CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-922

ADMINISTRATIVE DOCUMENTS

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: **NDA 20922/000**
Priority: **14S** Org Code: **540**
Stamp: **30-DEC-1997** Regulatory Due: **16-JAN-2000**
Action Goal: District Goal: **30-AUG-1998**
Applicant: **BRISTOL MYERS SQUIBB**
100 FOREST AVE
BUFFALO, NY 14213
Brand Name: **4-HYDROXYANISOLE 2%/TRETINOIN 0.01% TOP**
Established Name:
Generic Name: **4-HYDROXYANISOLE 2%/TRETINOIN 0.01% TOP**
Dosage Form: **SOL (SOLUTION)**
Strength: **2%/0.01%**

FDA Contacts:

F. CROSS JR	**(HFD-540)**	**301-827-2023**	**, Project Manager**
W. TIMMER	**(HFD-540)**	**301-827-2048**	**, Review Chemist**
W. DECAMP II	**(HFD-540)**	**301-827-2041**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 03-DEC-1999 by S. FERGUSON (HFD-324) 301-827-0062
ACCEPTABLE on 05-NOV-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 27-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062

Establishment:
DMF No:
AADA No:

Profile: OAI Status:
Last Milestone:
Milestone Date:
Decision:
Reason:
Responsibilities:

Establishment:
DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**
Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

Establishment:
DMF No:
AADA No:

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Profile: OAI Status: Responsibilities:
Last Milestone:
Milestone Date:
Decision:
Reason:

Establishment: DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **01-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Establishment: DMF No:
AADA No:

Profile: OAI Status: Responsibilities:
Last Milestone:
Milestone Date:
Decision:
Reason:

Establishment: **1314666** DMF No:
WESTWOOD SQUIBB PHARMACEUT AADA No:
100 FOREST AVE
BUFFALO, NY 14213

Profile: **LIQ** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **03-DEC-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

CDER LABELING AND NOMENCLATURE COMMITTEE

CONSULT # 1153	HFD# 540	PROPOSED PROPRIETARY NAME:	PROPOSED ESTABLISHED NAME:
ATTENTION: William C. Timmer		SOLAG'E	2% 4-hydroxyanisole/0.01% tretinoin

A. Look-alike/Sound-alike

	Potential for confusion:
	XXX Low ____ Medium ____ High
	____ Low XXX Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High
	____ Low ____ Medium ____ High

B. Misleading Aspects:

C. Other Concerns:

D. Established Name

XXX Satisfactory

____ Unsatisfactory/Reason

Recommended Established Name

E. Proprietary Name Recommendations:

XXX ACCEPTABLE ____ UNACCEPTABLE

F. Signature of Chair/Date /S/ 3/15/99

AUG 27 1998

Executive CAC
August 11, 1998

Committee: Joseph DeGeorge, Ph.D., HFD-024, Chair
Joseph Contrera, Ph.D., HFD-900, Member
Robert Osterberg, Ph.D.,Alternate Member
Norman See, Ph.D., Acting Team Leader
Amy Nostrandt, D.V.M., Ph.D., Presenting Reviewer

Author of Draft: Amy Nostrandt

The following information reflects a brief summary of the Committee discussion and its recommendations. Detailed study information can be found in the individual review.

NDA # 20-922
Drug Name: 4-hydroxyanisole (2%)/ all trans retinoic acid (0.01%)
Sponsor: Bristol-Myers Squibb

The drug that is the subject of this application is indicated for the treatment of solar lentigines [redacted] resulting from chronic sun exposure. The proposed labeling states that safety factors are based on use of the product over a maximum of 5% of body surface area, or approximately 37 mg 4-hydroxyanisole/0.185 mg tretinoin per m^2 total body surface area per day (0.074 mg 4-hydroxyanisole/0.00037 mg tretinoin or 3.7 μl of drug product applied to one cm^2 of skin).

Mouse Dermal Carcinogenicity Study

A dermal carcinogenicity study was performed in CD-1 mice using the following doses of the clinical formulation: untreated control, vehicle (100 μl) control, 10, 30, and 100 μl/mouse/day (0, 0, 8/.04, 24/.12, 80/0.4 mg/kg/day 4-hydroxyanisole/tretinoin, respectively, or 0, 0, 24/0.12, 72/0.36, 240/1.2 mg/m^2/day). The test material was applied once daily, unoccluded, to clipped sites on the animals' backs for 104 weeks. The most notable signs were related to dose-dependent dermal irritation, as is typical of topical retinoid drugs. Decreased survival was observed in mid and high dose males and high dose females. No treatment-related neoplasms were noted either systemically or at the application sites. Incidental tumors involving the lymphoreticular system, lung, and/or liver were found at single or low incidence, or were comparable among groups. They were considered not unusual for mice of this age and strain. The only primary skin tumor was one benign keratoacanthoma in dorsal skin of one high dose female, which has been reported to be a rare spontaneous tumor in this strain of mouse. Among females, there was a statistically significant evidence of trend in stromal sarcoma of the cervix, due to two occurrences, both in the high dose group, but this finding was within the range of historical controls.

Executive CAC Recommendations and Conclusions:

The Committee had concerns about survival of the test animals, and recommended that the following additional data be provided in order to make an appropriate analysis. The Committee requested a summary table of tumor incidence, by organ, and data to indicate that at least 50% of animals in the mid-dose group survived past week 84. This information was forwarded to the Committee after the meeting. The Committee also requested a survival-adjusted evaluation of the tumors, in particular the polyps and stromal sarcomas of the

uterus/cervix. This was requested from the statistical reviewer; results of the repeated analysis are pending.

Note: Survive exceeded 50% in both males and females through week 84, and the study was thus deemed to have had an adequate duration of exposure to the majority of the animals.

/S/ 5/27/98

Joseph DeGeorge, Ph.D.
Chair, Executive CAC

cc:\
/Division File, HFD 540
/Abby Jacobs, Team leader, HFD-540
/Amy Nostrandt, Reviewer, HFD-540
/ASeifried, HFD-024

APPEARS THIS WAY
ON ORIGINAL

NO DSI audits were requested of the sites studied in support of this NDA as of 11/19/98.

Printed by Frank Cross, Jr.

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 19-Nov-1998 12:46pm
From: Denise Cook
COOKD
Dept: HFD-540 CRP2 N232
Tel No: 301-827-2021 FAX 301-827-2075

TO: Frank Cross, Jr. (CROSSF)

Subject: NDA 20-922 and Pediatric Studies

Frank,

Below is a statement as per our conversation:

"Pediatric studies will not be needed for 2% 4HA/ 0.01%tretinoin solution for the indication sought is that of solar lentigines and These lesions do not occur in the pediatric population."

Hope this suffices.

Denise

/S/ 11/23/98

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA 20-922 Supplement # _____ Circle one:SE1 SE2 SE3 SE4 SE5 SE6

HFD-540 Trade and generic names/dosage form: SOLAGÉ (mequinol, 2%/tretinoin solution, 0.01%) Topical Solution Action: AP DEC 10 1999

Applicant Bristol-Myers Squibb Therapeutic Class 1,4S

Indication(s) previously approved None
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate___ **N/A**
Proposed indication in this application Treatment of solar lentigines.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.
IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? _Yes (Continue with questions) ___No (Sign and return the form) **N/A**

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply) **N/A**
___Neonates (Birth-1 month) _Infants (1 month-2yrs) _Children (2-12yrs) _ Adolescents(12-16yrs)

__ 1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

c. The applicant has committed to doing such studies as will be required.
(1) Studies are ongoing,
(2) Protocols were submitted and approved.
(3) Protocols were submitted and are under review.
(4) If no protocol has been submitted, attach memo describing status of discussions.

d. 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.

_X_ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? No
ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from Medical Officer: (e.g., E-mail from Medical Officer

Per the Medical Officer, pediatric studies are not needed because the approved indication is a disease entity that does not occur in children.

Signature of Preparer and Title /S/ Date 12/7/99

cc: Orig NDA 20-922
HFD-540/Div File
NDA 20-922 Action Package
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Cook
HFD-540/PM/Cross
HFD-006/KRoberts

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK) (revised 10/20/97)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: *November 30, 1996*

USER FEE COVER SHEET

See Instructions on Reverse Before Completing This Form.

1. APPLICANT'S NAME AND ADDRESS

Bristol-Myers Squibb
Pharmaceutical Research Institute
100 Forest Avenue
Buffalo, New York 14213-1091

2. USER FEE BILLING NAME, ADDRESS, AND CONTACT

Bristol-Myers Squibb
P.O. Box 4000
Princeton, NJ 08543-4000

3. TELEPHONE NUMBER *(Include Area Code)*

(716) 887-7794

4. PRODUCT NAME

4-Hydroxyanisole and All-Trans Retinoic Acid - Depigmenting Solution

5. DOES THIS APPLICATION CONTAIN CLINICAL DATA? ☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

6. USER FEE I.D. NUMBER

3343

7. LICENSE NUMBER/NDA NUMBER

NDA 20,922

8. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED BEFORE 9/1/92

☐ THE APPLICATION IS SUBMITTED UNDER 505(Bx2) *(See reverse before checking box.)*

☐ AN INSULIN PRODUCT SUBMITTED UNDER 506

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGIC PRODUCT LICENSED UNDER 351 OF THIS PHS ACT

9. a. HAS THIS APPLICATION QUALIFIED FOR A SMALL BUSINESS EXCEPTION? ☐ YES ☒ NO *(See reverse if answered YES)*

b. HAS A WAIVER OF APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☒ NO *(See reverse if answered YES)*

This completed form must be signed and accompany each new drug or biologic product original or supplement.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Donald J. Handley	Manager	December 30, 1997

Form FDA 3397 (12/93)

Redacted 1

page(s) of trade

secret and/or

confidential

commercial

information

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax: 716 887-3638

December 30, 1997

CERTIFICATION

Bristol-Myers Squibb Company certifies that it did not and will not use, in any capacity, the services of any person debarred under subsections (a) and (b) [Section 306(a) or (b)], in connection with this application.

Donald J. Handley
Manager, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax: 716 887-3638

December 30, 1997

CERTIFICATION

Bristol-Myers Squibb Company certifies that the field copy of this application is a true copy of the Application Summary and Chemistry, Manufacturing and Controls technical section contained in the archival and review copies of the application, and that the field copy has been provided to the Buffalo, New York FDA District Office.

Donald J. Handley
Manager, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

PATENT INFORMATION

PATENT INFORMATION

1) Patent No./Expiration: **U.S. Patent 5,194,247; expires March 16, 2010**

Type of Patent: **Composition and Method of Use**

Patent Owner: **Bristol-Myers Squibb Company**

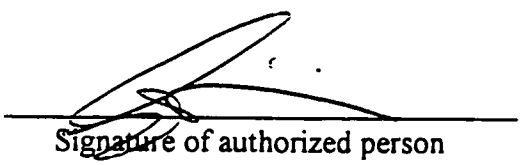
2) Patent No./Expiration: **U.S. Patent 5,470,567; expires March 16, 2010**

Type of Patent: **Composition and Method of Use**

Patent Owner: **Bristol-Myers Squibb Company**

DECLARATION

The undersigned declares that U.S. Patent Nos. 5,194,247 and 5,470,567 cover the composition and method of use of the combination of 2% 4-hydroxyanisole and 0.01% tretinoin in the treatment of hyperpigmentary disorders, the approval for which is being sought in this NDA.



Signature of authorized person

Anthony M. Santini
Name of authorized person

Associate Patent Counsel
Title of authorized person

August 28, 1997
Date

PATENT CERTIFICATION

PATENT CERTIFICATION

Patent information and a declaration as required under 21 CFR §314.53 for new drug applications submitted under 505(b) of the act, is provided on the Patent Information page of this NDA. As noted under 21 CFR §314.50(i), patent certifications are required for 505(b)(2) applications, and thus is not applicable to this NDA.

EXCLUSIVITY SUMMARY FOR NDA # 20-922

Trade Name SOLAGÉ Topical Solution Generic Name mequinol 2%/tretinoin solution, 0.01%

Applicant Name Bristol-Myers Squibb HFD-540

Approval Date ~~DEC 10 1999~~ DEC 1 0

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 question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

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 /_X_/ 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 /_X_/ NO /__/

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

3 years.

e) Has pediatric exclusivity been granted for this Active Moiety? No

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES /__/ NO /_X_/

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 /_X_/

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).

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 /___/ **N/A**

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 /_X_/ NO /__/

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

Retin Topical Solution and Swabs	NDA 16-921
Retin-A Cream, 0.1%	NDA 17-340
Retin-A Cream, 0.05%	NDA 17-522
Retin-A Gel	NDA 17-579
Retin-A Gel, 0.01%	NDA 17-955
Retin-A Cream, 0.025%	NDA 19-049
Renova Cream, 0.05%	NDA 19-963
Avita Gel, 0.025%	NDA 20-400
Avita Cream, 0.025%, 0.05%, 0.1%	NDA 20-404
Vesanoid, Oral Capsules, 10 mg	NDA 20-438
Retin-A Micro, 0.1%	NDA 20-475

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 /_X_/ 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.

(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 /_X_/ 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 /_X_/ 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 /_X_/

(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 /_X_/

(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 # DE132-005

Investigation #2, Study # DE132-010

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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, Study # DE132-005 YES /___/ NO /_X_/

Investigation #2, Study # DE132-010 YES /___/ NO /_X_/

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

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, Study # DE132-005 YES /___/ NO /_X_/

Investigation #2, Study # DE132-010 YES /___/ NO /_X_/

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 # DE132-005 YES /_X_/ NO /__/

Investigation #2, Study # DE132-010 YES /_X_/ NO /__/

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, Study # DE132-005 (IND [redacted]) YES /_X_/ NO /__/

Investigation #2, Study # DE132-010 (IND [redacted]) YES /_X_/ NO /__/

(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?

N/A

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 /_X__/

/S/
Signature of Senior Regulatory Management Officer

3/11/99
Date

/S/
Signature of DDDDP Division Director

3/17/99
Date

Form OGD-011347 Revised 10/13/98

cc: Original NDA 20-922 HFD-540 Division Files HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL