CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-922

CORRESPONDENCE

Printed by Frank Cross, Jr.

Electronic Mail Message

ivity: COMPANY CONFIDENTIAL

Date: 12-Feb-1999 11:03am
From: Peter Cooney
COONEY
Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

TO: Frank Cross, Jr. (CROSSF)
TO: Paul Stinavage (STINAVAGEP)

Subject: Re: NDA 20-922, 4-hydroxyanisole, 2%, tretinoin solution, 0.05%

>Hi Paul,
>
> Do you have any labeling comments for the label. None were
>mentioned/recommended in your reviews.
>
> Please let me know today since we are having the labeling day on
>Tuesday, 2/16 at 9:30.
>
> By the way are you planning on attending?
>
>
> Thanks,
>
> Frank

Frank:

looked at the labelling yesterday and has no comments. We are
rning the consult as "No Action Indicated" (NAI). Paul is not in
today, but he doesn't need to attend the meeting on Tuesday.

Peter

APPEARS THIS WAY
ON ORIGINAL

Printed by Frank Cross, Jr.

Electronic Mail Message

itivity: COMPANY CONFIDENTIAL

Date: 17-Mar-1999 02:01pm
From: Peter Cooney
COONEY
Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

TO: Frank Cross, Jr. (CROSSF)

Subject: NDA 20-922

Frank:

Micro has no comments concerning the letter, and has previously recommended approval for this application.

Peter

S4
ORIG AMENDMENT

DUPLICATE

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)

CENTER FOR DRUG EVALUATION AND RESEARCH RECD MAY 12 1998

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
Bristol-Myers Squibb Pharmaceutical Research Institute

DATE OF SUBMISSION
May 5, 1998

TELEPHONE NUMBER (*Include Area Code*)
(716) 887-7794

FACSIMILE (FAX) Number (*Include Area Code*)
(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*)
4-Hydroxyanisole and All-Trans Retinoic Acid

PROPRIETARY NAME (*trade name*) (IF ANY)

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*if any*)
4-Hydroxyanisole (monomethyl ether of hydroquinone, 4-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:
Solution

STRENGTHS:
2% 4-hydroxyanisole/0.01% tretinoin

ROUTE OF ADMINISTRATION:
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 005 - Four-Month Safety Update Report

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 (submitted 12/17/97)
DMF	Tretinoin
DMF	Packaging Components
DMF	Packaging Components

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50(e)(2)(I), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
	7. Clinical Microbiology section (e.g. 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g. 21 CFR 314.50(d)(5), 21 CFR 601.2)
✓	9. Safety update report (e.g. 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR.314.50(d)(6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12. Case reports forms (e.g. 314.50(f)(1), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306(k)(1))
	17. Field copy certification (21 CFR 314.5(k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (*Specify*)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate. **Warning:** a willfully false statement is a criminal offense. U.S.Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donald J Handley	Donald J. Handley, Manager	5/5/98

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
100 Forest Avenue, Buffalo, New York 14213-1091	(716) 887-7794

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

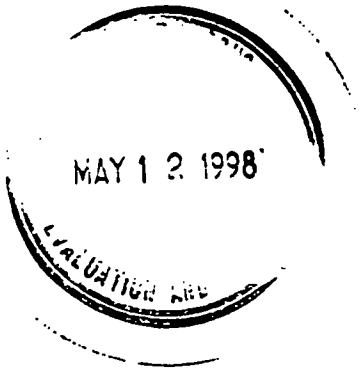
An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number

Please **DO NOT RETURN** this form to this address.

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

May 5, 1998



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
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-922
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #005 to a Pending Application
Four-Month Safety Update Report

Dear Dr. Wilkin:

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. Pursuant to 21 CFR 314.50(d)(5)(vi)(b), this submission provides a four-month safety update report to the NDA.

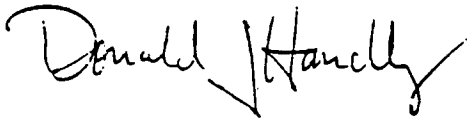
This submission includes an update on: 1) the sole ongoing

2) hypopigmentation adverse events from completed clinical studies reported in the NDA; and 3) relevant literature publications on 4-hydroxyanisole or tretinoin.

One nonclinical toxicology study with 2% 4-hydroxyanisole/0.01% tretinoin topical solution has been initiated since the submission of the NDA. Study 98612, entitled "2% BMS-181158/0.01% BMS-181159 Solution: Dermal Study of Embryo-Fetal Development in Rabbits" was initiated in March 1998. This study repeats a previously conducted dermal embryo-fetal developmental study in rabbits (Study 92714, NDA volumes 1.18 & 1.19), but uses extra preventive methods to eliminate potential ingestion of the test article. A report of Study 98612 is targeted to be available in the third quarter of 1998.

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

Sincerely,



Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

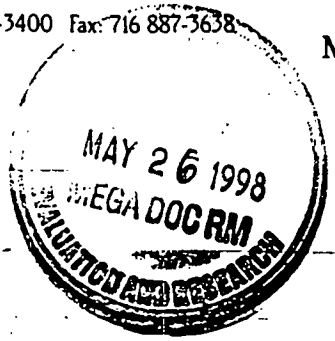
APPEARS THIS WAY
ON ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

ORIGINAL

May 19, 1998



bp

ORIG AMENDMENT

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
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-922
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #006 to a Pending Application

Dear Dr. Wilkin:

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 a telephone call from Mr. Frank Cross on May 18, 1998.

Mr. Cross noted a compilation error with the NDA, in that the Metabolism and Pharmacokinetics (MAP) report for Study 92714 ("Dermal Teratology Study in Rabbits with 2% BMS-181158/0.01% BMS-181159"), MAP Report No. 930740056, located on pages 1.19.173 - 1.19.221 of the NDA, inadvertently consists of a MAP report for a different study. This submission provides a full, correct copy of MAP Report No. 9307450056. The Regulatory Compliance Statement for Study 92714 which should immediately precede the MAP report is also provided in this submission, along with an abstract of the study.

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 "Donald_Handley@ccmail.bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate
Desk Copy: Frank Cross

T-I

RIG AMENDMENT

RIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

June 16, 1998

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
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #007 to a Pending Application

Dear Dr. Wilkin:

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 a facsimile message received from Mr. Frank Cross on May 11, 1998 which contained a comment from the microbiology review of the NDA. A response to the comment is provided in this amendment.

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 "Donald_Handley@ccmail.bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

June 17, 1998

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
5600 Fishers Lane
Rockville, MD 20857

GBS

ORIG AMENDMENT

ORIGINAL

RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #008 to a Pending Application

Dear Dr. Wilkin:

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 a telephone request from Mr. Frank Cross on June 3, 1998.

Mr. Cross requested the following statistical analyses:

1) Provide p-values calculated for the comparisons of the proportions of subjects with moderate or greater improvement in Tables 3 & 4 (Physician's Global Assessment) on page 1 47.7, from the clinical report synopsis of study DE132-005.

2) Provide p-values calculated for the comparisons of the proportions of subjects who rated themselves completely or mostly improved (overall appearance) and completely or much lighter (brown spots), instead of the p-values calculated on the full range of responses, in Table 5 of page 1.47.8, from the clinical report synopsis of study DE132-005.

3) Provide the same for Tables 3, 4 & 5, pages 1.70.6 - 1.70.8, from the clinical report synopsis of study DE132-010.

Revised tables with p-values as calculated per the above requests are provided in this amendment.

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 "Donald_Handley@ccmail.bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

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 CENTER FOR DRUG EVALUATION AND RESEARCH USE ONLY

APPLICATION NUMBER
N 20-928

REC'D
AUG 27 1998
MEGA DOC

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Pharmaceutical Research Institute	August 1998
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*)	CODE NAME (*if any*)
4-Hydroxyanisole (monomethyl ether of hydroquinone, 4-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)	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 009 - Amendment 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 Packaging Components
DMF Packaging Components

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

August 21, 1998

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
5600 Fishers Lane
Rockville, MD 20857

RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #009 to a Pending Application

Dear Dr. Wilkin:

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 a teleconference with representatives of Bristol-Myers Squibb (BMS) and the FDA on August 17, 1998, in which the status of [redacted] and the future supply of 4-hydroxyanisole was discussed.

This submission provides information on the status of [redacted] and our plans to qualify an alternate supplier of 4-hydroxyanisole, as discussed during the August 17th teleconference. This submission also amends the Drug Substance section of this application to name the alternate manufacturer of 4-hydroxyanisole.

[redacted]

On August 17, 1998, a teleconference was held with Mr. Frank Cross, Dr. Tony DeCamp and Dr. Bill Timmer of FDA, and Dr. Kathy Schrode and the undersigned of BMS, to discuss the supply status of 4-hydroxyanisole. In that teleconference, it was communicated that BMS began working with an alternate supplier of 4-hydroxyanisole several months ago. This new supplier, [redacted] has produced one lab scale batch and just recently completed three validation batches of 4-hydroxyanisole for BMS. The three validation batches are currently being shipped to BMS. The lab scale batch of 4-hydroxyanisole has been formulated into a lab scale batch of 4-hydroxyanisole/tretinoin topical solution which has shown acceptable stability over a three month period.

In order to qualify the [redacted] material, the following activities are planned:

- The three validation batches of [redacted] material will be placed on stability by [redacted] and will also be placed on stability by BMS, as requested by FDA during the teleconference.

- Three pilot scale batches of 4-hydroxyanisole/tretinoin topical solution will be produced with the three batches of [redacted] 4-hydroxyanisole and placed on stability.

Provided in this amendment is an updated Manufacturer's section of the Drug Substance section, listing the address of the [redacted] This is provided to expedite the request and scheduling of a pre-approval inspection of [redacted] Further details and documentation on the qualification of [redacted] will be provided in a future amendment. We are pursuing a commitment from [redacted] to file a drug master file with the initial stability data on the three batches by end-September. It is BMS's understanding from the teleconference that this approach will not extend the PDUFA date for this NDA.

Also, as requested during the teleconference, the quantity of bulk 4-hydroxyanisole material produced by [redacted] and held at BMS is [redacted] This quantity is sufficient to produce only [redacted] commercial lot of 4-hydroxyanisole/tretinoin topical solution.

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 "Donald_Handley@ccmail.bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

Redacted 2

pages of trade

secret and/or

confidential

commercial

information

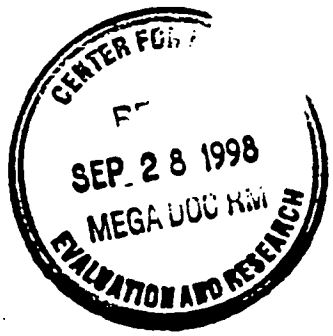
NDA ORIG AMENDMENT ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

September 17, 1998

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
5600 Fishers Lane
Rockville, MD 20857



RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #010 to a Pending Application

Dear Dr. Wilkin:

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. The purpose of this amendment is to update the proposed package insert, specifically the Pregnancy: Teratogenic Effects section, with new nonclinical reproductive toxicology data that have recently become available. As was noted in the Four-Month Safety Update to this NDA (Amendment #005, May 5, 1998), a repeat dermal embryo-fetal developmental study in rabbits, using extra preventative methods to eliminate potential ingestion of the test article, was initiated in March 1998. The final report of this study (Study No. 98612) is included in this submission.

The first dermal-teratology study in rabbits with 4-hydroxyanisole (4HA)/tretinoin solution (Study No. 92714, NDA volumes 1.18 & 1.19), showed a low incidence of teratogenic effects (marked hydrocephaly) in the mid-dose and high-dose 4HA/tretinoin groups, and the high-dose tretinoin group. Although these findings did not achieve statistical significance, they are consistent with effects that are known to be related to the retinoid component. The protocol-specified administration of the test articles in this study called for a collar to be placed on each animal prior to dosing and removed following the six-hour daily exposure period. However, the application site was not washed following the six-hour exposure period. It was thus possible that the animals could have ingested the test article in this study.

The repeat study, Study No. 98612, employed strict conditions to avoid ingestion of the test articles. Rabbits were restrained in stainless steel stocks during dose administration and for the subsequent six-hour exposure period. After the six-hour period, the application site was gently washed with warm water and a mild liquid soap, and then dried. Collars were then placed on the rabbits (worn continuously) and they were returned to a new set of clean cages. The procedures followed in this study are the same as employed in a recently published developmental toxicity study in rabbits of topically applied tretinoin[1]. Under the conditions in this repeat study, dermal administration of 4HA/tretinoin or tretinoin was not selectively toxic to development, and was neither embryo-fetal toxic nor teratogenic.

It has been recognized that the possible ingestion of the test article is a confounding factor in interpreting the results of topical tretinoin animal teratology studies.[1,2,3,4,5] While topical tretinoin has occasionally shown some evidence of teratogenicity in animal studies which were not strictly controlled for ingestion, studies that employed extra precautionary measures to avoid ingestion have not shown teratogenic effects.[1,6] The results from Study No. 98612 are consistent with other topical tretinoin products, and thus provide justification to label the 4HA/tretinoin topical solution accordingly. The attached proposed package insert therefore provides for [redacted] for this product, consistent with all other topical tretinoin products. Additionally, the low concentration of tretinoin in the 4HA/tretinoin topical solution (0.01%) compared with other marketed topical tretinoin products would not suggest any increased risk. Because animal studies are not always predictive of the human response, and as a matter of prudence, the proposed text conservatively contains restrictive wording that the product should not be used during pregnancy.

Included in this submission, besides a copy of the report for Study No. 98612, is a side-by-side comparison of the originally proposed package insert and the revised, proposed package insert noting text deletions and text additions. A non-marked-up proposed package insert is also provided.

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 "Donald_Handley@ccmail.bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

Submitted in duplicate

References:

Christian MS, Mitala JJ, Powers WJ, McKenzie BE, Latriano L. A developmental toxicity study of tretinoin emollient cream (Renova) applied topically to New Zealand white rabbits. J Am Acad Dermatol 1997;36:S67-76

Seegmiller RE, Ford WH, Carter MW, Mitala JJ, Powers WJ. A developmental toxicity study of tretinoin administered topically and orally to pregnant Wistar rats. J Am Acad Dermatol 1997;36:S60-66

Kochhar DM, Christian MS. Tretinoin: A review of the nonclinical developmental toxicology experience. J Am Acad Dermatol 1997;36:S47-59

Nau H. Embryotoxicity and Teratogenicity of Topical Retinoic Acid. Skin Pharmacol 1993;6(suppl 1):35-44

Buchan P, Evaluation of the Teratogenic Risk of Cutaneously Administered Retinoids. Skin Pharmacol 1993;6(suppl 1):45-52

Retin-A Micro (tretinoin gel) microsphere, 0.1%, package insert, February 1997

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 20922

JAN 21 1999

MEGA DOC Rin

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Pharmaceutical Research Institute	January 8, 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 013 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 test 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
DMF Depigmenting solution - Bristol-Myers Squibb Pharmaceuticals Research Institute
DMF 4-Hydroxyanisole
DMF Tretinoin DMF
DMF Packaging Components
DMF Packaging Components

FORM FDA 356h (4/97)

This application contains the following items: *(Check all that apply)*

	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50(c))
	4.	Chemistry section
		A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
		B. Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
		C. Methods validation package (e.g. 21 CFR 314.50(e)(2)(I), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
	7.	Clinical Microbiology section (e.g. 21 CFR 314.50(d)(4))
	8.	Clinical data section (e.g. 21 CFR 314.50(d)(5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR.314.50(d)(6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12.	Case reports forms (e.g. 314.50(f)(1), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306(k)(1))
	17.	Field copy certification (21 CFR 314.5(k)(3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER *(Specify)* Proposed Trade Name

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.
The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate.
Warning: a willfully false statement is a criminal offense. U.S.Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donald J Handley	Donald J. Handley, Manager	1/8/99

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
100 Forest Avenue, Buffalo, New York 14213-1091	(716) 887-7794

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

'HS, Reports Clearance Officer
)erwork Reduction Project (0910-0338)
.)ert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

Please DO NOT RETURN this form to this address.

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Bristol-Myers Squibb
Pharmaceutical Research Institute

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

January 8, 1999

than Wilkin, M.D., Director
sion of Dermatologic and Dental
)rug Products, HFD-540
ument Control Room
ce of Drug Evaluation V
ter for Drug Evaluation and Research
d and Drug Administration
) Fishers Lane
kville, MD 20857

RE: **NDA 20-922**
2% 4-hydroxyanisole/0.01% tretinoin
topical solution
Amendment #013 to a Pending Application

Vilkin:

erence is made to the original submission of NDA 20-922, for 2% 4-hydroxyanisole/0.01% noin topical solution, received at the Agency on December 30, 1997.

s submission requests the Division to submit the proposed trade name SOLAGÈ nounced so-la-jay) to the Nomenclature Committee for consideration as the trade name for 4-hydroxyanisole/tretinoin topical solution product that is the subject of this application.

here are any questions regarding this submission, please contact the undersigned by phone at 716-887-7794, by Fax at 716-887-3638, or by Internet Mail at ndleyd@bms.com".

Sincerely,

Donald J. Handley
Manager, Worldwide Regulatory Affairs

)r d in duplicate

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 2, 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% solution)
Amendment #020 to a Pending Application

Dear Dr. Wilkin:

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. The purpose of this submission is to inform the Agency that the United States Adopted Names (USAN) Council has recently adopted mequinol as the United States Adopted Name for 4-hydroxyanisole (BMS-181158). Mequinol is also the International Non-proprietary Name (INN) for 4-hydroxyanisole.

Bristol-Myers Squibb wishes to use the name mequinol in place of 4-hydroxyanisole as the established drug name in product labeling for Solagé Topical Solution. Attached, in this submission, is a letter from the USAN Council providing the Statement of Adoption for mequinol.

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 Affairs

Submitted in duplicate

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

DUPLICATE

NDA ORIG AMENDMENT
B2

February 5, 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**
2% 4-hydroxyanisole/0.01% tretinoin topical solution
Amendment #015 to a Pending Application

Dear Dr. Wilkin:

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 a telephone conversation with Mr. Frank Cross on January 22, 1999, in which Mr. Cross requested six copies of the draft labeling for the carton and bottle label in the form of color artwork proofs.

Included in this submission are six copies of the color artwork proofs of the proposed carton and bottle label. As a final trade name has not yet been approved for this product, a dummy name (Abcdgé) has been used in the artwork. Photocopies of the original color proof are being submitted. While the color of the carton and bottle label in the photocopies does not exactly match the original proof, all other style attributes are the same.

In addition, six copies of a revised package insert are included in this submission. The following changes have been made to the package insert since the last version submitted in Amendment #010, dated September 17, 1998:

1) Similar to other topical products containing tretinoin, the following statement has been added to the PRECAUTIONS: Information for Patients section:

This statement was added as item #3 of the Information for Patients section and all subsequent items were renumbered.

2) As noted in Amendment #014, dated February 5, 1999, and in response to an issue raised in the December 23, 1998 letter from the Agency, [redacted] has been removed from the INDICATIONS AND USAGE section. This phrase was also removed from the first sentence of the CLINICAL PHARMACOLOGY section and the second sentence of the PRECAUTIONS: Pediatric Use section.

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 Affairs

Submitted in duplicate

APPEARS THIS WAY
ON ORIGINAL

10 **Page(s) Redacted**

Draft

Labeling

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

February 18, 1999

NC

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**
2% 4-hydroxyanisole/0.01% tretinoin
topical solution
Amendment #017 to a Pending Application

Dear Dr. Wilkin:

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 a telephone conversation between the undersigned and Cmdr. Frank Cross on today's date.

As requested by Cmdr. Cross, Bristol-Myers Squibb hereby states that no patient package insert has been submitted for approval as part of this NDA.

Also, as requested, provided in a desk copy of this submission to Cmdr. Cross, is a 3.5" computer diskette containing a file of the package insert submitted on February 5, 1999 in amendment #015. The document is saved under the name [redacted] in Word 97 format.

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 Affairs

bmitted in duplicate
Desk copy and disk provided to Cmdr. Frank Cross

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

February 22, 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**
2% 4-hydroxyanisole/0.01% tretinoin
topical solution
Amendment #018 to a Pending Application
Declaration of Applicant: Exclusivity Information

Dear Dr. Wilkin:

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. In order to ensure that this application receives the exclusivity to which it is entitled, the following declarations are provided.

Bristol-Myers Squibb claims exclusivity for 2% 4-hydroxyanisole/0.01% tretinoin topical solution for three years from the date this application is approved. This application was submitted under Section 505 (b) of the Food, Drug and Cosmetic Act on December 30, 1997. This application (NDA 20-922) is for a drug product that contains an active moiety that was previously approved (tretinoin) in another application under Section 505 (b) of the Act, and contains reports of new clinical investigations (other than bioavailability studies) conducted or sponsored by the applicant, that are essential to the approval of the application.

The clinical studies qualify as "new clinical investigations" in that they were not previously relied upon for approval of another drug product, and do not duplicate any studies that were relied upon by the Agency for approval of another drug product. The studies are also "essential" in that there were no previously submitted studies that could support approval of this application. These studies were sponsored by the applicant under IND [redacted] for the product cited above.

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 Affairs

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

March 2, 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
(4-hydroxyanisole 2%, tretinoin 0.01% solution)
Amendment #019 to a Pending Application

Dear Dr. Wilkin:

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 a teleconference with Bristol-Myers Squibb personnel on February 22, 1999, in which members of FDA presented additional questions they have with the NDA. The purpose of this submission is to provide, as requested at the teleconference, a list of subjects who had halo hypopigmentation as an adverse event and were considered a treatment success.

Provided in this submission is a list of subjects from the two pivotal studies, DE132-005 and DE132-010, who were treated with 4-hydroxyanisole/tretinoin topical solution, had an event of halo hypopigmentation around at least one treated lesion on the face and/or arms, and were considered a treatment success. Each of the subjects were rated as having moderate improvement or greater (score of 3 or less) in the Physician's Global Assessment measure at the end of treatment. A total of 22 subjects are listed. This represents approximately 9% of the total population of subjects who were considered a treatment success.

In order to convey this information in product labeling, it is proposed to add a sentence under the Clinical Results section of the package insert, at the end of the paragraph shown below. The proposed sentence appears at the end of this paragraph in italics just for emphasis in this submission.

[redacted] *It should be noted that approximately 9% of patients who had moderate improvement or greater also* [redacted] *hypopigmentation of the skin surrounding at least one treated lesion.*

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 Affairs

Submitted in duplicate

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

March 4, 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

NEW CORRESP
NC

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

Request for Teleconference

Dear Dr. Wilkin:

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 teleconference held on February 22, 1999 with members of the Agency and Bristol-Myers Squibb.

The purpose of this submission is to request a teleconference with the Agency to discuss the Agency's rationale for pregnancy category X for this product. A written summary of specific points to be discussed in regard to the comments made by the Agency on the two rabbit dermal teratogenicity studies submitted in this NDA, will be submitted on or before March 9, 1999.

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

John Bedard, M.S., Vice President, Worldwide Regulatory Affairs
Robert Buroker, D.V.M., Director, Toxicology
Joseph Costa, Ph.D., Director, Drug Safety Evaluation
Elizabeth Lochry, Ph.D., Director, Reproductive Toxicology
Don Handley, M.S., Manager, Worldwide Regulatory Affairs
Kathy Schrode, Ph.D., Director, Worldwide Regulatory Affairs
Robert Williams, M.S., Manager, Toxicology

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 Affairs

Submitted in duplicate

CODE as BL
Per CSO

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 5, 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 021 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 Packaging Components
DMF Packaging Components
DMF

This application contains the following items: (*Check all that apply*)	
	1. Index
	2. Labeling (check one) √ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50(c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50(e)(2)(i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
	7. Clinical Microbiology section (e.g. 21 CFR 314.50(d)(4))
	8. Clinical data section (e.g. 21 CFR 314.50(d)(5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR.314.50(d)(6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12. Case reports forms (e.g. 314.50(f)(1), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306(k)(1))
	17. Field copy certification (21 CFR 314.5(k)(3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (*Specify*)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate. Warning: a willfully false statement is a criminal offense. U.S.Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donald J Handley	Donald J. Handley, Manager	3/5/99

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
100 Forest Avenue, Buffalo, New York 14213-1091	(716) 887-7794

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 5, 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% solution)
Amendment #021 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 with Bristol-Myers Squibb personnel on February 22, 1999, in which members of FDA presented additional questions they have with the NDA. The purpose of this submission is to provide proposed patient labeling and revised carton and bottle label artwork, as requested at the teleconference.

A copy of the proposed patient labeling is provided as a Word 97 document on a 3.5" computer diskette, under the filename "patient.doc." Six copies of the proposed patient labeling are included in this submission.

The carton and bottle label artwork have been revised with the following changes: 1) to add the trade name, Solagé; 2) to increase the prominence of the established drug names, mequinol and tretinoin, commensurate with the trade name; and, 3) to increase the prominence of the "Protect from light" storage statements. Six copies of the carton and bottle label artwork are 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 Affairs

Submitted in duplicate
Desk copy with computer diskette
provided to Cmdr. Frank Cross

APPEARS THIS WAY
ON ORIGINAL

11 **Page(s) Redacted**

Draft

Labeling

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

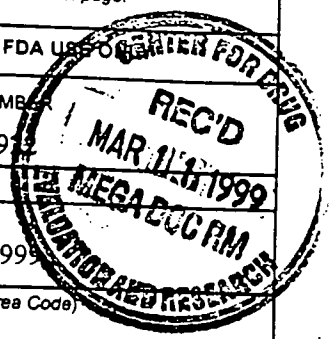
APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(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 20,9[illegible]



APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Pharmaceutical Research Institute	March 9, 199[illegible]
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 [redacted] 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 022 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
DMF — Depigmenting solution - Bristol-Myers Squibb Pharmaceuticals Research Institute
DMF — 4-Hydroxyanisole
DMF — Tretinoin
DMF — Packaging Components
DMF — Packaging Components
DMF [redacted]

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 9, 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% solution)
Amendment #022 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 with Bristol-Myers Squibb personnel on February 22, 1999, in which members of FDA presented additional questions they have with the NDA.

In the February 22 teleconference, the Agency indicated that labeling for this product should reflect pregnancy category X, and also provided comments on the two rabbit dermal teratogenicity studies submitted in the NDA. A teleconference has been scheduled for March 11, 1999 to further discuss these comments. A summary is provided in this submission to facilitate our discussion of these comments at the March 11 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 Affairs

Submitted in duplicate

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 20922

RECD MAR 17 1999 4:00 PM

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Bristol-Myers Squibb Pharmaceutical Research Institute	March 16, 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 023 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

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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
DMF	Tretinoin	
DMF	Packaging Components	
DMF	Packaging Components	

This application contains the following items: (*Check all that apply*)		
	1.	Index
	2.	Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3.	Summary (21 CFR 314.50(c))
	4.	Chemistry section
√	A.	Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
	B.	Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
	C.	Methods validation package (e.g. 21 CFR 314.50(e)(2)(I), 21 CFR 601.2)
	5.	Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
	6.	Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
	7.	Clinical Microbiology section (e.g. 21 CFR 314.50(d)(4))
	8.	Clinical data section (e.g. 21 CFR 314.50(d)(5), 21 CFR 601.2)
	9.	Safety update report (e.g. 21 CFR 314.50(d)(5)(vi)(b), 21 CFR 601.2)
	10.	Statistical section (e.g. 21 CFR.314.50(d)(6), 21 CFR 601.2)
	11.	Case report tabulations (e.g. 21 CFR 314.50(f)(1), 21 CFR 601.2)
	12.	Case reports forms (e.g. 314.50(f)(1), 21 CFR 601.2)
	13.	Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14.	A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
	15.	Establishment description (21 CFR Part 600, if applicable)
	16.	Debarment certification (FD&C Act 306(k)(1))
	17.	Field copy certification (21 CFR 314.5(k)(3))
	18.	User Fee Cover Sheet (Form FDA 3397)
	19.	OTHER (*Specify*)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge, are certified to be true and accurate. Warning: a willfully false statement is a criminal offense. U.S.Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Donald J Handley	Donald J. Handley, Manager	3/16/99

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
100 Forest Avenue, Buffalo, New York 14213-1091	(716) 887-7794

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to , a collection of information unless it displays a currently valid OMB control number

Please **DO NOT RETURN** this form to this address.

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 16, 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% solution)
Amendment #023 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 with the undersigned and Cmdr. Frank Cross and Dr. William Timmer on March 15, 1999. In that teleconference, Dr. Timmer requested stability data on batches of Solagé Topical Solution made with mequinol from [redacted]

Included in this submission are two stability reports. Report No. KRAZ-RJ-99004, entitled "4-Hydroxyanisole Drug Substance Stability Report," provides data generated by Bristol-Myers Squibb on three batches of mequinol from [redacted] It also includes data from studies continued by Bristol-Myers Squibb on three batches of mequinol obtained from [redacted] following [redacted] Report No. [redacted] 99007, entitled "BMS-181158/BMS-181159 Solution Stability Report," provides updated data on the stability studies reported in the original NDA filing, and includes data on three batches of Solagé Topical Solution made with mequinol from [redacted]

ORIGINAL

Bristol-Myers Squibb
Pharmaceutical Research Institute

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

March 22, 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

NEW CORRESP

NC

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

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.

The purpose of this submission is to request a teleconference with the Agency to discuss the changes made to the draft labeling components. We request that the teleconference be scheduled for Thursday, March 25, and also include Dr. Robert DeLap. The specific sections of the package insert we would like to discuss and the planned attendees from Bristol-Myers Squibb will be forwarded in a subsequent letter.

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

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