Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 23, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01%)
Request for Teleconference

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 20-922, for 2% mequinol (4-hydroxyanisole)/0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to the facsimile transmission from the Agency, dated March 18, 1999, containing FDA's changes to the draft Package Insert, Medication Guide and Carton/Container labeling. Reference is further made to the March 22, 1999 letter submitted under this NDA requesting a teleconference with the Agency to discuss the changes made to the draft labeling components.

As requested, the purpose of this submission is to provide the sections of the package insert that we wish to discuss and a list of planned attendees from Bristol-Myers Squibb. In regards to the package insert, we wish to discuss changes that have been made in the CLINICAL PHARMACOLOGY, INDICATIONS, CONTAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, DOSAGE AND ADMINISTRATION, and CLINICAL STUDIES sections, and in the Patient Medication Guide.

The following attendees from Bristol-Myers Squibb are planned to participate in the teleconference:

David Altman, M.D., Ph.D., Director, Dermatology Clinical Research
John Bedard, M.S., Vice President, Worldwide Regulatory Affairs
Don Everett, Ph.D., Group Leader, Metabolism and Pharmacokinetics
Jerry D. Frantz, V.M.D., Executive Director, Drug Safety Evaluation
Don Handley, M.S., Manager, Worldwide Regulatory Affairs
Elizabeth Lochry, Ph.D., Director, Reproductive Toxicology
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Robert Williams, M.S., Manager, Toxicology

Also, in response to a comment made in the March 18 facsimile from the Agency, Bristol-Myers Squibb intends to spell the trademark, Solagé, with an initial capital S followed by lowercase letters. This convention will be used consistently throughout the package insert, patient Medication Guide, and Carton/Container labels.

If there are any questions, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER
NDA 20,922

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Pharmaceutical Research Institute	March 25, 1999
TELEPHONE NUMBER *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(716) 887-7794	(716) 887-3638
APPLICANT ADDRESS *(Number, Street, City, State, Country, Zip Code or Mail Code, and U.S. License number if previously issued)*: 100 Forest Avenue, Buffalo, New York 14213-1091	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, State, and ZIP Code, Telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued)

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) (IF ANY)
4-Hydroxyanisole and All-Trans Retinoic Acid	

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*: 4-Hydroxyanisole (monomethyl ether of hydroquinone, 40-methoxyphenol, paramethoxyphenol, BMS 181158, BMY 30586; Tretinoin (3,7-dimethyl-9(2,6,6-trimethyl-1-cyclohexene-1-yl)-2,4,6,8-nonatetraenoic acid, all trans retinoic acid, vitamin A acid, BMS 181159, BMY 30585)

CODE NAME *(if any)*: BMS 181158, BMY 30586; BMS 181159, BMY 30585

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Solution	2% 4-hydroxyanisole/0.01% tretinoin	Topical

(PROPOSED) INDICATIONS FOR USE:
Treatment of solar lentigines resulting from chronic sun exposure

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug: Holder of Approved Application:

TYPE OF SUBMISSION
(check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Amendment 024 to a Pending Application

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide location of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

Cross Reference (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND	Depigmenting solution - Bristol-Myers Squibb Pharmaceuticals Research Institute	
DMF	4-Hydroxyanisole	
DMF	Tretinoin	DMF
DMF	Packaging Components	
DMF	Packaging Components	

Bristol-Myers Squibb
Pharmaceutical Research Institute

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March 25, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01%)
Amendment #024 to a Pending Application

Dear Dr. Wilkin:

This is in response to the recent communications with the Agency (reference February 22, March 11 and March 16, 1999 teleconferences) in which you have expressed that Solagé should be labeled as Pregnancy Category X. Bristol-Myers Squibb (BMS) seeks Pregnancy Category [redacted] based on sound scientific data that are consistent with other marketed topical tretinoin containing products approved by the Agency and labeled with Category [redacted]

- There are multiple tretinoin containing products on the market at concentrations up to 10 fold higher than in Solagé. The proposed twice-daily dosing regimen with Solagé, compared to the once daily regimen of marketed products, potentially reduces this excess to five fold.

- The human pharmacokinetic study conducted by BMS (DE132-008) on Solagé showed that the percutaneous absorption of tretinoin was approximately 4.4%. Human pharmacokinetic studies conducted with Renova (ref. package insert) showed up to 2% absorption of tretinoin. While not a direct comparison, these data suggest similar daily systemic exposure levels with the two products, if similar quantities of the products were applied. It is important to note that Solagé is designed for spot application while Renova is designed for wide surface application.

- Further support that the combination product Solagé does not enhance the penetration of tretinoin is obtained from the *in vitro* pharmacokinetic data which indicate that tretinoin absorption from the combination product is lower than from product containing tretinoin alone.

- The marketed tretinoin products have indications for acne, which in general is a disease of a much younger population than the population likely to use Solagé. The population with acne is much more likely to be of childbearing potential and less likely to use adequate birth control methods.

- In the second teratogenicity study in rabbits conducted by BMS, paw abnormalities were observed in two fetuses from tretinoin treated rabbits. These abnormalities were considered by the laboratory which conducted the study to be within the historical control range. More importantly, the paw abnormality is not typical of tretinoin effects seen in rabbits. In rabbits, the cardinal signs of tretinoin teratogenicity are domed heads, hydrocephaly, and cleft palate[1,2]. In addition, paw abnormalities were not seen in any of the Solagé combination treated groups.

- The teratology data supporting the marketed products are similar to those obtained with Solagé. Most pertinent is the recently approved (January 14, 1997) product, Avita. Teratogenic events typical of tretinoin were observed in the single study conducted by the sponsor. However, Avita was given category C labeling with reference to reports of studies with other formulations. It is also noted from reviewer notes from the Retin-A microsphere NDA (20-475) that they conducted a second rabbit dermal teratology study using the same precautionary measures, used by BMS in their second study, to control for ingestion. A low incidence of fetal malformations was observed in some groups in that study that were deemed unrelated to drug treatment because 1) the incidences were sporadic, 2) there was no dose dependency and 3) the incidence rates were within historical control values. It was further concluded that high plasma concentrations observed in some animals in that study may have been due to ingestion as well as enhanced percutaneous absorption due to washing procedures after each treatment.

- The Agency has indicated that further toxicokinetic data are necessary to show that ingestion may have contributed to teratogenic effects seen in the first study. BMS is not aware that similarly conducted rabbit dermal teratology studies with other topical tretinoin products have shown any correlation between the toxicokinetic data collected in those studies and the absence or presence of any teratogenic effects seen.

- The proposed label drafted by the Agency mentions a nonGLP exploratory study which found drug-related increases in preimplantation losses in rats treated with mequinol throughout gestation. In contrast, the GLP study of fertility and early embryonic development (Segment I) with Solagé in rats found no evidence of any drug-related effects on preimplantation losses, despite treatment prior to mating and throughout the entire preimplantation period.

  While the rabbit studies show small differences among groups in the absolute number of fertilized ova failing to implant, preimplantation loss data are notoriously variable, and as such, are better evaluated as a percent loss per animal [(no. of corpora lutea – no. of implantations) divided by (no. of corpora lutea x 100)]. Evaluation of preimplantation loss data from each rabbit teratology on this basis confirms the lack of any drug-related effects on preimplantation loss on the following basis: 1) there were no statistically significant differences in either study (P values of 0.57 and 0.99 for the first and second teratology studies respectively); 2) there were no dose-dependent trends in the first teratology study, despite wide degrees of variability within each group; and 3) all preimplantation loss values were within approximately 1% of the concurrent control value in the second teratology study.

  Additionally, the possibility of an effect on preimplantation loss in rabbits becomes even more remote when considering that implantation in the New Zealand white rabbit is underway on gestation day 6 (first day of dosing) and completed by gestation day 7^3, making any drug-related effect on this endpoint a single-dose phenomenon. If this were the case, the Segment I study in rats would have revealed Solage to be a clear potent inhibitor of implantation, which it definitely did not.

- BMS originally proposed Pregnancy Category X for this product since we felt that was the appropriate category based on the data available at that time. We have since conducted a repeat dermal rabbit teratology study under an established, state-of-the-art protocol used in industry for topical tretinoin-containing products to control for the possibility of ingestion of the test article. The possibility of ingestion is a confounding factor in this type of study, which is well-known and acknowledged in package inserts for several topical tretinoin-containing products. The results from the second rabbit study, consistent with studies done with other topical tretinoin-containing products, show no incidence of teratogenic effects in the product formulation groups, and no incidence above historical control levels in the tretinoin treated group. It is our opinion, based on these results and in consideration of historical data on topical tretinoin products, that Solagé should receive its original approval with Pregnancy Category [redacted] labeling.

Bristol-Myers Squibb strongly feels that this is a serious matter that deserves a written response from the Agency stating your conclusions from the data presented in the application.

Sincerely,

Kathy Schrode

Kathy Schrode, Ph.D.
Director, Worldwide Regulatory Affairs

Desk Copies: Frank Cross, MA, CDR, Senior Regulatory Management Officer
Robert DeLap, MD, Director, Office of Drug Evaluation V
Mary Jane Walling, Associate Director, Regulatory Affairs, ODEV

References:

[1]Kenel MF, Krayer JH, Merz EA, Pritchard JF, Teratogenicity of N-(4-hydroxyphenyl)-all-trans-retinamide in rats and rabbits. Teratog., Carcinog., Mutagen. 1988; 8(1),1-11.

[2]Kochhar DM, Jiang H, Soprano DR, Harnish DC, Early Embryonic Cell Response in Retinoid-Induced Teratogenesis, Retinoids, Progress in Research and Clinical Applications, Marcel Dekker, Inc., New York, NY, pp. 383-396, 1993.

[3]Garside DA, Charlton A, Heath KJ, Establishing the Timing of Implantation in the Harlan Porcellus Dutch and New Zealand White Rabbit and the Han Wistar Rat. Regulatory Toxicology and Pharmacology, 1996; 23, 69-73.

Bristol-Myers Squibb
Pharmaceutical Research Institute

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March 25, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
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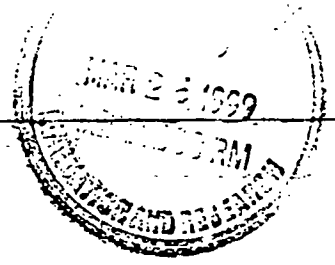

RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01% solution)
Amendment #025 to a Pending Application

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 20-922, for 2% mequinol (4-hydroxyanisole)/0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to a teleconference on March 24, 1999 with Cmdr. Frank Cross and Dr. Tony DeCamp, and Dr. Prakash Parab, Dr. Kathy Schrode and undersigned. In that teleconference, Dr. DeCamp requested a revised provision governing the reprocessing of Solagé batches. Provided below is the revised provision.

If, during post-production QA, it is determined by assay or record review that an incorrect quantity of an ingredient has been added to a batch, and thus the batch is subpotent or superpotent in that ingredient, the batch may be reprocessed. For ingredients that are assayed, no reprocessing will occur if the ingredient is within the specification limits. If an ingredient assay is outside the specified limits, but within 10% of the upper or lower limit, the batch may be reprocessed. For ingredients that are not assayed, no reprocessing will occur if the ingredient was added within [redacted] of the target amount. However, if the ingredient was added outside +/- 5%, but within +/- 20% of the target amount, the batch may be reprocessed.

In any event, a reprocessed batch will be tested for release and held from distribution until approval is granted on a supplement submitted under this NDA covering the reprocessed batch. Additionally, any batches reprocessed according to this provision will be placed into the post-approval stability program.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affair

Submitted in duplicate

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

ORIGINAL

NAS 1st
4/2/99

March 26, 1999

NDA ORIG AMENDMENT
BL

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
Office of Drug Evaluation V
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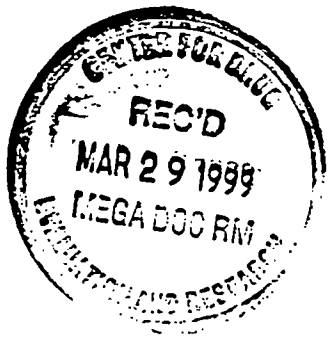
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01% solution)
Amendment #026 to a Pending Application

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 20-922, for 2% mequinol (4-hydroxyanisole)/ 0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to the teleconference on March 25, 1999, with members of the Agency and Bristol-Myers Squibb (BMS), in which BMS reviewed our position on the appropriate Pregnancy Category for this product, and discussed proposed changes to the draft package insert and patient medication guide as provided by FDA in a facsimile transmission on March 18, 1999.

The purpose of this submission is to provide a revised draft package insert and patient medication guide based on our proposed changes as discussed in the teleconference. BMS further maintains that Pregnancy Category [redacted] is the appropriate category for Solagé and is willing to commit to a [redacted] The enclosed labeling, however, still reflects Pregnancy Category X, as instructed by the Agency.

Enclosed in this submission is the revised package insert and patient medication guide noting all text deletions by strikethrough, and all text additions by underlining. Also enclosed is a list providing the rationale for the various proposed changes. A copy of the package insert and patient medication guide are provided in this submission on a 3.5" computer diskette in Word 97 format.

BMS hereby commits to the two Phase 4 commitments, as sent by Cmdr. Frank Cross by facsimile on March 26, 1999; a copy of which is included in this submission.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affair

Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

ORIGINAL

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

April 6, 1999

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
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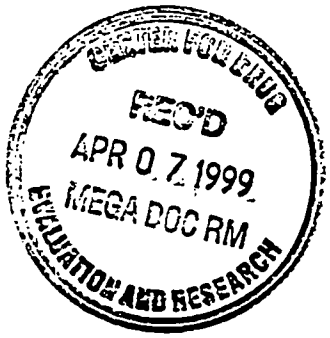
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01% solution)
Amendment #027 to a Pending Application

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 20-922, for 2% mequinol (4-hydroxyanisole)/ 0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to the Action letter from the Agency, dated March 30, 1999.

The purpose of this submission is to notify you, pursuant to 21 CFR 314.110, of our intent to file an amendment to address the outstanding issues noted in the Action letter.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affair

Submitted in duplicate

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

Noted /S/ 6/26/99

Meet. Request

June 15, 1999

Cancelled

per Dr. Wilkin a# Applicant. Applicant to submit protocol for review. /S/ 7/9/99

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NEW CORRESP NC

RE: **NDA 20-922**
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01%)
Amendment #028 to a Pending Application

Request for a Meeting

Dear Dr. Wilkin:

Reference is made to the original submission of NDA 20-922, for 2% mequinol (4-hydroxyanisole)/ 0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to the Action letter from the Agency, dated March 30, 1999.

As noted in the March 30 Action letter, product labeling issues have not yet been resolved to our mutual satisfaction concerning reproductive toxicology and the product pregnancy category. Additionally, the Agency mentions in the March 30 letter that we have previously discussed the "potential value of additional preclinical research to help address some of these issues." Bristol-Myers Squibb (BMS) plans to submit a paper that provides a scientific review and assessment of the labeling issues in question, and provide a draft protocol for an additional investigative study. ✓

BMS requests a "Type A" meeting with the Agency to discuss the acceptability of the information presented in the paper to address some of the labeling issues, and the adequacy of the proposed study to support Pregnancy Category [ ] labeling for Solagé. BMS believes the meeting qualifies as a Type A meeting since, as per the Agency's request in the March 30 letter, we are not able to proceed with the conduct of the additional study, and thus progress approval of this NDA, until the protocol for the study has been reviewed and agreed. The information package for the meeting, including the paper and draft protocol, will be submitted by July 7, 1999. BMS requests that the meeting be scheduled within 30 days of receipt of the information package. ✓

Planned attendees from BMS for the meeting include:

Marvin Cohen, Ph.D., Senior Research Investigator, Metabolism and Pharmacokinetics
Donald Everett, Ph.D., Group Leader, Metabolism and Pharmacokinetics
Jerry Frantz, V.M.D., Executive Director, Drug Safety Evaluation
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Robert Williams, M.S., Manager, Toxicology

BMS requests the following attendees from FDA at the meeting: Abby Jacobs, Ph.D., Amy Nostrandt, Ph.D., D.V.M., Jonathan Wilkin, M.D., Robert DeLap, M.D., Ph.D, and biopharmaceutics personnel, as appropriate.

Assuming the meeting will occur between July 19 and August 6, the following dates are not available for the BMS attendees: July 20 - 23.

A specific agenda for the meeting can be developed closer to the meeting date with input from the Agency following review of the information package. The objectives of the meeting and outcomes expected are to: 1) reach agreement on the labeling statements in question as addressed in the forthcoming paper, and 2) discuss the proposed study and agree on its design such that, pending supportive results, will allow Pregnancy Category [redacted] labeling for this product.

The meeting may not be necessary should the Agency only have minor comments to forward to BMS following review of the position paper and draft protocol. If there are more substantive comments, BMS prefers that these be discussed in a face-to-face meeting, as this would be more productive in resolving any issues than having a teleconference.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affair

Submitted in duplicate

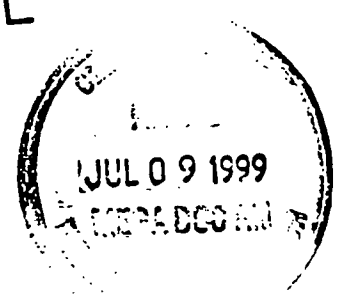
Bristol-Myers Squibb
Pharmaceutical Research Institute

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

July 8, 1999

ORIGINAL

NC



Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental
Drug Products, HFD-540
Document Control Room
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Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NEW CORRESP

RE: IND [redacted]
Solagé Topical Solution
(mequinol 2%, tretinoin 0.01%)

FDA Feedback Requested

Dear Dr. Wilkin:

Reference is made to the above cited IND and the original submission of NDA 20-922 for 2% mequinol (4-hydroxyanisole)/ 0.01% tretinoin topical solution. Reference is also made to the Action letter from the Agency for NDA 20-922, dated March 30, 1999.

The purpose of this submission is to provide, as indicated in our amendment of June 15, 1999 to NDA 20-922, a paper that provides a scientific review and assessment of the outstanding reproductive toxicology labeling issues along with a protocol for an additional investigative study. The proposed study, [redacted] will clarify the [redacted] study.

Originally, the June 15 amendment requested a meeting with the Agency to discuss the acceptability of the information presented in the paper to address the labeling issues, and the adequacy of the proposed study to support Pregnancy Category [redacted] labeling for Solagé. However, in response to the meeting request, Cmdr. Frank Cross indicated in a telephone conversation with the undersigned on June 18, 1999, that the Agency would prefer to review the submitted information before determining if a meeting is necessary. While Bristol-Myers Squibb (BMS) agrees with that approach, a timely review of the submitted information and protocol is requested since the proposed study can not be started, and thus approval of NDA 20-922 can not be progressed, until we receive feedback from the Agency.

One of the main objectives of the previously requested meeting for BMS is to receive a commitment from the Agency that, should the proposed [redacted] design be found acceptable and the results of the study are supportive, Pregnancy Category [redacted] labeling for this product would be granted. If a meeting is not deemed necessary by the Agency, BMS still wishes to receive such a commitment from the Agency before initiating the proposed study.

BMS plans to initiate the proposed study in [redacted] on or around [redacted] Therefore, we would appreciate receiving feedback from the Agency with specific comments on the study design, or the acceptability of the study to support Pregnancy Category [redacted] labeling by August 9, 1999.

If there are any questions regarding this submission, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley

Donald J. Handley
Manager, Worldwide Regulatory Affair

Five copies submitted
~~Cover Letter copy to NDA 20-922~~

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

P.O. Box 4000 Princeton, NJ 08543-4000

NEW CORRESP
~~NE~~
A2

Worldwide Regulatory Affairs

NDA 20-922
Solagé (mequinol 2%, tretinoin 0.01%) Topical Solution

November 15,.1999

Jonathan Wilkin. M.D.
Director, Division of Dermatologic and Dental
Drug Products (HFD-540)
Office of Drug Evaluation V
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room
9201 Corporate Boulevard
Rockville. MD 20850

Dear Dr. Wilkin:

Reference is made to our new drug application (NDA 20-922) dated December 30. 1997 for Solagé (mequinol 2%, tretinoin 0.01%) Topical Solution for the treatment of solar lentigines and to the approvable letter issued by the FDA on March 30, 1999.

Bristol-Myers Squibb would like to accept the draft labeling proposed for the package insert and patient medication guide, immediate container, and carton labels in the March 30. 1999 letter and move to the approval for this product.

Once approval is obtained, Bristol-Myers Squibb would like to continue our interactions with the FDA to help the company generate additional preclinical data that might support a change in the product labeling to [redacted]

We acknowledge the Phase 4 commitments specified in our submission dated March 26, 1999.

If additional information is required to obtain approval of the product please contact me at 609-252-6463.

Sincerely yours,

K. P. Schrode for

Kathy Schrode, Ph.D.
Director, Regulatory Science

Desk Copy: Commander Frank Cross

Bristol-Myers Squibb
Pharmaceutical Research Institute

100 Forest Avenue Buffalo, NY 14213-1085 716 887-3400 Fax: 716 887-3638

August 5, 1994

Dr. Jonathan Wilkin, M.D., Director
Division of Topical Drug Products (HFD-540)
Food and Drug Administration
Center for Drug Evaluation and Research
Document Control Room 12B30
5600 Fishers Lane
Rockville, MD 20857

Re: IND [redacted]
Depigmenting Solution (BMS 181158/BMS 181159)
2% 4-hydroxyanisole/0.01% tretinoin
Informational Correspondence re Chemistry, Manufacturing & Control [redacted]

Dear Dr. Wilkin:

Reference is made to our Investigational New Drug Application IND [redacted] for Depigmenting Solution (2% 4-hydroxyanisole/0.01% tretinoin) and a telephone conversation on August 3, 1994 between Ms. N. Rejali, Reviewing Chemist, Food and Drug Administration and Dr. Kathy Schrode on Bristol-Myers Squibb Pharmaceutical Research Institute.

In this conversation, Ms. Rejali confirmed that she had consulted with Dr. Wilson DeCamp, Supervisory Chemist, Division of Topical Products, FDA. They had agreed that BMS-PRI could proceed with development of the Depigmenting Solution product with a [redacted] tretinoin overage. Their decision was based on the USP 23 which allows for a 35% tretinoin overage in solution products.

With the current USP specification, a product with a [redacted] overage would be acceptable at both the IND and NDA stage. Should the USP specifications for the allowable overage in tretinoin solution products change within the next several years, Ms. Rejali did not anticipate it would drop below [redacted]

Ms. Rejali encouraged BMS to work to reduce the overage. We assured the Agency that we have made efforts,and would continue to do so, to minimize the required overage.

If there are any questions concerning this summary please contact me by telephone (716-887-7680), fax (716-887-3638) or Internet (IN%"SCHRODE"@BMS.COM").

Sincerely yours,

Kathy B Schrode

Kathy B. Schrode, Ph.D.
Director, Worldwide Regulatory Affairs

Submitted in triplicate

MEMORANDUM OF TELECONFERENCE

DATE: August 17, 1998, 2:00 p.m.

APPLICATION NUMBER: NDA 20-922, 4-hydroxyanisole and All-Trans retinoic Acid

BETWEEN:

Name: Donald J. Handley, Manager, Worldwide Regulatory Affairs
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Phone: 716-887-7794
Representing: Bristol-Myers Squibb Pharmaceutical Research Institute

AND

Name: Wilson H. DeCamp, Ph.D., Chemistry Team Leader
Bill Timmer, Ph.D., Chemistry Reviewer and
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer
Division of Dermatologic and Dental Drug Products, HFD-540

SUBJECT: Discussion of Site Manufacture for 4-hydroxyanisole Drug Substance

Agency:

With regard to the recent [redacted] the Agency asked the Applicant for an update on its plans for the manufacture of the 4-hydroxyanisole drug substance that will be used in the manufacture of this drug product.

Applicant:

The Applicant has contracted with a new supplier located [redacted] The Applicant committed to providing the following information to the Agency:

- Stability data and the COA's on the laboratory and the first of three validation batches by the end of the third week of August 1998 (tentative).
- Stability data and the COA's on two additional validation batches by the end of August 1998 (tentative).
- Identity test results on the new supplier's 4-hydroxyanisole bulk drug
- Details of the manufacturing procedure at the new facility.
- The new bulk drug substance supplier will submit a DMF to the Agency by the end of September 1998 (tentative).

Agency:

- A delay in the submission of the above items past October 1, 1998, will result in a 3 month extension of the User Fee Due Date from December 30, 1998, to March 30, 1999.

- The Applicant should update us as to the levels of bulk drug substance that they currently have on hand.

Subsequent to this teleconference, a facsimile dated August 21, 1998, was received, providing the requested identification of the alternate manufacturer. This submission was to be submitted officially to the NDA.

/S/

Frank H. Cross, Jr, M.A., CDR
Senior Regulatory Management Officer
Division of Dermatologic and Dental Drug Products, HFD-540

Attachment: August 21, 1998, facsimile transmission

APPEARS THIS WAY
ON ORIGINAL

MAR 17 1999

Teleconference Date: February 22, 1999 Time: 1020 Location: N225

NDA 20-922, for 4-hydroxyanisole, 2%/tretinoin solution, 0.01%

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Susan Walker, M.D., Dermatology Team Leader
Denise Cook, M.D., Medical Officer, DDDDP, HFD-540
R. Srinivasan, Ph.D., Biostatistics Team Leader, DOBIV, HFD-725
Valeria Freidlin, Ph.D., Biostatistician, DOBIV, HFD-725
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Amy Nostrandt, Ph.D., D.V.M., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Donald J. Handley, M.S., Manager, Worldwide Regulatory Affairs
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Edmund Schwartzel, Ph.D., Associate Director, Biostatistics and Data Management
David Altman, M.D., Director, Clinical Research
James Staszak, M.S., Associate Director, Biostatistics and Data Management
Susan Colby, B.A., Senior Clinical Scientist
Robert Williams, M.S., Manager, Toxicology

Discussion:

The following discussion took place:

Agency:

1. During the teleconference the Applicant was asked to provide the following:

   a. A list of any patients with halo hypopigmentation that were considered a success.

   b. Patient Package Insert.

   c. Final Carton/Container Labeling that incorporates the following revisions:

i. The statement "Protect from light. Return bottle to carton..." should be more prominent in accordance with 21 CFR 201.15(a)(6).

ii. The generic name should be more prominent in accordance with 21 CFR 201.10(g)(2)

iii. Replace "Abcdgè" with SOLAGÈ

2. During the teleconference we conveyed our Pregnancy Category X thoughts to the Applicant as the Applicant proposed in their original Package Insert submitted December 30, 1997.

3. The significance of the [redacted] impurity presence in the 4-hydroxyanisole, 2%, drug substance, manufactured by [redacted] is still a review issue.

The Applicant will make the requested submission.

Signature, minutes preparer: /S/
Concurrence Chair (or designated signatory): /S/

cc:

HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Cook
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Nostrandt
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Timmer
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Tandon
HFD-540/PM/Cross
Drafted by: fhc/February 22, 1999
[redacted]
Initialed by:
final:

MEMORANDUM OF TELECONFERENCE

Teleconference Date: July 23, 1999 Time: 1145 Location: N225

NDA 20-922, Solagé (mequinol, 2%, tretinoin, 0.01%) Topical Solution
IND [redacted] Solagé (mequinol, 2%, tretinoin, 0.01%) Topical Solution

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs

Discussion:

With reference to IND [redacted] FDA Feedback Requested, the following discussion took place:

Applicant:

The Applicant asked to receive a commitment from the Agency that, should the proposed [redacted] be found acceptable and the results of the study are supportive, could [redacted] labeling be granted for this product.

Agency:

The results of the proposed study will need to be reviewed before we can comment further.

Applicant:

Approval of the NDA can not be progressed until we receive feedback from the Agency.

Agency:

The NDA could have already been approved with a Pregnancy Category X and the Applicant could be marketing the drug now.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/

cc:

HFD-540
HFD-105/OFFICE DIR/DeLap
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Cook
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Nostrandt
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Timmer
HFD-880/BIOPHARM TL/Bashaw
HFD-880/BIOPHARM/Tandon
HFD-540/PM/Cross
Drafted by: fhc/August 17, 1999

Initialed by:
final:

MEMORANDUM OF TELECONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: August 20, 1999 Number of Pages (including cover sheet) – 1

TO: Kathy B. Schrode, Ph.D., Director, Worldwide Regulatory Affairs
COMPANY: Bristol Myers Squibb
FAX #: 716-887-3638

MESSAGE: Please find attached to this facsimile transmission, comments from our review of IND [redacted] submitted August 5, 1999.

With reference to paragraph 2 of said submission, the paragraph should read:

"Dr. Wilkin indicated that the study protocol submitted July 8, 1999, was of an appropriate design to address the issues concerning [redacted] designation for this product. He said that the data generated from this study might, upon review, provide the information needed to support [redacted] for Solagé."

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: September 2, 1999 Number of Pages (including cover sheet) – 3

TO: Kathy B. Schrode, Ph.D., Director, Worldwide Regulatory Affairs
COMPANY: Bristol Myers Squibb
FAX #: 716-887-3638

MESSAGE: Please find attached to this facsimile transmission, minutes from our August 31, 1999, teleconference.

Thank you.

FROM: Frank H. Cross, Jr., M.A., CDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

APPEARS THIS WAY
ON ORIGINAL

Teleconference Date: August 31, 1999 Time: 0945 Location: N225

NDA 20-922, Solagé (mequinol, 2%, tretinoin, 0.01%) Topical Solution
IND [redacted] Solagé (mequinol, 2%, tretinoin, 0.01%) Topical Solution

Sponsor: Bristol-Myers Squibb Pharmaceutical Research Institute

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader, DDDDP, HFD-540
Amy Nostrandt, D.V.M., Ph.D., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Joseph Costa, Ph.D., Director, Drug Safety Evaluation
Robert Williams, M.S., Manager, Toxicology
Elizabeth Lochry, Ph.D., Director, Reproductive Toxicology
Marvin Cohen, Ph.D., Senior Research Investigator

Discussion:

With reference to IND [redacted] FDA Feedback Requested, the Agency offered the following suggested features for a [redacted]

Agency:

[redacted]

Sponsor:

The Sponsor may request a meeting to further discuss this issue.

Agency:

The Sponsor is encouraged to submit the protocol for review and is invited to further discuss this issue.

Signature, minutes preparer: /S/

Concurrence Chair (or designated signatory): /S/ 9/1/99

APPEARS THIS WAY
ON ORIGINAL

Division of Dermatologic and Ophthalmologic Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

Blatt
540

FACSIMILE TRANSMISSION RECORD

DATE: 10-9-96 Pages (including cover) 2

TO: Don Handley

COMPANY: Bristol Myers Squibb

ADDRESS:

FAX PHONE#: (716) 887-3638 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Enclosed are our pharmacologists recommendations on your IND amendment dated 12-27-93

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: /S/

TITLE: PROJ MGR

TELEPHONE: (301) 827-2020

IND
DIV FILES
HFD-540/ ALAM
HFD-540/ BLATT

Regulatory Recommendations:

1. If not already done, the teratogenic effects reported in this dermal rabbit study should be included in the Investigator's Brochure for any further clinical investigation.

2. This fact should be taken into account for any future labeling for the drug, depigmenting solution.

APPEARS THIS WAY
ON ORIGINAL

Division of Dermatologic and
Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 1-27-97 Pages (including cover) 2

TO: Don Handly

COMPANY:

ADDRESS:

FAX PHONE#: (716) 887-3638 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

Our Biopharmaceutics has asked that I copy the attached comments on your IND

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if your have any questions regarding the contents of this transmission.

FROM: /S/

TITLE: PROJMGR

TELEPHONE: (301) 827-2020

APPEARS THIS WAY
ON ORIGINAL

Comments:

1) The sponsor should provide a description of assay method, validation (sensitivity, specificity, recovery, accuracy and precision) and in process control data for the analytical methods in the final report.

2) The sponsor should consider determining if metabolites (degradation products) are present in the plasma, urine and feces after topical application.

APPEARS THIS WAY
ON ORIGINAL

151

JAN 30 1997

540

Division of Dermatologic and Dental Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, HFD-540
Rockville, MD 20857

FACSIMILE TRANSMISSION RECORD

DATE: 1-30-97 Pages (including cover) 2

TO: Don Nunley

COMPANY:

ADDRESS:

FAX PHONE#: (716) 887-3638 Our Fax # (301) 827-2075

Voice # (301) 827-2020

MESSAGE:

As per your request I am sending you our pharmacologists comments regarding your 12-19-96 amendment to IND [redacted]

NOTE: We are providing the attached information via telephone facsimile for your convenience. This material should be viewed as unofficial correspondence. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: JANL BLATT

TITLE: PROJ. MGR

TELEPHONE: (301) 827-2020

IND [redacted] HFD-540/ALAm

Recommendations for the Sponsor:

1. The Sponsor should be asked to provide explanation(s) for higher serum concentration of 4-HA observed at week 21 as compared to that at week 4, and for increased percutaneous absorption of 4-HA in the presence of tretinoin.

2. The Sponsor should be asked to perform with the the clinical formulation two additional genotoxicity studies previously recommended by Dr. Sheevers, and agreed to by the Sponsor.

APPEARS THIS WAY
ON ORIGINAL

1. As per request, the Sponsor may be informed that no further mutagenicity tests are required to be performed with the present clinical formulation for an NDA submission..

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

Division of Dermatologic and Dental Drug Products

Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard, HFD-540
Rockville, MD 20850

FACSIMILE TRANSMISSION

DATE: May 11, 1998 Number of Pages (including cover sheet) - 1

TO: Donald Handley, Manager, Worldwide Regulatory Affairs
COMPANY: Bristol Myers Squibb
FAX #: 716-887-3638

MESSAGE: Reference is made to your New Drug Application dated 30 December 1997 for 4-Hydroxyanisole and All-Trans Retinoic Acid (NDA 20-922). The submission was reviewed for microbiological issues concerning microbial attributes and the following issue was not completely addressed. Please provide an amendment to address the following concern:

Microbial limits for the product should be established. It may be possible to test several of the initial batches, then depending on the results obtained, reduce or eliminate testing.

Thank you.

FROM: Frank H. Cross, Jr., M.A., LCDR
TITLE: Senior Regulatory Management Officer
PHONE #: 301-827-2063
FAX #: 301-827-2075/2091

Printed by Frank Cross, Jr.

Electronic Mail Message

see Chem Review #1 dated 4/13/99

3/30/99

'tivity: COMPANY CONFIDENTIAL

Date: 18-Mar-1999 03:35pm
From: William Timmer
TIMMERW
Dept: HFD-540 CRP2 N224
Tel No: 301-827-2048 FAX 301-827-2075

TO: Frank Cross, Jr. (CROSSF)

CC: Wilson DeCamp (DECAMP)
Subject: Re: NDA 20-922, SOLAGE - EA

Frank:

> There are no extraordinary circumstances for this NDA. The applicant is granted a categorical exclusion.

Bill

APPEARS THIS WAY
ON ORIGINAL

Printed by Frank Cross, Jr.

Electronic Mail Message

Date: 19-Nov-1998 07:56am
From: Nancy Sager
SAGERN
Dept: HFD-357 WOC2 3073
Tel No: 301-594-5633 FAX 301-827-2772

Subject: Re: FWD: NDA 20922 & EA

Yes they can have a categorical exclusion as long as there are no extraordinary circumstances. The information that should be included in the applicant's CE request is specified in 25.15(d).

Nancy

Printed by Frank Cross, Jr.

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 18-Nov-1998 04:07pm
From: William Timmer
TIMMERW
Dept: HFD-540 CRP2 N224
Tel No: 301-827-2048 FAX 301-827-2075

TO: Nancy Sager (SAGERN)

CC: Mary Jean Kozma-Fornaro (KOZMAFORNARO)
CC: Frank Cross, Jr. (CROSSF)
Subject: FWD: NDA 20922 & EA

Nancy: You answered the attached e-mail some time ago, but I forgot to save your response. As we are now preparing the action package for the sponsor, I need your response.

Would you please re-answer the question? Thank you.

Bill Timmer

APPEARS THIS WAY
ON ORIGINAL

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

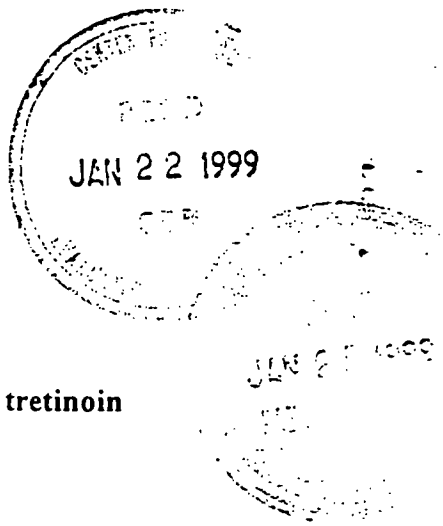
100 Forest Avenue Buffalo, NY 14213-1091 716 887-3400 Fax 716 887-3638

VIA FACSIMILE

January 8, 1999

DRIG NEW CORRES

Frank H. Cross, Jr., M.A., CDR
Senior Regulatory Management Officer
Office # N229
Division of Dermatologic and Dental
Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850



RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin topical solution

Request for Teleconference

Dear Mr. Cross:

Reference is made to the original submission of NDA 20-922, for 2% 4-hydroxyanisole/0.01% tretinoin topical solution, received at the Agency on December 30, 1997. Reference is also made to the Information Request letter dated December 23, 1998.

The purpose of this communication is to request a teleconference with Division personnel to discuss some of the issues identified in the Information Request letter. Specifically, we wish to discuss the issues identified below corresponding to the numbers from the Information Request letter:

CHEMISTRY, MANUFACTURING AND CONTROLS:
Items #3, 4. 5, 6, 7.

PHARMACOLOGY/TOXICOLOGY
(Single item)

CLINICAL
Item #1.

The following people from Bristol-Myers Squibb are tentatively planned to participate in the teleconference:

Rao Gadde, Ph.D., Director, Analytical R&D
Don Handley, M.S., Manager, Worldwide Regulatory Affairs
Prakash Parab, Ph.D., Senior Principal Scientist, Pharmaceutics R&D
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Edmund Schwartzel, Ph.D., Associate Director, Clinical Research
James Staszak, M.S., Associate Director, Biostatistics and Data Management
Robert Williams, M.S., Manager, Toxicology
Tony Yu, Ph.D., Associate Director, Basic Pharmaceutics and Stability

Over the next two weeks, one or more of the above participants would not be able to attend and thus are not considered good days for the teleconference: January 11, 12, 14, 15, 19 and 21.

If there are any questions, please contact the undersigned by telephone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at "handleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

MAR 1 8 1999

Teleconference Date: January 20, 1999 Time: 1020 Location: N225

NDA 20-922, for 4-hydroxyanisole, 2%/tretinoin solution, 0.01%

Applicant: Bristol-Myers Squibb Pharmaceutical Research Institute

Meeting Chair: Jonathan K. Wilkin, M.D.

Meeting Recorder (CSO/Project Manager): Frank H. Cross, Jr., M.A., CDR

FDA Attendees, titles and offices:

Jonathan K. Wilkin, M.D., Division Director, DDDDP, HFD-540
Susan Walker, M.D., Dermatology Team Leader
Denise Cook, M.D., Medical Officer, DDDDP, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, DNDCIII, HFD-830
Bill Timmer, Ph.D., Chemist, DNDCIII, HFD-830
Amy Nostrandt, Ph.D., D.V.M., Pharmacology/Toxicology Reviewer, DDDDP, HFD-540
Frank H. Cross, Jr., M.A., CDR, Senior Regulatory Management Officer, DDDDP, HFD-540

Applicant Attendees, titles and offices:

Donald J. Handley, M.S., Manager, Worldwide Regulatory Affairs
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Rao Gadde, Ph.D., Director, Analytical Research and Development
Prakash Parab, Ph.D., Senior Principal Scientist, Pharmaceutics Research and Development
Edmund Schwartzel, Ph.D., Associate Director, Biostatistics and Data Management
Robert Williams, M.S., Manager, Toxicology
Tony Yu, Ph.D., Associate Director, Basic Pharmaceutics and Stability
James DiNunzio, Ph.D., Associate Director, Analytical Research and Development

Discussion:

With reference to NDA 20-922, Request for Teleconference, submitted January 8, 1998, the following discussion took place:

Agency:

Chemistry Manufacturing and Controls (CMC):

1. Only CMC Items 1 and 2 from the Information Request (IR) Letter of December 23, 1998, are potential Not Approvable issues. The other items listed in the IR Letter are informational items.

2. CMC Item 3 from the December 23, 1998, IR Letter: A range should be submitted per the IR Letter.

3. CMC Item 4 from the December 23, 1998, IR Letter: The item was reiterated to the Applicant.

4. CMC Item 5 from the December 23, 1998, IR Letter: The Applicant was strongly encouraged to address this item in their response. The Applicant said that they would take our advice under advisement.

5. CMC Item 6 from the December 23, 1998, IR Letter: The item was reiterated to the Applicant.

6. CMC Item 7 from the December 23, 1998, IR Letter: The Applicant should submit information on the light source used in the photostability studies.

7. CMC Item 2 from the December 23, 1998, IR Letter: The Agency asked if the Applicant has received notification from the DMF Holders about the timing of their response to the deficiencies. The Applicant said that they have not had any communication from the DMF Holders and will contact them for an update.

Pharmacology/Toxicology:

Pharmacology/Toxicology Item from the December 23, 1998, IR Letter: The Applicant will be revising the specifications for finished drug product to include an additional impurity, [redacted] This impurity is present at [redacted] and therefore has been Generally Recognized As Safe (GRAS) as a food additive per 21 CFR 172.515. This information will be submitted to the NDA.

Clinical:

Clinical Item 1 from the December 23, 1998, IR Letter: The Applicant mentioned that their database has a listing of adverse events in approximately 98 non-Caucasian patients. The Agency asked the Applicant to provide details on the exact number of patients in the patient subsets and in which arm of the study each patient participated.

Applicant:

The Applicant will submit their response to the IR Letter as soon as possible.

Agency:

The Agency stated that it expects to issue an Action Letter by the User Fee Due Date of March 30, 1999.

Signature, minutes preparer: /S/
Concurrence Chair (or designated signatory): /S/

cc:

HFD-540
HFD-540/DIV DIR/Wilkin
HFD-540/DERM TL/Walker
HFD-540/MO/Cook/1.20.99
HFD-540/PHARM TOX TL/Jacobs
HFD-540/PHARM TOX/Nostrandt/1.20.99
HFD-540/CHEM TL/DeCamp
HFD-540/CHEM/Timmer/1.28.99
HFD-540/PM/Cross
Drafted by: fhc/January 20, 1999

Initialed by:
final:

MEMORANDUM OF TELECONFERENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-922

DEC 23 1998

Bristol-Myers Squibb Pharmaceutical Research Institute
Attention: Donald J. Handley, Manager, Worldwide Regulatory Affairs
100 Forest Avenue
Buffalo, New York 14213-1091

Dear Mr. Handley:

Please refer to your new drug application (NDA) dated December 30, 1997, received December 30, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for 4-hydroxyanisole, 2%/tretinoin solution, 0.01%. We acknowledge receipt of your submissions dated January 19, February 3 and 9, April 27, May 5 and 19, June 16 and 17, August 21, September 17 and 18, and December 11, 1998.

The original user fee goal date for this application was December 30, 1998. However, your submission dated December 11, 1998 is considered a major amendment, and the revised user fee goal date for this application is now March 30, 1999.

At this time, we have identified several issues in the review of this application, and we request additional information as follows:

CHEMISTRY, MANUFACTURING AND CONTROLS:

1. Prior to your submission of December 11, 1998, information regarding the manufacture of the 4-hydroxyanisole bulk drug substance was not available. Manufacturing information must be made available for review, whether it is included in the NDA itself or incorporated into a drug master file (DMF). Your submission of December 11, 1998 is currently under review; however, it is premature to comment on the adequacy of the information provided in that submission.

2. The container/closure drug master files have been reviewed and found deficient. The DMFs are:

   a. DMF [redacted] held by the [redacted] for the cap, wiper, applicator rod and tip.

   b. DMF [redacted] held by [redacted] for the high-density polyethylene bottle.

3. A range should be specified for the quantities of the individual excipients of the drug product.