinical studies with 2% and 5% MTS, postmarketing AE reporting for these products, and new clinical data with the foam formulation.

7.2.8 Assessment of Quality and Completeness of Data

No additional studies are needed for the 5% MTF from the safety point of view.

7.2.9 Additional Submissions, Including Safety Update

On October 13, 2005, the sponsor submitted the safety update which included information in accordance with 21 CFR 314.50 (d) (5) (vi) (b). This submission included results of the extension part of the Study 006 and a Post-Marketing Safety Update Report covering the time period from August 1, 2004 through May 31, 2005. These additional data are discussed in this section of the review.

<u>Review of the MINOB-9140-006 Open-Label Safety Phase</u>

Study 006 was a randomized, double-blind, placebo-controlled, multicenter efficacy and safety trial, which enrolled a total of 352 male subjects with androgenetic alopecia. Following a sixteen week efficacy and safety phase, subjects were recruited to continue into in the open-label phase of the study to collect longer term use safety data. Subjects were allowed a two-week window after completion of double-blind phase before starting on the open-label phase. Subjects from both treatment arms (5% MTF and vehicle) were allowed to enroll. Subjects who were randomized to 5% MTF during the double-blind phase used the active product for an additional eight months (up to Week 52); subjects who were randomized to vehicle during the double-blind phase were given the active 5% MTF for 12 months (up to Week 68). According to the ICH-E1A guidance, at least 100 subjects are required for long term safety evaluation. Actual enrollment into the extension phase of the study was 143 subjects, 53.1% of the 352 subjects.

A total of 68 subjects who were on the vehicle foam treatment group and 75 subjects who were on the 5% MTF group in the double-blind study continued into the open-label phase of twice-daily use of 5% MTF. The completion rate was 86.7% in the 5% MTF group and 72.1% in the

vehicle foam treatment group. Table 20 below summarizes the continuation and disposition of subjects enrolled in the open-label phase from the double-blind phase of the study.

Table 20. Disposition of Subjects Enrolled in the Open-Label Safety Phase

	Treatment Group (Double-blind phase)	
Disposition	**Vehicle**	**5% MTF**
Continues into the open-label phase	68	75
Completed the open-label phase, N (%)	49 (72.1)	65 (86.7)
Subjects withdrawn, N (%)	19 (27.9)	10 (13.3)
Reasons for withdrawal:		
Adverse event	3 (4.4)	1 (1.3)
Protocol violation	2 (2.9)	1 (1.3)
Consent withdrawal	8 (11.8)	3 (4.0)
Lost to follow-up	6 (8.8)	5 (6.7)

Four subjects (2.8%) discontinued study because of adverse events. Two of the four subjects discontinued due to non-study related AEs (Subject 108: Bone necrosis and Subject 442: Addiction). The other two subjects discontinued because of AEs that the investigator considered possibly related to study drug. Subject 149 experienced a rash and Subject 575 experienced hypertension and weight gain. These AEs were of moderate intensity. The rash and hypertension resolved. The event of weight gain remained unresolved.

The overall incidence of AEs was similar in the safety extension phase as compared to the double-blind phase. There were 186 reported AEs. Seventy six subjects (53.1%) experienced at least one AE. Among the most frequently reported AEs were infection (14.7%), accidental injury (11.2%), pharyngitis (6.3%), sinusitis (6.3%), and headache (4.9%). Table 21 summarizes AEs that occurred in more than 2% of subjects.

Table 21. Adverse Events Occurring in ≥ 2% of Subjects

Body System	Adverse event	Total (N=143), N (%)
Number of subjects who experienced at least one AE		76 (53.1)
Body as whole	Accidental injury	16 (11.2)
	Allergic reaction	3 (2.1)
	Flu syndrome	3 (2.1)
	Headache	7 (4.9)
	Infection	21 (14.7)
	Pain	4 (2.8)
Cardiovascular system	Hypertension	4 (2.8)
Musculoskeletal system	Arthritis	3 (2.1)
Nervous system	Depression	3 (2.1)
	Insomnia	3 (2.1)
Respiratory system	Pharyngitis	9 (6.3)
	Rhinitis	3 (2.1)
	Sinusitis	9 (6.3)
Skin	Acne	3 (2.1)
	Rash	3 (2.1)

The overall incidence of drug-related adverse events was 7.0%. The only drug-related adverse events to occur in more than one subject were headache (3 subjects) and hypertension (2 subjects).

No deaths occurred during this open-label extension study.

Three subjects had serious adverse events (bone necrosis, joint disorder, and abdominal pain with fever). All of the serious AEs were considered unlikely to be related to study drug.

Blood was drawn for serum minoxidil laboratory testing on three subjects due to elevated blood pressure and/or weight gain. Serum minoxidil tests results on two subjects showed serum levels of 1.12 ng/ml and 1.02 ng/ml, which were considered by the sponsor non-clinically significant. Based on the historical data, minoxidil level of 21 ng/dl or above is associated with cardiac effects. Serum minoxidil level for the third subject was not available at the time of this submission.

Two subjects had elevated LFTs during the study, neither of them were considered by the investigator to be related to 5% minoxidil topical foam.

There were no significant changes in the mean values of vital signs (pulse rate, systolic and diastolic blood pressure) and body weight over the course of the study.

Overall, the incidence of contact dermatitis (scalp irritation) was 11.9% (17 of 143 subjects). Signs of contact dermatitis (dryness/scaling, erythema and folliculitis) were observed in 10.5% of the overall population. All of these observations were mild in nature, except for moderate folliculitis. Five subjects (3.4%) reported symptoms of contact dermatitis (burning, stinging and or itching). One of five subjects reported moderate symptoms; another reported moderate and severe symptoms; the remaining three subject's symptoms were mild in nature.

Comments:
The sponsor fulfilled FDA's request for long term safety data. The extension phase of the study did not reveal any new or unknown adverse events associated with the long-term use of the 5% minoxidil foam formulation.

Post-Marketing Safety Update Report

Pfizer's safety database (ARISg) was searched for cases of 5% MTS and 2% MTS that were received and entered into the database between August 1, 2004 through May 31, 2005. A total of 1,897 cases involving 5% MTS and 3,376 cases involving 2% MTS were received by Pfizer during this period, which comprised a total of 3,903 and 5,572 AE terms for 5% and 2% MTS respectively.

The vast majority of all cases were nonserious:

- For 5% MTS:
    - 1,866 (98.37%) nonserious

  - 29 (1.53%) serious
  - 2 (0.11%) deaths
- For 2% MTS:
  - 3,320 (98.34%) nonserious
  - 56 (1.66%) serious
  - 0 deaths

Two death cases associated with the use of 5% MTS are described below.

No. 2004074406, a consumer reported that her 43-year-old son, with a history of a "bad" automobile accident approximately 10 years prior, used Rogaine 5% (details of product use was not provided). He had a "bad cold" with complications and trouble breathing. Approximately one month later he died, no other information was provided.

No. 2004084341, a consumer report of a 73-year-old female with a history of diabetes and arthritis, who used Rogaine 5% (duration of product use was not specified). She complained of a headache, dizziness, scalp soreness and blurred vision. She consulted a physician for the blurred vision who changed her medication (consumer was concomitantly taking unspecified medications including rofecoxib). The consumer took an unspecified over the counter "pain killer" to treat her headache. At an unspecified time she had an aneurysm and subsequently died. No further information was provided.

All adverse event terms for 5% MTS and 2% MTS that were reported at a rate of at least 2% are presented by MedDRA SOC and preferred term in Table 22.

Table 22. AE Terms Associated with All Cases Reported at a Rate of at Least 2% for 5% MTS and 2% MTS

MedDRA SOC	Preferred term	MTS 2%	MTS 5%
Skin and subcutaneous tissue disorders	Pruritus	600 (10.77)	348 (8.91)
	Alopecia	733 (13.16)	295 (7.55)
	Skin exfoliation	199 (3.57)	157 (4.02)
	Dry skin	200 (3.59)	126 (3.23)
	Hair texture abnormal	260 (4.67)	116 (2.97)
	Hypertrichosis	238 (4.27)	107 (2.74)
	Dandruff	85 (1.57)	87 (2.23)
	Hair color changes	142 (2.55)	53 (1.36)
General Disorders and administration site conditions	No adverse effect	48 (0.54)	264 (6.76)
	Drug ineffective	515 (9.24)	192 (4.92)
	Application site irritation	181 (3.25)	128 (3.28)
Injury, poisoning, and procedural complications	Medication error	142 (2.55)	776 (19.87)
Nervous system disorders	Headache	116 (2.08)	51 (1.31)

Comments:
This safety update report did not reveal any new unexpected safety information for topical minoxidil. The most common AE associated with the use of minoxidil topical solutions, again,

were restricted to local irritation effects. Most of the AEs were non-serious in nature. Relationship between topical minoxidil and the two death cases reported during the safety update reporting time period could not be determined due to limited information and confounding factors.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.4 General Methodology

To analyze adverse events by organ system or syndrome in the total study population, all adverse events reported in Study 001,004, 005 and 006 were converted to a common adverse event coding dictionary (MedDRA 7.0). The results of this analysis are as follows: Adverse events that occurred in 1% or more of the subjects, drug-related treatment-emergent AEs that were reported in 2 or more subjects, all SAEs, and all AEs that led to discontinuation.

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

In all, approximately 28% (194/694) of the subjects experienced at least one treatment-emergent AE. Infection NOS was the most commonly reported treatment-emergent AE, affecting 5.0% of the subjects (35/694). Headache (3.5%, 24/694 subjects) and injury NOS (2.3%, 16/694 subjects) were the only other treatment-emergent AEs reported in more than 2% of the subjects. All drug-related treatment-emergent AEs occurred in less than 1% of the subjects, with the most common being headache (5/694 subjects). All SAEs and AEs causing subjects to discontinue were reported as single events.

7.4.1.1 Pooled data vs. individual study data

The studies under safety review were of different design and methodology. As discussed in Section 7.1.5, there were no signals of particular adverse event in individual studies. The incidence of individual adverse events did not differ across the studies (Table 23).

Table 23. Adverse Events in Total Subject Population

Preferred Terms	Number (%) of Subjects			
	TEAE	Drug-Related TEAE	SAE	AE Leading to Discontinuation
Total number of subjects	694	694	694	694
Subjects with TEAE, drug-related TEAE, SAE, and AE leading to discontinuation	194 (28.0)	29 (4.2)	5 (<1.0)	9 (1.3)
Infection NOS	35 (5.0)	0	0	0
Headache	24 (3.5)	5 (<1.0)	0	1 (<1.0)
Injury NOS	16 (2.3)	0	1 (<1.0)	1 (<1.0)
Acne NOS	8 (1.2)	2 (<1.0)	0	0
Bronchitis NOS	8 (1.2)	0	0	0
Rash NOS	8 (1.2)	2 (<1.0)	0	1 (<1.0)
Upper respiratory tract infection	8 (1.2)	0	0	0
Influenza	7 (1.0)	0	0	0
Nasopharyngitis	7 (1.0)	0	0	0
Pruritus	7 (1.0)	3 (<1.0)	0	1 (<1.0)
Pain NOS		3 (<1.0)	0	0
Hirsutism		2 (<1.0)	0	0
Cholelithiasis			1 (<1.0)	0
Grand mal convulsion			1 (<1.0)	0
Pneumonia NOS			1 (<1.0)	0
Renal failure acute			1 (<1.0)	0
Alopecia				1 (<1.0)
Excoriation				1 (<1.0)
Hyperventilation				1 (<1.0)
Nausea				1 (<1.0)
Skin ulcer				1 (<1.0)
Tachycardia NOS				1 (<1.0)
Toothache				1 (<1.0)

AE: adverse event; NOS: not otherwise specified; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

7.4.1.2 Combining data

Because of different designs and methodologies of the studies, no pooling of data was done. There were no additional analyses performed by the sponsor.

7.4.2 Explorations for Predictive Factors

There were no extrapolations for predictive factors performed by the sponsor. Data from the extension part of the Study 006 is discussed in Section 7.2.9 of the review.

7.4.3 Causality Determination

In Studies 001, 004, and 005, five subjects experienced mild, non-serious AEs that were considered related to test material, for which no action was taken with respect to study drug and all of which resolved without residual effects. In Study 001, one male subject experienced rash at the application site; in Study 004, one subject had pruritus; and in Study 005, one subject each had tingling scalp, itching on the test site, and heat rash on the head.

In Study 006, 12 vehicle subjects (7.0%) and 12 subjects (6.7%) in the 5% minoxidil foam group experienced drug-related AEs. Of these, the only events that occurred in more than 1% of subjects in either treatment group were headache (2 vehicle subjects [1.2%], 3 minoxidil subjects [1.7%]); Pruritus (no vehicle subjects [0%], 2 minoxidil subjects [1.1%]); rash (no vehicle subjects [0%], 2 minoxidil subjects [1.1%]); and pain (2 vehicle subjects [1.2%], 1 minoxidil subject [<1%]). The drug-related AEs occurring in more than 1% of subjects in either treatment group were primarily minor conditions related to pain or to application of study drug to the skin.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

One of the concerns raised by FDA during the drug development phase was the ability of consumers to accurately dispense 1 gram of 5% MTF without a metered device. FDA encouraged the sponsor on several occasions to develop a quantitative measurement device. Instead, the sponsor chose to provide data that consumers will dispense acceptable amount of the product after reading directions on the container.

To evaluate this, the sponsor conducted three studies with 25, 25, and 61 subjects. The primary variable was the quantity of clinical test material dispensed by subjects after reading usage instructions. Quantities were determined by weight of the container prior to use and post-use. With minor variations, all studies were of similar design: open, label, single center, one-day test involving one product application (only dispensed, not applied). Summary of the results for each study are presented below. Table 24 summarizes the results for all three studies.

1. First study enrolled 25 healthy males 18 years and older. The subjects were given verbal and written usage directions for the product and were asked to dispense 1 dose. Each subject dispensed the product twice, in random order to the palm of his hand and across the fingers, with the cap as a guide.

   The average quantity of the product dispensed in this study was 0.98 gm with a standard deviation of 0.36 on the palm and 0.96 gm with a standard deviation of 0.47 when dispensed across the fingers.

2. Second study enrolled 25 healthy females ages 18 and older. Each subject was given usage directions (similar to minoxidil labeling) and was asked to dispense one dose.

Over one week period, each subject dispensed the test product twice. The visits were scheduled at least 24 hours apart.

The average quantity of the test product dispensed was 0.75 gm with a standard deviation of 0.41 gm on Day 1 and 1.14 gm with a standard deviation of 0.58 gm on Day 2.

3. Third study enrolled 31 healthy males (24-57 years of age) and 30 healthy females (23 to 70 years of age). Subjects enrolled had to be either existing users or had a desire to use a topical hair re-growth product for hair loss. Following provided written instructions (similar to minoxidil labeling). Each subject dispensed the product onto their fingertips. Each subject was given an opportunity to perform practice "pumps" before dispensing a measured amount. When the subject felt that they are able to dispense an appropriate amount, they dispensed one dose, which was assessed by weighing the container prior to and after the dispensing. Subjects returned again following day (+2 days), read the instructions and dispensed the product one time.

   For the test product dispensed on Visit 1, the average quantity was 1.2 gm with a standard deviation of 0.62, and on Visit 2, the average quantity dispensed was 1.16 gm with a standard deviation of 1.34.

Table 24. Summary of Data from Three Dispensation Studies

		Range of the Amount Dispensed					CI
		< 0.5 gm	0.51-1.0 gm	1.01-1.50 gm	1.51-2.00 gm	> 2 gm	
Study 1 (N=25)	Dispensed on the palm	1 (4%)	15 (60%)	8 (32%)	0	1 (4%)	0.83, 1.13
	Dispensed across the fingers	3 (12%)	11 (44%)	8 (32%)	2 (8%)	1 (4%)	0.77, 1.16
Study 2 (N=25)	Day 1	8 (32%)	11 (44%)	4 (16%)	2 (8%)	0	0.59, 0.92
	Day 2	2 (8%)	10 (40%)	9 (36%)	3 (12%)	1 (4%)	0.91, 1.37
Study 3 Females	Visit 1	2 (7%)	15 (50%)	6 (20%)	3 (10%)	4 (13%)	0.97, 1.43
	Visit 2	8 (27%)	10 (33%)	8 (27%)	1 (3%)	3 (10%)	0.67, 1.65
Study 3 Males (N=31)	Visit 1	8 (26%)	14 (45%)	4 (13%)	4 (13%)	1 (3%)	0.69, 1.16
	Visit 2	6 (19%)	17 (55%)	6 (19%)	2 (6%)	0	0.67, 0.96

Comments:
Data from the three dispensation studies show that there is a wide variation in the amounts of the product dispensed. Up to a third of the subjects participating in the studies dispensed less than a half of the specified dose. Fewer subjects (up to 23%) dispensed more than 1.5 of the specified dose. The majority of subjects (58% to 82%) dispensed amounts within the 0.5 to 1.5 gm range. It is interesting that women were enrolled in 2 of the 3 studies even though the product is for men. Women were more inclined to overdose; a higher percentage of women compared to men dispensed amounts above 1 gm. Perhaps it is related to the fact that women are used to applying cosmetic hair mousses that do not have a metered dosing device. There were two women in study #3 that dispensed more than 3 gm of the test product. One woman

dispensed 1.1 gm on Visit 1 and 3.1 gm on Visit 2. The second woman dispensed 2.5 gm on Visit 1 and 7.5 gm on Visit 2. The sponsor states that an excessive amount was dispensed due to rapid melting in the subject's hand.

It appears that men don't have a worrisome inclination to overdose. Only one man dispensed the amount over 3 gm (3.1 gm) during one of the two visits in study #3; on Visit 2 the same subject dispensed 1.7 gm. Reported results do not suggest a potential for significant overdosing in the targeted population.

In addition to these actual use/dispensation studies, the sponsor conducted an exaggerated use pharmacokinetic study. The study results showed that there was no clinically important absorption of minoxidil from the foam when applied 2 or 3 times higher than the recommended amount.

Comment:
Based on the overall data, the sponsor provided sufficient data to assure safety of the dosing method. In the opinion of this reviewer, marketing of the 5% topical minoxidil foam without a quantitative measurement device is acceptable.

8.2 Drug-Drug Interactions

No special drug-drug interaction studies were requested by FDA or performed by the sponsor. Adverse event data on possible drug-drug interactions come only from the sponsor's postmarketing surveillance ARGUS/ARISg database.

Among the 15,299 cases for 5% MTS, 9 cases involved a possible drug interaction, representing 0.06% of all cases (all non serious):

- Two reports involved a potential interaction of 5% MTS with other topical products: Retrieve Cream (tretinoin 0.05%) with an adverse event of dermatitis (Case no. 2001074212AU) and retinoic acid 0.025% with adverse events of fluid retention and headache (Case no. 2000011301AU).
- Two reports involved a potential interaction of 5% MTS with finasteride: Propecia with adverse events of burning sensation (Case no. 2001060760US) and Proscar with adverse events of dry skin and hypertrichosis (Case no. 1999003961US).
- Two reports involved a potential interaction of 5% MTS with shampoos: Progaine Shampoo with adverse events of hair color changes and hypertrichosis (Case no. 2000027125US) and a dandruff (pyrithione) shampoo with adverse events of dandruff, skin desquamation, and Pruritus (Case no. 2002114072US).
- One report of potential drug interaction with 5% MTS and Zantac (ranitidine) with adverse events of dizziness and malaise (Case no. 2000032654AU);
- Lipitor (atorvastatin) with adverse events of hair color changes (Case no. 2001059772US); and
- Provera (medroxyprogesterone acetate tablets, 50 mg) with an adverse event of polymenorrhea (Case no. 2003175845US).

Among the 17,514 cases for 2% MTS, 6 cases involved a possible drug interaction, representing 0.03% of all cases (all non serious):

- Three reports involved a potential interaction of 2% MTS with other topical products: Kevis Hair and Scalp Solution with adverse events of burning sensation, alopecia, chest pain, and swollen tongue (Case no. 2000011854US); Progaine Shampoo with an adverse events of alopecia (Case no. 2000022863US); and an unspecified hair coloring product with an adverse event of pruritus (Case no. 2001083663US).
- One report of potential interaction with 2% MTS and Nardil (phenelzine) with an adverse event of palpitations (Case no. 2001040894US);
- an unspecified antihypertensive agent with an adverse event of hypertension (Case no. 200002531-5US); and
- Provera (medroxyprogesterone acetate tablets, 50 mg) with an adverse event of polymenorrhea (this is the same report described above for Case no. 2003175845US, i.e., the event occurred with both 2% MTS and 5% MTS).

The sponsor states that, these reported cases of drug interaction are isolated incidences with no new signals or trends identified.

Comment:
Most of the reported adverse events were related to reactions with other topical drug or cosmetic products. Current package information included with marketed 5% MTS lists a warning that the product should not be used by persons using other medications on the scalp. The proposed labeling for 5% minoxidil foam is consistent with this current warning.

8.3 Special Populations

No analyses by ethnic group were performed; most of the subjects in the four clinical studies were Caucasian, so the numbers of subjects in other ethnic or racial groups were insufficient to detect meaningful differences between groups. No other intrinsic factors were analyzed.

Current 5% MTS labeling states that the product should not be used by any person whose scalp is red, inflamed, infected, irritated, or painful. Labeling for 5% minoxidil foam is consistent with this caution.

8.4 Pediatrics

None of the studies in the clinical development program for 5% minoxidil foam enrolled pediatric patients. Although the protocol for Study 006 allowed the recruitment of subjects as young as 15 years, the youngest subject actually enrolled was 20 years old. Furthermore, this NDA includes a request for a full waiver from the requirement to conduct clinical studies in the pediatric population for the androgenetic alopecia indication.

The Pediatric Research Equity Act (PREA) requires that applications submitted under section 505 of the Federal Food, Drug, and Cosmetic Act for a new active ingredient, a new indication, a new dosage form, a new dosing regimen, or a new route of administration must contain a pediatric assessment unless the assessment is waived or deferred. PREA is indication specific, and therefore, the required pediatric assessment must be for the indication for which the application is submitted. The Office of Counter-Terrorism and Pediatric Drug Development was consulted on this MTF NDA, and recommended that a full waiver be granted to Pfizer for the indication of hair regrowth treatment.

The proposed package label directs consumers to consult a physician if the patient is under 18 years of age.

8.5 Advisory Committee Meeting

No advisory committee meetings were held for this NDA.

8.6 Literature Review

In support of this application, the sponsor conducted a comprehensive search of published literature (MEDLINE and EMBASE databases) for minoxidil from January 1, 1999 through January 31, 2005. The search retrieved 166 relevant abstracts and articles. The main focus of the literature review was to identify any possible safety concerns or trends. Adverse events for topical minoxidil noted in the literature were mostly mild, self-limiting, non-serious and/or expected. Four serious adverse events were identified (1 labeled event and 3 unlabeled events). All of these events were incorporated within the post-marketing safety data (Section 7.1.17).

8.7 Postmarketing Risk Management Plan

There is no postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials submitted for the review.

9 OVERALL ASSESSMENT

9.1 Conclusions

Experience with already approved minoxidil topical drug products do not suggest an unusual pattern of toxicity, either in terms of frequency or severity of adverse reactions reported. The safety profile of 5% minoxidil topical foam is acceptable for OTC use. Therefore, this application should be approved from a clinical safety standpoint.

9.2 Recommendation on Regulatory Action

The proposed 5% minoxidil topical foam has an acceptable safety profile for the OTC marketing. This NDA should be approved from the safety standpoint. Final approvability depends on the outcome of the clinical efficacy study MINOB-9140-006, and the adequacy of chemistry, pharmacotoxicology, and biopharm data.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

No special postmarketing risk management activities are recommended.

9.3.2 Required Phase 4 Commitments

No special Phase 4 commitments are recommended.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

The proposed name for the product is Men's Rogaine® Extra Strength Topical Foam. In the opinion of this reviewer, this name is not acceptable. The qualifying part of the name "extra strength" is not based on clinical data and should be removed. There are two other minoxidil formulations already on the market, 2% regular strength and 5% extra strength topical solutions. Clinical trials for the treatment of androgenic alopecia in men have demonstrated that the twice daily use of the minoxidil topical solution, 5% offers more benefit than minoxidil topical solution, 2%. Therefore, the qualifying statements "extra strength" and "regular strength" are acceptable for the two already marketed topical solution formulations. In case of minoxidil topical foam, 5% we do not have any data that the efficacy of this formulation is superior to minoxidil topical solution, 2% or equal in efficacy to the minoxidil topical solution, 5%. In fact, based on the pharmacokinetic data, the bioavailability of 5% topical foam is about 50% of the 5% topical solution, which may or may not translate into lower efficacy.

The proposed Drug Facts labeling is presented below. Detailed labeling review is being done by the interdisciplinary scientist in the Office of Nonprescription Products. The sponsor incorporated all the important warnings for minoxidil. The proposed label is acceptable from the clinical safety point of view.

Drug Facts

Active Ingredient: Minoxidil 5% w/w (without propellant)

Purpose: Hair regrowth treatment for men

Use: to regrow hair on the top of the scalp (vertex only, see pictures inside label)

Warnings
For external use only. For use by men only.
Extremely Flammable: Avoid fire, flame, or smoking during and immediately following application.

Do not use if
- you are a woman
- your amount of hair loss is different than that shown on the inside of this label or your hair loss is on the front of the scalp. 5% minoxidil topical foam is not intended for frontal baldness or receding hairline.
- you have no family history of hair loss
- your hair loss is sudden and/or patchy
- you do not know the reason for your hair loss
- you are under 18 years of age. Do not use on babies and children.
- your scalp is red, inflamed, infected, irritated, or painful
- you use other medicines on the scalp

Ask a doctor before use if you have heart disease

When using this product
- do not apply on other parts of the body
- avoid contact with the eyes. In case of accidental contact, rinse eyes with large amounts of cool tap water
- some people have experienced changes in hair color and/or texture
- it takes time to regrow hair. Results may occur at 2 months with twice a day usage. For some men, you may have to use this product for at least 4 months before you see results.
- the amount of hair regrowth is different for each person . This product will not work for all men.

Stop use and ask a doctor if
- chest pain, rapid heartbeat, faintness, or dizziness occurs
- sudden, unexplained weight gain occurs
- your hands or feet swell
- scalp irritation or redness occurs
- unwanted facial hair growth occurs
- you do not see hair regrowth in 4 months

May be harmful if used when pregnant or breast-feeding. Keep out of reach of children. If swallowed get medical help or contact a Poison Control Center right away.

Directions

- apply half a capful 2 times a day to the scalp in the hair loss area
- see enclosed booklet for complete directions on how to use
- using more or more often will not improve results
- continued use is necessary to increase and keep your hair regrowth or hair loss will begin again

Other Information
- see hair loss pictures on right
- before use, read all information on package and enclosed booklet
- keep the package. It contains important information.
- store at controlled room temperature 20° to 25°C (68° to 77°F)
- contents under pressure. Do not puncture or incinerate container. Do not expose to heat or store at temperatures above 120° F (49°C)

Inactive ingredients: butane, butylated hydroxytoluene, cetyl alcohol, citric acid, glycerin, isobutane, lactic acid, polysorbate 60, propane, purified water, SD alcohol 40-B, stearyl alcohol

Questions?
- call us at 1-800-ROGAINE (1-800-764-2463)
- visit rogaine.com

9.5 Comments to Applicant

The trade name of the product should be revised to Men's Rogaine® Topical Foam, unless data are provided to support the superior efficacy of this formulation over the 2% minoxidil topical solution.

10 APPENDICES

10.1 Review of Individual Study Reports

Not applicable.

10.2 Line-by-Line Labeling Review

See labeling review by the interdisciplinary scientist in the Office of Nonprescription Products.

10.3 Appendix I.

Table 8. AAPCC Data: Clinical Effect Terms for Topical Minoxidil by Route of Exposure in Descending Order by Total Frequency N (%)

Clinical effect term	Ingestion	Dermal	Ocular	Other	Total
Ocular Irritation/Pain	11 (3.7)	11 (4.6)	91 (77.1)	1 (3.2)	114 (16.6)
Other	25 (8.4)	26 (10.8)	1 (0.8)	7 (22.6)	59 (8.6)
Dizziness/Vertigo	14 (4.7)	35 (14.6)	1 (0.8)	2 (6.5)	52 (7.6)
Vomiting	37 (12.4)	5 (2.1)	1 (0.8)	0	43 (6.3)
Tachycardia	29 (9.7)	11 (4.6)	0	0	40 (5.8)
Nausea	21 (7.0)	14 (5.8)	0	1 (3.2)	36 (5.2)
Hypotension	29 (9.7)	2 (0.8)	0	0	31 (4.5)
Headache	12 (4.0)	14 (5.8)	0	0	26 (3.8)
Dermal Irritation/Pain	5 (1.7)	15 (6.3)	1 (0.8)	5 (16.1)	26 (3.8)
Chest Pain	7 (2.3)	12 (5.0)	0	2 (6.5)	21 (3.1)
Dermal Erythema/Flushed	7 (2.3)	13 (5.4)	1 (0.8)	0	21 (3.1)
Edema	6 (2.0)	12 (5.0)	1 (0.8)	0	19 (2.8)
Fever/Hyperthermia	17 (5.7)	2 (0.8)	0	0	19 (2.8)
Drowsiness/Lethargy	12 (4.0)	0	1 (0.8)	0	13 (1.9)
Oral Irritation	11 (3.7)	1 (0.4)	0	1 (3.2)	13 (1.9)
Rash	1 (0.3)	12 (5.0)	0	0	13 (1.9)
Throat Irritation	10 (3.3)	1 (0.4)	0	2 (6.5)	13 (1.9)
Pruritus	1 (0.3)	10 (4.2)	0	0	11 (1.6)
Dyspnea	1 (0.3)	6 (2.5)	0	2 (6.5)	9 (1.3)
Hives/Welts	2 (0.7)	5 (2.1)	0	0	7 (1.0)
Lacrimation	0	0	7 (5.9)	0	7 (1.0)
Abdominal Pain	5 (1.7)	1 (0.4)	0	0	6 (0.9)
Agitated/Irritable	2 (0.7)	3 (1.3)	0	1 (3.2)	6 (0.9)
Blurred Vision	1 (0.3)	1 (0.4)	4 (3.4)	0	6 (0.9)
Cough/Choke	2 (0.7)	0	0	4 (12.9)	6 (0.9)
Diaphoresis	2 (0.7)	3 (1.3)	0	0	5 (0.7)
Red Eye	0	0	5 (4.2)	0	5 (0.7)
Ataxia	3 (1.0)	0	1 (0.8)	0	4 (0.6)
Diarrhea	4 (1.3)	0	0	0	4 (0.6)
Dysrhythmia	3 (1.0)	1 (0.4)	0	0	4 (0.6)
Hypertension	2 (0.7)	1 (0.4)	0	1 (3.2)	4 (0.6)
Numbness	2 (0.7)	2 (0.8)	0	0	4 (0.6)
Peripheral Neuropathy	1 (0.3)	3 (1.3)	0	0	4 (0.6)
Muscle Weakness	0	3 (1.3)	0	0	3 (0.4)
Burns,2-3 degree	0	1 (0.4)	1 (0.8)	0	2 (0.3)
Conduction Disturbance	2 (0.7)	0	0	0	2 (0.3)
Corneal Abrasion	0	0	2 (1.7)	0	2 (0.3)
Pain	0	1 (0.4)	0	1 (3.2)	2 (0.3)
Papilledima	0	2 (0.8)	0	0	2 (0.3)
Seizure	0	2 (0.8)	0	0	2 (0.3)
Visual Defect	0	2 (0.8)	0	0	2 (0.3)

10.4 Appendix II.

Table 10. Adverse Events (Nonserious, Serious, Death, and Overall) for Minoxidil 2% Topical Solution, by MedDRA SOC (Pfizer's Database)

MedDRA SOC	Minoxidil 2% Topical Solution			
	Nonserious	Serious	Death	Overall
Skin and subcutaneous tissue disorders	17,084 (67.00)	41 (11.85)	0	17,125 (66.26)
General Disorders and Administration Site Conditions	3,161 (12.40)	29 (8.38)	0	3,190 (12.34)
Nervous System Disorders	1,839 (7.21)	48 (13.87)	0	1,887 (7.30)
Investigations	969 (3.80)	21 (6.07)	0	990 (3.83)
Injury, Poisoning and Procedural Complications	588 (2.31)	20 (5.78)	0	608 (2.35)
Eye Disorders	417 (1.64)	26 (7.51)	0	443 (1.71)
Gastrointestinal Disorders	309 (1.21)	14 (4.05)	0	323 (1.25)
Cardiac Disorders	175 (0.69)	40 (11.56)	0	215 (0.83)
Psychiatric Disorders	163 (0.64)	4 (1.6)	0	167 (0.65)
Respiratory, Thoracic and Mediastinal Disorders	147 (0.58)	12 (3.47)	0	159 (0.62)
Musculoskeletal and Connective Tissue Disorders	148 (0.58)	3 (0.87)	0	151 (0.58)
Vascular Disorders	98 (0.38)	15 (4.34)	0	113 (0.44)
Reproductive System and Breast Disorders	91 (0.36)	2 (0.58)	0	93 (0.36)
Infections and Infestations	72 (0.28)	7 (2.02)	1 (33.33)	80 (0.31)
Immune System Disorders	66 (0.26)	4 (1.16)	0	70 (0.27)
Ear and Labyrinth Disorders	49 (0.19)	3 (0.87)	0	52 (0.20)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	14 (0.05)	26 (7.51)	0	40 (0.15)
Metabolism and Nutrition Disorders	35 (0.14)	2 (0.58)	0	37 (0.14)
Pregnancy, Puerperium and Perinatal Conditions	19 (0.07)	7 (2.02)	1 (33.33)	27 (0.10)
Blood and Lymphatic System Disorders	22 (0.09)	4 (1.16)	0	26 (0.10)
Renal and Urinary Disorders	15 (0.06)	3 (0.87)	0	18 (0.07)
Hepatobiliary Disorders	4 (0.02)	7 (2.02)	0	11 (0.04)
Surgical and Medical Procedures	1 (0.00)	7 (2.02)	1 (33.33)	9 (0.03)
Endocrine Disorders	5 (0.02)	0	0	5 (0.02)
Congenital, Familial and Genetic Disorders	3 (0.01)	1 (0.29)	0	4 (0.02)
Social Circumstances	3 (0.01)	0	0	3 (0.01)
Total No. of AE Terms	25,497	346	3	25,846
Total No. of Cases	17,340	173	1	17,514
Total No. of AE Terms / Total No. of Cases	1.47	2	3	1.48

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Table 11. Adverse Events (Nonserious, Serious, Death, and Overall) for Minoxidil 5% Topical Solution, by MedDRA SOC (Pfizer's Database)

MedDRA SOC	Minoxidil 5% Topical Solution			
	Nonserious	Serious	Death	Overall
Skin and subcutaneous tissue disorders	17,321 (71.96)	24 (8.96)	0	17,345 (71.26)
General Disorders and Administration Site Conditions	2,365 (9.83)	26 (9.70)	0	2,391 (9.82)
Nervous System Disorders	1,431 (5.95)	40 (14.93)	0	1,471 (6.04)
Injury, Poisoning and Procedural Complications	979 (4.07)	24 (8.96)	0	1,003 (4.12)
Investigations	591 (2.46)	24 (8.96)	0	615 (2.53)
Eye Disorders	284 (1.18)	8 (2.99)	0	292 (1.20)
Gastrointestinal Disorders	202 (0.84)	8 (2.99)	0	210 (0.86)
Psychiatric Disorders	141 (0.59)	9 (3.36)	0	150 (0.62)
Cardiac Disorders	114 (0.47)	31 (11.57)	1 (100)	146 (0.60)
Reproductive System and Breast Disorders	125 (0.52)	9 (3.36)	0	134 (0.55)
Respiratory, Thoracic and Mediastinal Disorders	113 (0.47)	20 (7.46)	0	133 (0.55)
Musculoskeletal and Connective Tissue Disorders	114 (0.47)	6 (2.24)	0	120 (0.49)
Vascular Disorders	62 (0.26)	11 (4.10)	0	73 (0.30)
Immune System Disorders	55 (0.23)	4 (1.49)	0	59 (0.24)
Infections and Infestations	57 (0.24)	2 (0.75)	0	59 (0.24)
Ear and Labyrinth Disorders	40 (0.17)	0	0	40 (0.16)
Metabolism and Nutrition Disorders	22 (0.09)	5 (1.87)	0	27 (0.11)
Renal and Urinary Disorders	16 (0.07)	3 (1.12)	0	19 (0.08)
Blood and Lymphatic System Disorders	16 (0.07)	1 (0.37)	0	17 (0.07)
Pregnancy, Puerperium and Perinatal Conditions	6 (0.02)	6 (2.24)	0	12 (0.05)
Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)	6 (0.02)	5 (1.87)	0	11 (0.05)
Hepatobiliary Disorders	2 (0.01)	1 (0.37)	0	3 (0.01)
Social Circumstances	2 (0.01)	0	0	2 (0.01)
Surgical and Medical Procedures	1 (0.00)	1 (0.37)	0	2 (0.01)
Endocrine Disorders	2 (0.01)	0	0	2 (0.01)
Congenital, Familial and Genetic Disorders	2 (0.01)	0	0	2 (0.01)
Total No. of AE Terms	24,070	268	1	24,339
Total No. of Cases	15,200	98	1	15,299
Total No. of AE Terms / Total No. of Cases	1.58	2.73	1	1.59

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