CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-676

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA 20-676

Jean R. Grieve, R.A.C.
Director, Regulatory Affairs
Bristol-Myers Products
1350 Liberty Avenue
Hillside, NJ 07207-6050

Dear Ms. Grieve:

We acknowledge receipt of your November 10, 1995 submission of the supplement to your new drug application (NDA), NDA 19-355 for Vagistat® 1 Vaginal Ointment (tioconazole 6.5%). This submission provides for a change in the marketing status from prescription (Rx) to over-the-counter.

For purposes of post-marketing surveillance and adverse event reporting, we are administratively converting this supplement into a new drug application, NDA 20-676, effective as of November 13, 1995.

The due date for this NDA is November 13, 1996.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Federal Food, Drug, and Cosmetic Act on January 13, 1995.

Please cite the NDA number listed above at the top of the first page of any future communications concerning this application, and addressed as follows:

Food and Drug Administration
Division of Anti-Infective Drug Products, HFD-520
Attention: Document Control Room
5600 Fishers Lane
Rockville, Maryland 20857

Should you have any questions concerning this NDA, please contact:

Christina H. Chi, Ph.D.
Project Manager
(301) 443-0257.

Sincerely yours,

Mary Fanning, M.D., Ph.D., FACP
Director
Division of Anti-Infective Drug Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

cc: Orig. NDA 20-676
NDA 19-355
HFD-5/THassal
HFD-80
HFD-520
HFD-520/SMO/RAlbrecht
HFD-520/MO/JWinfield
HFD-520/SPM/JBona
HFD-520/PM/CChi
CChi:11/16/1995

Concurrence:

HFD-520/SPM/JBona 11/17/95
MF 11/22/95

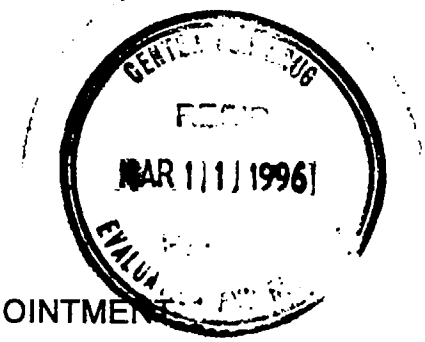
ACKNOWLEDGEMENT

BRISTOL-MYERS PRODUCTS
1350 Liberty Avenue Hillside, NJ 07207-6050 908 851-6126 Fax 908 851-6249

March 8, 1996

Jean R. Grieve, R.A.C.
Director, Regulatory Affairs

Center for Drug Evaluation and Research
Mary Fanning, M.D., Ph.D., FACP
Food and Drug Administration
Division of Anti-Infective Drug Products, HFD-520
5600 Fishers Lane
Rockville, MD 20857
Attention: Document Control Room



RE: **NDA 20-676 (cross reference NDA 19-355)**
VAGISTAT®-1 (tioconazole 6.5%) VAGINAL OINTMENT

SAFETY UPDATE REPORT

Dear Dr. Fanning:

Pursuant to 21 CFR 314.50 (d)(5)(vi)(b) and section 505(i) of the FD&C Act, enclosed please find the 120-day safety report for the above-mentioned NDA. NDA 20-676 was submitted for the over-the-counter use of VAGISTAT-1 (tioconazole 6.5%) on November 10, 1995.

There are no ongoing clinical studies or new information from the clinical studies conducted and submitted in support of this NDA. Eight non-serious reports totalling eleven adverse experiences were received through the safety surveillance and monitoring for the marketed prescription product. A full report on these adverse experiences is attached. Based upon the new data, no conclusions of product safety are changed and no labeling revisions are warranted. In accordance with 21 CFR 314.80(c)(2), reports of these spontaneous experiences were included in the annual (periodic) adverse drug experience report for this NDA (submitted on January 19, 1996).

Please do not hesitate to contact me at 908-851-6126 if you have any questions.

Thank you.

Sincerely,

Jean R. Grieve

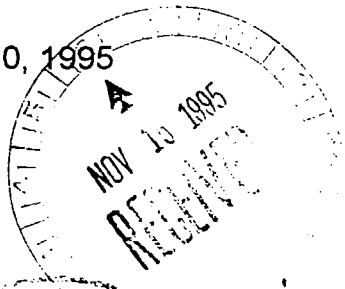
Enclosures:

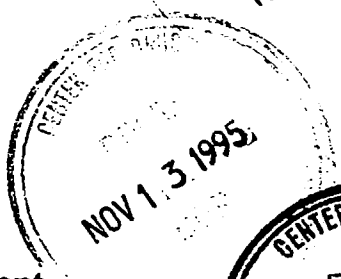
Acknowledgment copy
Form 356h
Table of contents

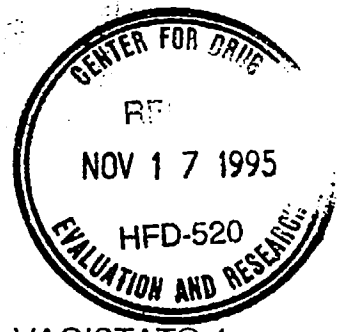
BRISTOL-MYERS PRODUCTS
1350 Liberty Avenue Hillside, NJ 07207-6050 908 851-6126 Fax: 908 851-6249

Jean R. Grieve, R.A.C.
Director, Regulatory Affairs

November 10, 1995







Ms. Mary, Fanning, M.D./Ph.D.
Director, Division of Anti-Infective Drug Products (HFD-520)
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
ATTENTION: Document Control Room 12B-30

RE: SUPPLEMENT SUBJECT TO APPROVAL
NDA 19-355
VAGISTAT®-1 (tioconazole 6.5%) Vaginal Ointment
Rx-to-OTC Switch
User Fee ID. 2889

Dear Dr. Fanning:

Reference is made to our approved New Drug Application 19-355 for VAGISTAT®-1 (tioconazole 6.5%) vaginal ointment for the treatment of vulvovaginal candidiasis. Bristol-Myers Products, a division of Bristol-Myers Squibb Company, herewith submits a supplemental application in triplicate, pursuant to the provisions of 21 CFR 314.70. This supplemental application provides for a change in the marketing status of VAGISTAT®-1 ointment from prescription (Rx) to over-the-counter (OTC), for the treatment of recurrent vulvovaginal candidiasis.

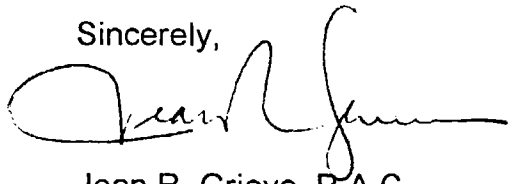
This supplemental application includes two new adequate and well-controlled clinical trials (Item 8) which are considered essential to the approval of the Rx-to-OTC switch of the product. In pre-IND conversations with the Division, including a meeting on September 14, 1993, Bristol-Myers Products was advised that the criteria for an OTC switch in the vaginal yeast infection category included the establishment of equivalent efficacy between the switch candidate and an approved 7-day OTC treatment regimen in two adequate and well-controlled clinical trials. In addition to the new clinical trial information, this application includes a review of safety and efficacy information from published and unpublished trials, domestic and international literature and marketing experience (Item 2); proposed labeling for the OTC product (Item 4); a report from a broad-based, nationally projectible market research study regarding treatment compliance among users of OTC vaginal yeast infection remedies (Item 15.1); and a report of a market research study designed to evaluate the relative communication effectiveness of "new" labeling messages

unique to a one-dose therapy product, contained in the draft labeling (Item 15.2). The required debarment statement and an appropriate statement of exclusivity regarding this supplemental application have been included in Item 1. Neither the VAGISTAT®-1 product nor tioconazole, the drug substance, is currently subject to an approved patent in the U.S.

As demonstrated in this supplemental application, VAGISTAT®-1 ointment is appropriate for conversion from prescription to over-the-counter status. It has a safety profile comparable to other OTC imidazole products. The efficacy of VAGISTAT®-1 has been shown to be overall therapeutically equivalent to an approved OTC 7-day therapy in the treatment of vulvovaginal candidiasis in all patients tested and in those patients who have experienced a vaginal yeast infection in the prior year. The virtually guaranteed compliance with this single-dose product is a major benefit. The absence of any new risks, coupled with predictable, early effectiveness and guaranteed compliance speak strongly for the approval of VAGISTAT®-1 for OTC use with the recommended labeling.

We respectfully request that this supplemental request be included in our NDA 19-355. A total of four copies of the draft labeling has been included within the three official copies of the application. Desk copies have been individually labeled and provided as listed at the conclusion of this letter. To aid in the review of this application, the statistical review desk copy includes a "Notes" section with the statistical data sets (SAS) on a computer diskette for each of the two new clinical studies reported in this application, along with a Database User's Guide. The appropriate user fee payment was forwarded on November 2, 1995, User Fee I.D. 2889. Should you have any questions on this supplement for OTC marketing status or require any additional information, please contact me directly at 908/851-6126.

Sincerely,



Jean R. Grieve, R.A.C.

DESK COPIES:
J. Winfield, M.D. (medical review, volumes 1-37)
D. Bowen, M.D. for L. Chin, M.D. (OTC Consult copy, volumes 1-37)
C. Chi (CSO, volumes 1-3)
R. Harkins, Ph.D. (statistical review, volumes 2 and 4-29)
K. Feather (labeling, DDMAC review, volumes 1 and 3)
L. Palmer, Pharm. D. (labeling, DDMAC review, volumes 1 and 3)

Copy retained by sponsor until requested:
M. Thomas, M.D. (clinical study investigation, volumes 1-37)

MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: January 23, 1997

FROM: Division of OTC Drug Products (HFD-560)

SUBJECT: NDA 20-676: Vagistat-1 Vaginal Ointment

TO: Acting Director
Division of Anti-infective Drug Products (HFD-520)

We have reviewed the draft labeling for Vagistat-1 (tioconazole 6.5%), a one-dose vaginal antifungal drug product, submitted by Bristol-Myers Squibb Company, dated November 11, 1996. In several of our comments below, we noted inconsistencies in the labeling between the various OTC antifungal drug products. It would be useful to standardize the labeling among all of these products. We have the following comments:

A. Carton Labeling

Front Panel

1. The phrase "full prescription strength" on labeling is not allowed where the prescription product is no longer available. It should be changed to "Same as former prescription strength."

2. Phrases referring to "prescription strength" and "now available without a prescription" should be included in the labeling for no longer than 6 months.

3. The milligram amount of active ingredient is not on the front panel.

Side Panel

4. We checked with the Division of Labeling and Nonprescription Drug Compliance and neither of us is aware of any requirement for the phrase "Active ingredient made in U.K." to be included on the label. If this information remains in the labeling, we see no reason for it to appear in bold print and in a larger type size than the active and inactive ingredient information.

Back Panel

5. The sponsor has used an easier to read format for the labeling; however, it should be pointed out that under the agency's proposed new labeling format that is expected to be

published soon, headings and subheadings will be in bold type and in upper and lower case letters. In the proposed new labeling format, the headings are presented in the following order: Active ingredient(s), Purpose(s), Use(s), Warning(s), and Direction(s). Note that the term "Use" is used instead of "Indication." The company should be aware of that proposal, when it publishes, for future label design.

6. Indication: The "Indication" states that Vagistat-1 is "For the treatment of recurrent vaginal yeast infection (candidiasis)." However, the term "recurrent" is not included in the indications of other approved OTC vaginal antifungal drug products. A November 28, 1995 telecon between FDA staff (attached) states that "FDA requires the word "recurrent" to be used [in the educational pamphlet] to differentiate the condition from that of an initial infection. FDA was to ask sponsors of other products not having "recurrent" in the reference to vaginal infection to update their label via labeling supplements within the next 6 months. Has your division actively followed-up for labeling changes for these products?

Although not specifically referred to in the telecon, the carton label should accurately reflect the information found in the educational pamphlet. We think that "recurrent" is more appropriate since the intended use for the OTC population is not for first-time infections. Because the same terminology should be used for all OTC vaginal antifungal drug products, this issue needs to be resolved.

7. Directions: We suggest that the first statement under Directions read: "Tear open foil packet just before using." This additional statement is consistent with the directions on the foil pouch and the prescription labeling that states that the applicator should be opened just prior to administration to prevent contamination. Additionally, it might be better to state "see detailed directions inside package," rather than "see directions on enclosed brochure."

8. Warnings:
Regarding the first warning "Do not use . . . chills, nausea, vomiting, diarrhea . . .," these specific symptoms are not on all the other OTC vaginal antifungal product labels. We note that in our August 22, 1995 labeling review of Femstat 3 (NDA 20-421), we concurred with Dr. Winfield's recommended change that these four symptoms be included in the educational brochure and in the warning section of the carton and internal packaging labeling for Femstat 3. We also noted that we assumed that all manufacturers of vaginal antifungal drug products would be required to add these additional symptoms to their product labeling.

9. The warning about symptoms not improving may need to be strengthened given the efficacy data. There should be a referral to see a doctor if symptoms do not improve/resolve within a specific time frame, e.g., such as 3 days mentioned in the

"Warnings." Also, see comments 10 and 11 below, there needs to be clarification of and consistency in the number of days in which to expect relief.

10. The reference to symptoms not improving, etc., should include the explanatory language seen in other labels, with more explicit language about the time frame within which symptoms should resolve, i.e., "If your symptoms return within 2 months or if you have infections that do not clear up in 3 days with proper treatment, consult your doctor. You could be pregnant, or there could be a serious underlying medical cause for your infections, including diabetes, or a damaged immune system (including damage from infection with HIV - the virus that causes AIDS). The phrase "if you think you have been exposed" does not alert people who are exposed, but still don't think they may have been exposed.

11. Shaded box: There should be clarification of the number of days within which relief can be expected, rather than "a few days." This information should be consistent with the rest of the label.

B. Educational Brochure

The sponsor has made a good attempt at bulleting to make the information in the educational brochure more consumer friendly.

12. Item 2 - We suggest adding "odorless" to the bulleted statement concerning "Vaginal discharge." In the bulleted statement concerning "Rash or redness," for consistency with other antifungal labeling (e.g. Gyne-Lotrimin 3), the statement "Sometimes red spots or sores may develop on the irritated skin of the vulva" should be added.

13. Item 3 - A better explanation should be provided for the "Antibiotics" bulleted statement as follows: Because antibiotics can kill the normal bacteria in the vagina, this changes the normal balance of microorganisms that live in the vagina. This may result in an overgrowth of yeast.

14. Item 4 - The first warning bullet only mentions "abdominal pain." Another OTC vaginal antifungal product brochure (Monistat 3) also mentions "pain in the back or either shoulder." The MO from Anti-Infectives should determine if "back and shoulder" should be included. If so, it should be included in labeling for all of the OTC vaginal antifungal products.

15. Item 8 - The information regarding a 3 day wait because of damage to condoms and diaphragms and the effect on pregnancy and STD prevention is provided in the answer to the third question. However, this information is not mentioned in the warnings on the carton label, foil pouch, or the warnings in item 4 of the educational brochure, nor

on other product labels. What is the 3 day wait statement based on? If there is a basis for this information, we think this information should be included on all OTC vaginal antifungal product labeling and in the warnings in the aforementioned locations, particularly because Vagistat-1 is for one day use, and consumers may not realize that condoms and diaphragms may be affected for 3 days.

The statement about the possible interference of the vaginal antifungal preparation with the efficacy of barrier contraceptive methods made of latex should also be standard and applied to all these products.

16. Item 8 - The answer to the fourth question would read better if the words "any of the following symptoms:" were deleted, and the word "vaginal" was added before "yeast infection" at the end of the sentence.

The information about vaginal yeast infection and sexual transmission is another area where there is inconsistency among all the OTC products. This is another example where class labeling needs to be instituted for all the OTC vaginal antifungal products. The MO from Anti-Infectives should decide whether the statements about transmission should be based on male symptoms or a woman's propensity for recurrent yeast infections or both.

17. Item 8 - The sponsor states in the answer to the fifth question in this section that it is best not to use any vaginal preparation in the presence of yeast infections. Once again, this statement should be standardly applied to all the products in this class.

Note to medical reviewers: In light of the reported association between douching and PID, a stronger statement may be needed such as "It is best not to use any vaginal preparations while you have a yeast infection including feminine hygiene sprays, contraceptive foams, inserts, or jellies. Unless directed by a doctor, douches should not be used while you have any vaginal infection." A joint advisory committee meeting to discuss the issue of douches and adverse consequences is being planned for sometime in the next several months. This meeting will be jointly held by 3 centers; CFSAN, CDER, and CDRH. Therefore, any changes in the labeling would be contingent on the outcome of the meeting.

18. It appears that Gyne-Lotrimin 3 is the only 3 day product that mentions that the product may affect vaginal spermicides, although Vagistat-1 mentions that it is "best not to use . . . contraceptive foams, inserts, or jellies." Is the sponsor or agency aware of any adverse effects of Vagistat-1 on vaginal spermicides?

19. Same comment as in A.4 above re: UK manufacture.

C. Foil Pouch

20. Same comment as in A.4 above re: UK manufacture.

Finally, the labeling should also be forwarded to OTC Compliance for their input.

Linda Katz, M.D., M.P.H. Gerald Rachanow, P.D.,J.D.

Ling Chin, M.D., M.P.H. Helen Cothran

Attachment

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-676 Trade (generic) names [illegible]

Check any of the following that apply and explain, as necessary, on the next page:

____ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

____ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

____ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

____ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

____ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

____ a. The applicant has committed to doing such studies as will be required.

____ (1) Studies are ongoing.
____ (2) Protocols have been submitted and approved.
____ (3) Protocols have been submitted and are under review.
____ (4) If no protocol has been submitted, on the next page explain the status of discussions.

____ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

V 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: This drug is not to be used in patients under 12 years of age.

Signature of Preparer

2/12/97
Date

cc: Orig NDA
HFD-520/Div File
A Action Package

EXCLUSIVITY SUMMARY for NDA # 20-676 SUPPL # _____

Trade Name Vaginal Ring Generic Name Estrogen

Applicant Name Bristol-Myers Squibb HFD-520

Approval Date 12-11-97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA?

   YES /✓/ NO /___/

   b) Is it an effectiveness supplement?

   YES /___/ NO /✓/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /✓/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /✓/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

Three

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /✓/*

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

* Rx-to-OTC Switch

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /✓/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 19-355 Rx. Vagistat-1

NDA # _____

NDA # _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____

NDA # _____

NDA # _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_v_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

   For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

   (a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

   YES /_√_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /✓/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # 145-01-93

Investigation #2, Study # 145-02-93

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # 145-01-93

Investigation #2, Study # 145-02-93

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /✓/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ | NO /___/ Explain _____

_____ | _____

_____ | _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /V/

If yes, explain: _____

_____

_____

_____

_____ 02/13/97

Signature Date

Title: Consumer Safety Officer

_____ 2-13-97

Signature of Division Director Date

cc: Original NDA Division File HFD-85 Mary Ann Holovac