

NOV 10 1999

NDA 21-108

INFORMATION REQUEST LETTER

Johnson and Johnson Consumer Companies, Inc.
Attention: Mr. Paul Manley
Worldwide Director, Regulatory Affairs
199 Grandview Road
Skillman, NJ 08558

Dear Mr. Manley:

Please refer to your August 31, 1999 new drug application (NDA 21-108) for Renova (tretinoin emollient cream), 0.02%.

We also refer to your submissions dated October 13 and 25, 1999.

We are reviewing the clinical, chemistry, manufacturing, and controls, pharmacology and toxicology; biopharmaceutics, and statistical sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

Please submit the following information:

Clinical:

1. Please provide/describe any materials (i.e., as contained in investigator teaching materials) used to educate investigators regarding use of the 10-point scale for each of the proposed indications: the mitigation (palliation) of fine _____ wrinkles, mottled hyperpigmentation, _____ and tactile roughness of the facial skin.
2. On page 008-0128 (volume 1.21) under Efficacy Variables, you indicate that "A set of reference photographs depicting different grades of photodamage was given to each study center prior to the study to standardize grading criteria over time and across investigators. Grades for overall severity of photodamage and individual signs were assigned to the reference photographs by an expert consultant in conjunction with PRI. These photographs included subjects from a previous photodamage study depicting each grade of overall severity of photodamage." Please provide these photographs.

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3. Please provide information regarding the "custom designed table-top photographic system" that was used to take these photographs. A description of the equipment and layout used (including lighting, screens, and filters) should be provided.
4. Please provide in a table: initiation date, date first patient enrolled, date first patient treated, date last patient enrolled, date last patient treated, date of last patient visit, and completion dates for each of the studies referenced/included in your application. If this is already provided, please indicate the volume and page on which this table might be found and update this to include any additional studies submitted subsequent to the initial application.
5. Please provide a listing of original dates of protocol with dates of all subsequent amendments for studies J89-024 and J89-025. Please submit an original protocol with all amendments attached for the studies.

Chemistry:

1. Provide a line-by-line comparison between TEC I and TEC II formulations.
2. Provide a comprehensive list of investigational formulations used in the clinical studies.

Pharmacology/Toxicology:

1. As discussed in the teleconference on 12/5/97, the final reports of the Segment I studies should be submitted to the NDA in a timely manner while it is under review. Please provide complete draft reports within three months of submission of this NDA and final reports as soon as possible.
2. An 18-month photo co-carcinogenicity study was referenced in the briefing package for the pre-NDA meeting. The Sponsor was requested at that meeting to submit this study with the NDA. Please provide the final report for that study.

Biopharmaceutics:

Please provide the assay validation for _____ method.

Statistics:

For the pivotal trials, please provide a set of annotated case report forms indicating which data set has the results and the associated variable name for each recorded item on the form.

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NDA 21-108

Page 3

If you have any questions, contact Olga Cintron, Project Manager at (301) 827-2020.

Sincerely,

[/S/]

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FORWARD PLANNING MEETING MINUTES

NDA 21-108

Renova (tretinoin emollient cream), 0.02%

OCT 26 1999

Date: October 5, 1999.
Sponsor: Johnson & Johnson Consumer Companies, Inc.
Pharmacologic class: retinoid
Type: 3S
Indication: For use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.
Active ingredient: tretinoin
Filing Date: 10/29/99
Regulatory Due Date: 2/28/00
User Fee Due Date: 7/1/00 (10 month)

Attendees: Jonathan Wilkin, M.D., Director, HFD-540
Markham Luke, M.D., Ph.D., Medical Officer, HFD-540
Bill Timmer, Ph.D., Chemist, HFD-540
Mamta Guatam-Basak, Ph.D., Chemist, HFD-540
Wilson DeCamp, Ph.D., Chemistry Team Leader, HFD-540
Amy Nostrandt, Ph.D., Pharmacologist/Toxicologist, HFD-540
Abby Jacobs, Ph.D., Pharm/Tox Team Leader, HFD-540
Steve Thomson, Ph.D., Statistician, HFD-725
R. Srinivasan, Ph.D., Biostatistics Team Leader, HFD-725
D. Bashaw, Pharm.D., Biopharmaceutics Team Leader, HFD-880
Sue Chih Lee, Ph.D., Biopharmaceutics Reviewer, HFD-880
Tapash Ghosh, Ph.D., Biopharmaceutics Reviewer, HFD-880
Olga Cintron, R.Ph., Project Manager, HFD-540
Millie Wright, Project Manager, HFD-640

The meeting was convened to determine the fileability of NDA 21-108. All disciplines presented their comments in terms of general content and format requirements with respect to their section of the new drug application.

From a preliminary evaluation of the general content and format as well as the chemistry, manufacturing, and controls, pharmacology and toxicology, human pharmacokinetics, CMC microbiology, and statistical section of the application, it was recommended that NDA 21-108 be filed. It was recommended that an information request letter be issued to the sponsor.

From a clinical standpoint, a potential fileability issue was identified. The sponsor did not provide studies/evidence to support comparative efficacy between the TEC II (0.02%) formulation and the approved TEC I (0.05%) formulation.

It was concluded that filing of NDA 21-108 would be contingent to the sponsor providing this information before October 29, 1999.

Expected date of draft reviews if filed:	Chemistry	May 15, 2000
	Pharmacology	April 1, 2000
	Biopharmaceutics	March 15, 2000
	Biostatistics	March 30, 2000
	Clinical	March 1, 2000
	Microbiology (CMC)	October 30, 1999

The Labeling Day was estimated to be conducted by early June 2000.

Plan: Final fileability determination will be contingent to Sponsor providing data comparing the TEC II formulation and TEC I formulation before OCTOBER 29, 1999.

If the application is filed, an IR letter will be issued with the following requests (additional requests may be added by time the IR letter is issued):

1. Final reports of the Segment I studies should be submitted to the NDA in a timely manner while it is under review. At the very least, draft reports should be submitted within three months of submission of this NDA and final reports should be forthcoming.
2. As requested at the 5/5/97 Pre NDA meeting, the 18-month photo co-carcinogenicity study should be submitted to the NDA immediately.
3. A line-by-line comparison between TEC I and TEC II formulations needs to be submitted to the NDA.
4. A comprehensive list of investigational formulations used in the clinical studies needs to be submitted to the NDA.
5. Provide any representative photographs (i.e, as contained in investigator teaching materials) to support the use of a 10-point scale for each of the proposed indications: the mitigation (palliation) of fine _____ wrinkles, mottled hyperpigmentation, _____ and tactile roughness of the facial skin.

Addendum to the minutes:

On October 13, 1999, the Sponsor faxed to the Agency additional information to address the above mentioned fileability issue. The Agency noted that the Sponsor still failed to provide adequate comparative information between Renova 0.02% (TEC II - new formulation) and Renova 0.05% (TEC IA-marketed formulation).

The Sponsor was informed on October 25, 1999, that the application was filed. Additional questions may arise during the review process (i.e. dose ranging, differences in formulation,

cc:

Original NDA

21-108

HFD-540/DIV FILE

HFD-540/Wilkin

HFD-540/CHEM/Timmer

HFD-540/TL CHEM/DeCamp

HFD-540/PHARM/Nostrandt

HFD-540/TL PHARM/Jacobs

HFD-725/BIOSTAT/Thomson

HFD-725/TL BIOSTAT/Srinivasan

HFD-540/MO/Luke

HFD-880/SR BIOPHARM/Bashaw

HFD-880/BIOPHARM/Leei

HFD-540/SUPV PROJ MGR/Kozma-Fornaro

HFD-540/PROJ MGR/Cintron

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM OF TELEPHONE CONVERSATION

DATE: October 5, 1999.
DRUG: Renova (tretinoin emollient cream), 0.02%
NDA: 21-108
SPONSOR: Diana Uhl, Regulatory Affairs
Johnson and Johnson Consumer Companies, Inc.
FDA: Dr. Jonathan Wilkin, Director, DDDDP, HFD-540
Dr. Markham Luke, Medical Officer, DDDDP, HFD-540
Olga Cintron, Project Manager, DDDDP, HFD-540
Subject: Potential Fileability Issue for NDA 21-108

OCT 26 1999

U - 10/26/99

The Sponsor was contacted to request additional information and to find out if there was any information included in the NDA that would explain the clinical difference between the Renova 0.05% and Renova 0.02% formulations.

The Sponsor was encouraged to provide this information, if available, as quickly as possible, since this was being considered a fileability concern.

The Sponsor informed that this issue was to be forwarded to the team and that they would be working on it diligently.

Conversation ended amicably.

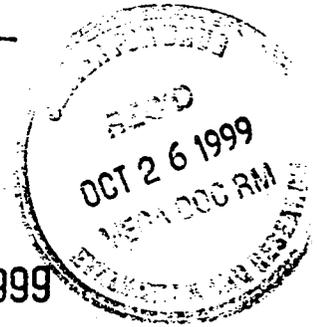
**APPEARS THIS WAY
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cc:
NDA 21-108
HFD-540/Div Files
HFD-540/Cintron

ORIGINAL

Johnson & Johnson
CONSUMER COMPANIES, INC.

BZ



OCT 25 1999

Dr. Jonathan Wilkin, Director
Div. of Dermatologic and Dental Drug Products
Food and Drug Administration
Center Drug Evaluation and Research
Document and Records Section
12229 Wilkins Avenue
Rockville, MD 20852

NDA 21-108
RENOVA®
(tretinoin emollient cream) 0.02%

Amendment to NDA

ORIG AMENDMENT

Dear Dr. Wilkin:

RENOVA® (tretinoin emollient cream) 0.02%

Purpose of Submission This submission amends NDA 21-108, which was submitted August 31, 1999 with information that may be helpful to your review.

Letters of Authorization Volume 1.3, page 0004 00037 references DMF — for the ingredient — which has been retired. This submission updates the NDA with the authorization letter for DMF —, the correct and valid DMF for this ingredient.

Item 19 Financial Disclosure: We are providing Form FDA 3454, a certification for the investigators of the pivotal studies to supplement the statement found in Volume 1.1, page 019 00001. This attests to the absence of financial interests and arrangements, as described in 21CFR54. All clinical studies submitted in NDA 21-108 concluded prior to the end of 1994; this was well before implementation of the financial disclosure rule. Aside from the pivotal trials, no other financial disclosure forms are available.

Item 3B Pharmacologic Class. Scientific Rationale. Intended Use. and Potential Clinical Benefits: The clinical differences between currently marketed RENOVA® (tretinoin emollient cream) 0.05% and TEC-II 0.02% are described in this supplement, which should be added to Volume 1.2 following page 003 00010.

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OCT 25 1999

RENOVA((tretinoin emollient cream) 0.02%, Continued

Item 4A Chemistry, Manufacturing and Controls: Volume 1.3, page 004 00037 references a retired DMF. Please replace this with the authorization letter to reference DMF —

Clinical Data The study synopses of five clinical trials that evaluated a 0.05% concentration of the TEC-II formulation are submitted to provide additional perspective on the development of this product.

SAS data sets Enclosed you will find a CD-ROM, that contains all of the SAS datasets and the code used to create the datasets. In addition, a listing of all coding formats used for each study is submitted.

Pediatric Use We are applying for a full waiver of the requirements under 21 CFR 314.55(a), because the drug product does not represent a meaningful therapeutic benefit and is not likely to be used in a substantial number of pediatric patients.

Additional Information The cut-off dates for the TEC-II NDA (21-108) ISS, ISE and Commercial Foreign Marketing Experience are as follows:

- ISS/Adverse events:
RETIN-A – 10/20/71 - 3/31/98
RENOVA (tretinoin 1A 0.05%) - 12/29/95 - 3/31/98
TEC-II- the cut-off date was 3/31/98; computer reports have a cut-off date for the end of the month preceding the print date, thus, the PRI data report was 4/3/98; the pages were compiled on 11/18/98

- ISS/Distribution:
RETIN-A- distribution of approximately 82,200.00 units as of 12/31/98.
RENOVA(tretinoin TEC 1A 0.05%) - distribution of approximately ——— units as of 12/31/98.
TEC-II- not yet distributed.

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ON ORIGINAL**

OCT 25 1999

RENOVA((tretinoin emollient cream) 0.02%, Continued

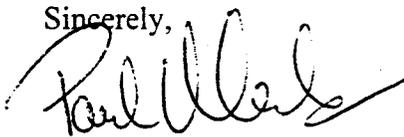
- **Commercial Marketing Experience:**
As of the date of this application, Tretinoin Emollient Cream 0.02%(TEC II) is not marketed anywhere in the world. Tretinoin Emollient Cream 0.05%(TEC-1A/Renova) is approved or under review in several countries worldwide.
- **ISE:**
PRI supporting data reports were run on 3/9/98, the pages were compiled on 8/19/98.

Questions

Should you have any questions, please contact me:

Directly	908-874-1625
FDA only line	908-874-1700
Fax	908-874-1118
e-mail	kville1@cpcus.jnj.com

Sincerely,



for Kathleen K. Wille, Ph.D.
Manager, Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

FORWARD PLANNING MEETING CHECKLIST

October 5, 1999.

OCT 15 1999

NDA 21-108 Renova (tretinoin emollient cream), 0.02%

Indication: For use in the mitigation (palliation) of fine _____ wrinkles, mottled hyperpigmentation, _____ and tactile roughness of facial skin.

Sponsor: Johnson & Johnson Consumer Companies, Inc.

Type: 3S

Filing Date: October 29, 1999. (Actual: October 31, 1999-Sunday)

User Fee Date: September 1, 2000.

Regulatory Due Date: February 28, 2000.

FILEABILITY:

On initial overview of the NDA application:

PROJECT MANAGEMENT:

- (1) Do any of the following apply to this application (i.e., if YES, the application **MUST BE REFUSED TO FILE** under 314.101 (e) and there is no filing over protest):
 - (a) Is the drug product already covered by an approved application?
No.
 - (b) Does the submission purport to be an abbreviated application under 314.55; however the drug product is not one for which FDA has made a finding that an abbreviated application is acceptable under 314.55(b)?
No.
 - (c) Is the drug product subject to licensing by FDA under the Public Service Act and Subchapter F of Chapter I of Title 21 of the CFR?
No.

- (2) Do any of the following apply to this application (i.e., if NO, the application **MAY BE REFUSED TO FILE** under 314.101(d) and there is the potential for filing over protest):
 - (a) Does the application contain a completed application form as required under 314.50 or 314.55?
Yes.
 - (b) On its face, does the application contain the sections of an application required by regulation and Center guidelines?
Yes. (Clinical, Biopharm, Statistics, Pharm/Tox, Chemistry)
 - (c) Has the applicant submitted a complete environmental assessment which addresses each of the items specified in the applicable format under 25.31 or has the applicant submitted evidence to establish that the product is under 25.24 of the CFR?

The sponsor is claiming categorical exclusion. Located in Volume 1.3, page 004 00088.

(d) On its face, is the NDA formatted in compliance with Center guidelines including integrated efficacy and safety summaries?

Yes. The ISE is located in Volume 1.56, page 008 15953, and the ISS is located in Volume 1.73, page 008 22888, of the NDA.

(e) Is the NDA indexed and paginated?

Yes.

(f) On its face, is the NDA legible?

Yes.

(g) Has the applicant submitted all required copies of the submission and various sections of the submission?

Yes.

(h) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor?

No. The following information requested at the 5/5/97 Pre NDA meeting was not submitted :

- 1. The 18-month photocarcinogenicity study,**
- 2. It was agreed with the sponsor in 1997 that the final reports of the Segment I reproductive study be submitted to the NDA in a timely manner. The sponsor did not provide an indication as to when these reports will be submitted.**
- 3. A line-by-line comparison between TEC I and TEC II formulations.**
- 4. A comprehensive list of investigational formulations used in the clinical studies.**

(i) Does the application contain a statement that all nonclinical laboratory studies were conducted in compliance with the requirements set forth in Part 58 or a statement why a study was not conducted in compliance with those requirements?

No. However, the pharmacologist confirmed that most non clinical studies submitted are referencing those for the Renova approved NDA.

(j) If required, has the applicant submitted carcinogenicity studies?

Sponsor was granted a waiver for carcinogenicity studies at the Pre NDA meeting.

(k) On its face, does the application contain at least two adequate and well-controlled clinical trials?

Yes. (Two placebo-controlled studies: J89-024 AND J89-025)

- (l) Does the application contain a statement that all clinical trials were conducted in accord with the IRB/Declaration of Helsinki provisions of the CFR?
Yes. Located in several volumes, per each clinical study performed.
- (m) Have all articles/study reports been submitted whether in English or translated into English?
Yes.
- (n) Has the applicant submitted draft labeling in compliance with 210.56 and 210.57 of the CFR?
Yes, located in Volume 1.1.
- (o) Has the applicant submitted the required FRAUD POLICY notice?
Yes. Located in Volume 1.1.
- (p) Has the applicant submitted copies of all package inserts (or their equivalent) from all countries in which this product has been previously approved for marketing? Have all non-English package inserts been translated?
Not applicable.
- (q) Has the applicant stated that the integrated summary of safety includes all safety data for this product of which they are aware from all sources, domestic and foreign? What is the cut-off date for the preparation of the ISS?
Yes. The cut off-date is not provided.
- (r) If this is a CANDAs submission, has the applicant submitted a statement to the archival NDA that the text, tables, and data in the CANDAs and the archival hardcopy NDA are identical? If they are not identical, is there a letter to the archival NDA that specifies distinctly ALL of the differences in the two submissions?
Not applicable.
- (3) From a project management perspective, is this NDA fileable? If "no". please state on the reverse why it is not.

The financial disclosure requirements seems to be adequately addressed, although the FDA 3454 was not included in the NDA.

The sponsor still needs to meet the Pediatric Rule requirements. An acknowledgement letter was issued to the sponsor on September 17, 1999, indicating that if they believe that this drug qualifies for a waiver, a request should be submitted with supportive information in accordance with the provisions of 21 CFR 314.55.

This NDA is fileable from a project management perspective.

Although not fileability issues, the following items are required from the sponsor:

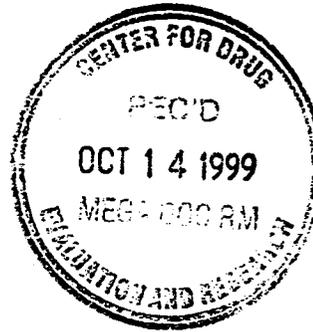
1. Cut off-date for the ISS preparation (item Q)
2. FDA 3454 form- Certification: Financial interests and arrangements of clinical investigators

[/S/] 10/15/99
Project Manager

[/S/] 10/15/99
Supervisory Project Manager

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Johnson & Johnson
CONSUMER COMPANIES, INC.



13 October, 1999

ORIG NEW CORRE
NC

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

NDA 21-108
RENOVA® (tretinoin emollient cream) 0.02%

Attn: Olga Cintron, Project Manager

Dear Dr. Wilkin,

Enclosed you will find copies of the study synopses of five clinical trials which were conducted under IND _____ and are included here in reference to NDA 21-108. IND _____ was opened to all tretinoin formulations for photodamage, and included studies for the marketed RENOVA® 0.05% formulation and all additional formulations that have been conducted under this IND. The study synopses that follow describe studies conducted to evaluate a new formulation, which is internally referred to as TEC-II 0.05% and a vehicle control in photodamaged skin.

We believe these studies may be helpful to your consideration of NDA 21-108 because they involve a higher concentration of the active ingredient, tretinoin. Since the program for the TEC-II 0.05% was discontinued, these synopses focus more on safety experience than the efficacy of the higher concentration formulation.

For your reference, study reports for all five of these protocols were submitted to IND _____ on November 6, 1996 in serial submission number 167.

Overview of protocols:

Three **Protocols (J89-022, J89-023 and J89-033)** shared a common design: each was a double-blind, randomized, single-center, vehicle-controlled, parallel study of either TEC-II 0.05% in 40 patients or vehicle in 40 patients applied to the face once at bedtime for a treatment period of 24 weeks. Patients from these studies were eligible for **Protocol K-90-010**, which was an additional 12 weeks of observation; patients did not use any treatment during this 12-week period.

Protocol J89-035 used a double-blind, randomized, single-center, vehicle-controlled, design with four treatment groups with TEC-II 0.05% applied to one or two of three of the following treatment areas: the face, the right forearm/hand, and the left forearm/hand. Originally intended to recruit 10 non-Caucasian patients for each treatment group, the study was discontinued after enrolling 17 patients because enrollment had been slow and because the program for this formulation was discontinued. Please note that biopsies were obtained from patients in this study. The specimens were sent to _____ and embedded in paraffin blocks. However, no sections were prepared, stained or read. We have been informed by the pathologist at _____ that the paraffin blocks are not available and we therefore considered these specimens lost for purpose of analysis.

A synopsis of each of these studies is included in this submission.

Assessment of safety in Protocols with treatment (J89-022, J89-023, J89-033 and J89-035):

Three tables are attached to give an indication of the safety experience in studies (J89-022, J89-023, J89-033 and J89-035) in which there was actual treatment with either TEC-II 0.05% or vehicle. These tables do not include information from Protocol K-90-010 because it involved patients who had stopped treatment with either TEC-II 0.05% or vehicle at the end of the preceding protocol.

Table 1 presents the percentage of patients in each treatment group who completed the study. At least 88% of all treatment groups completed the study, indicating that few patients were lost to follow-up.

Table 2 presents a listing of the patients who discontinued treatment because of an adverse event by treatment group. One patient using vehicle was hospitalized for rupture of a vertebral disc and one patient using TEC-II 0.05% died of an acute myocardial infarction. Neither of these serious adverse events was considered by either the investigator or the sponsor to be related to treatment.

Table 3 presents the number of patients with common adverse events associated with the treatment site for the four efficacy studies involving treatment with TEC-II 0.02% (J89-024, J89-025, J89-045 and K90-011) and the four studies involving TEC-II 0.05% (J89-022, J89-023, J89-033, J89-035). Also presented are the pooled results for the TEC-II 0.02% and TEC-II 0.05% studies and their odds ratios, incidence rates and confidence intervals.

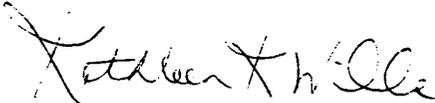
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The following observations can be made:

- The odds ratios for the four TEC-II 0.02% studies are consistent (Breslow-Day p-value 0.680)
- The odds ratios for the four TEC-II 0.05% studies are consistent (Breslow-Day p-value 0.536)
- The pooled odds ratio for the TEC-II 0.05% studies is about twice that of the TEC-II 0.02% studies
- The proportion of Vehicle-treated patients with treatment site adverse events is consistent for the TEC-II 0.02% and TEC-II 0.05% studies
- The proportion of TEC-II 0.05% patients with treatment site adverse events is approximately 50% greater than that of TEC-II 0.02% patients in these studies.

Please do not hesitate to contact me at 908-874-1625 if you have any questions.

Sincerely,



Kathleen K. Wille, Ph.D.
Regulatory Affairs Manager
Johnson & Johnson Consumer Companies

**APPEARS THIS WAY
ON ORIGINAL**

**STATISTICAL REVIEW AND EVALUATION: 21 DAY FORWARD PLANNING
MEETING REVIEW**

(COMPLETED REVIEW FOR INTERNAL DISTRIBUTION ONLY)

NDA: 21-108
 DRUG CLASS: 3S
 NAME OF DRUG: RENOVA® (tretinoin emollient cream), 0.02%
 APPLICANT: Johnson & Johnson

FILING DATE: 10/27/99
 INDICATION(S): Mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.

NUMBER AND TYPE OF CONTROLLED CLINICAL STUDIES: Reports for two completed randomized, double-blinded, vehicle controlled, parallel group studies were provided.

STATISTICAL REVIEWER: S. Thomson
 CLINICAL REVIEWER: M. Luke
 PROJECT MANAGER: O. Cintron

FORWARD PLANNING MEETING DATE: 10/05/99
 WAS THE NDA FILED: YES
 IF YES, REG.DUE DATE: 28/02/00
 USER FEE DATE: 09/01/00

I. ORGANIZATION AND DATA PRESENTATION

YES NO N/A

- | | | | |
|--|---------------------------------|---|---|
| *A. Is there a comprehensive table of contents with adequate indexing and pagination? | √ | — | — |
| *B. Are the original protocols, protocol amendments, and proposed label provided? | √ | — | — |
| *C. Are the following tables/listings provided in each study report? | | | |
| 1. Patient profile listings by center (includes all enrolled patients). | √ | — | — |
| 2. Lost subject tables by center which includes reason and time of loss. | √ | — | — |
| 3. Intermediate analysis summary tables (gender, age, race/ethnic, etc.). | — | √ | — |
| | (Baseline characteristics only) | | |
| 4. Pathogen listings. | — | — | √ |
| *D. Adverse event listings by center and time of occurrence relative to enrollment date. | √ | — | — |

- *1. Are adverse events from cited sources (foreign and domestic) provided?
- *E. Is a CANDAR or an electronic submission of the data necessary?
- *F. If the data have been submitted electronically, has adequate documentation of the data sets been provided?
- G. Are inclusion/exclusion (evaluability) criteria adequately coded and described:
- *H. Are there discrepancies between CRF information and CANDAR/Jacket data?
- I. If the data have been submitted electronically, can laboratory data be easily merged across studies and indications?

II. STATISTICAL METHODOLOGY

YES NO N/A

- *A. Are all primary efficacy studies of appropriate design to meet basic approvability requirements, within current Divisional policy statements or to the extent agreed upon previously with the sponsor by the Division?
- *B. For each study, is there a comprehensive statistical summary of the efficacy analyses which covers the intent-to-treat population, evaluable subject population and other applicable sub populations (age, gender, race/ethnicity, etc.)?
(evaluable only)
- C. Based on the summary analyses of each study, do you believe:
 - *1. The analyses are appropriate for the type data collected, the study design, and the study objectives (based on protocol and proposed label claims)?
 - *2. Intent-to-treat (ITT and MITT) analyses are properly performed?
 - 3. Sufficient and appropriate references were included for novel statistical approaches?
- *D. If interim analyses were performed, were they planned in the protocol and were appropriate significance level adjustments made?

E. Are there studies which are incomplete or ongoing? _____ √ _____

F. Is there a comprehensive, adequate analysis of safety data as recommended in the Clinical/Statistical Guideline? _____ √ _____

III. FILEABILITY CONCLUSIONS

From a statistical perspective is this submission, or indications therein, reviewable with only minor further input from the sponsor?

Provided data and codebooks are sent, Yes.

[/S/] 10-07-99

Steve Thomson
Mathematical Statistician, Biometrics III

[/S/] 10/07/99

Concur: R Srinivasan, Ph.D.
Team Leader, Biometrics III

cc:
Archival NDA 21-108
HFD-540
HFD-540/Dr. Wilkin
HFD-540/Dr. Luke
HFD-540/Dr. Walker
HFD-540/Ms. Cintron
HFD-725/Dr. Huque
HFD-725/Mr. Thomson
HFD-725/Dr. Srinivasan
HFD-344/Dr. Lepay
Chron.

* These items, if not included or if incorrect, are justifiable reasons for not filing the NDA.

* These items, if not acceptable, are reason to consider not filing.

* It is the Agency's intent that all submissions be CANDARs or electronic in format in 1995. Clearly, we do not need CANDARs for every submission, but, just as clearly, we need data on disks if we are to do an expeditious review. Since the company, in all likelihood, used computers to do their evaluations, all data should be readily available to us on disk, at least, for our use in the review action.

√ At this point of time, not applicable.

NDA 21-108

45 DAY MEETING CHECKLIST

FILEABILITY:

On initial overview of the NDA application:

YES

NO

BIOPHARMACEUTICAL:

- (1) On its face, is the biopharmaceutics section of the NDA organized in a manner to allow substantive review to begin? ✓
- (2) Is the biopharmaceutical section of the NDA indexed and paginated in a manner to allow substantive review to begin? ✓
- (3) On its face, is the biopharmaceutics section of the NDA legible so that substantive review can begin? ✓
- (4) Are the Phase 1 studies of appropriate design and breadth of investigation to meet basic pharmacokinetic characterization requirements for approvability of this product? ✓
- (5) If several formulations of the product were used in the clinical development of the product, has the sponsor submitted biopharmaceutics data to allow comparisons of and establish the equivalence of the product to be marketed and the product(s) used in the clinical development? N/A
- (6) From a biopharmaceutic perspective, is the NDA fileable? If "no", please state below why it is not? ✓

[/S/] 10/5/99

Reviewing Medical Officer

Biopharm Reviewer

[/S/] 10/10/99

Supervisory Medical Officer

APPEARS THIS WAY ON ORIGINAL

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

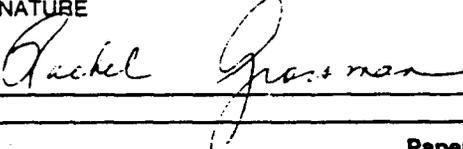
Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether: the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	
------------------------	--

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Rachel M. Grossman, MD	Worldwide Medical Director
FIRM/ORGANIZATION	
Johnson & Johnson Consumer Products Worldwide	
SIGNATURE	DATE
	October 5, 1999

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

The sponsor was also told at the pre-NDA meeting that the vehicle may affect photo co-carcinogenicity test results. The sponsor was asked to address this and justify cross-reference to a previous study if a new study was not performed. The pre-NDA meeting minutes note mention of an 18-month photo co-carcinogenicity study and a request that the study be submitted with the NDA. There does not appear to be a study report for such a study included with the submission.

- (5) If the formulation to be marketed is different from the formulation used in the toxicology studies, has the Sponsor made an appropriate effort to either repeat the studies using the to be marketed product or to explain why such repetition should not be required? X

Comments?

Most of the nonclinical data to support this application is being cross-referenced from NDA 19-963 for Renova 0.05% cream. The proposed drug product has a different formulation. The sponsor was told at the pre-NDA meeting that the decision to request additional animal studies would depend on human percutaneous absorption data with the proposed drug product.

- (6) Are the proposed labeling sections relative to pharm/tox appropriate (including human dose multiples expressed in either mg/m² or comparative serum/plasma levels) and in accordance with 201.57? X

Comments?

Human dose multiples are expressed on a mg/kg basis and will need to be revised.

- (7) Has the Sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor?

Comments? not applicable

- (8) On its face, does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the Sponsor submitted a rationale to justify the alternative route? X

Comments?

- (9) Has the Sponsor submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations? X

Comments?

- (10) Has the Sponsor submitted the data from the nonclinical carcinogenicity studies, in the STUDIES electronic format, for the review by Biometrics?

Comments? not applicable

(11) Has the Sponsor submitted a statement(s) that the pharm/tox studies have been performed using acceptable, state-of-the-art protocols which also reflect agency animal welfare concerns? _____ X _____
Comments?

(12) From a pharmacology perspective, is this NDA fileable? If "no", please state below why it is not. _____ X _____

(13) If the NDA is fileable, are there any issues that need to be conveyed to Sponsor? If so, specify: _____ X _____

As discussed in the teleconference on 12/5/97, the final reports of the segment I studies should be submitted to the NDA in a timely manner while it is under review. At the very least, draft reports should be submitted within three months of submission of this NDA and final reports should be forthcoming.

An 18-month photo co-carcinogenicity study was referenced in the briefing package for the pre-NDA meeting. The sponsor was requested to submit this study with the NDA at that meeting. That study should be submitted immediately.

(14) Issues that should not be conveyed to the Sponsor:

[/S/] 10/5/99
Reviewing Pharmacology Officer

[/S/] 10/5/99
Pharmacology Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

OCT 5 1999

NDA 21-108: RENOVA

Tretinoin Emollient Cream 0.02%

45-Day Forward Planning Meeting

1. The checklist is attached to this document
2. The classification code is 3, S: 3 since it is a new formulation and S for standard review.
3. DMFs which are cited:

DMF
DMF
DMF
DMF
DMF
DMF
DMF

DMF Number	Date of LOA	Date of Last Review	Completion Date
—	8/5/98	NA	1/00
—	8/14/98	NA	1/00
—	6/15/98	8/98	1/00
—	6/29/98	NA	1/00
—	7/1/98	8/93	1/00
—	2/10/98	NA	1/00
—	6/25/98	NA	1/00

4. RENOVA is an approved tradename.
5. A microbiological consult will be required.

6. The EER request was submitted in 9/99. There are a total of 9 facilities of which two are foreign. All of the inspections are complete (and acceptable) except for
7. The sponsor is claiming a categorical exclusion to the environmental assessment.
8. The estimated date of completion of the NDA is May 2000.

**APPEARS THIS WAY
ON ORIGINAL**

CMC SECTION CHECKLIST:

YES NO

- (1) Is the CMC section organized in a manner to allow substantive review to begin? -X-
- (2) Is the CMC section indexed and paginated in a manner to allow substantive review to begin? -X-
- (3) Is the CMC section legible so that substantive review can begin? -X-
- (4) Are all the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full street addresses? -X-
- (5) Has the sponsor submitted an environmental impact assessment or a categorical exclusion? -X-
- (6) Has the sponsor developed appropriate controls assessment procedures that are currently ready for FDA verification? -X-
- (7) For an antibiotic, has the sponsor submitted an appropriate validation package and committed to the readiness of exhibit samples? -X-
- (8) Has the sponsor submitted all special studies/data requested by the Division during pre-submission discussions with the sponsor? -X-
- (9) Has the sponsor submitted draft labeling consistent with 21 CFR 201.56 and 201.57, current Division labeling policies, and the design of the development package? -X-
- (10) Has the sponsor submitted stability data to support and justify the proposed expiry? -X-
- (11) Has the sponsor submitted a summary which lists the batch size, formulation, and site of production, for all pivotal clinical batches manufactured in support of the NDA? -X-
- (12) Is this NDA fileable from a CMC perspective? If "No," please explain. -X-

[/S/]

Reviewing Chemist

[/S/] 10/5/99

Chemistry Team Leader

5 October 99.

5 DAY MEETING CHECKLIST

OCT -4 1999

FILEABILITY:

On initial overview of the NDA application: YES (Fileable)

CLINICAL:

1. On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin? YES
2. Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin? YES
3. On its face, is the clinical section of the NDA legible so that substantive review can begin? YES
4. If needed, has the sponsor made an appropriate attempt to determine the most appropriate dosage and schedule for this product (i.e., appropriately designed dose- ranging studies)? Metered dosing (not in packaging?)

Study Number:

Study Title:

Sample Size:

Arms:

NDA Volume:

Pages:

Reviewer's Comment - No dose ranging studies, no efficacy studies comparing TEC-II and Renova 0.05% (TEC-IA).

5. On its face, do there appear to be the requisite number of adequate and well-controlled studies in the application? YES

Application Type: 505(b)(1) (Y/N)

505(b)(1)

505 (b) (2) (Y/N) Reference drug:

Is this correct filing?

Potential fileability issue: How is 0.02% TEC-II different from 0.05% in clinical effect? What are the claimed additional clinical benefits? Does the Sponsor plan to remove the 0.05% product from the market? This NDA was not filed as a line extension. Many changes are proposed in the label.

If there is a difference should a different drug product name be used (for chemistry)?

Identification of pivotal trials:

YES

Pivotal Study #1: Protocol Number:

J89-024

Location in NDA: Protocol:

Study Report:

Vol. 1.21 p008-1094

Study Title: Double-Blind, Multi-Center, Vehicle-Controlled Study to Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II) 0.02% in the Treatment of Photodamaged Skin.

Study design: Randomized (Y) Double Blind (Y) Placebo controlled (Y)
Multicentered (3) Caucasian (100%)

Indication: Photodamaged skin

Study arms (dosage, duration, treatment length for each arm):
TEC-II vs. vehicle
0.25 g per application q.h.s.
24 weeks

Efficacy endpoints (Primary and secondary):

Primary Endpoints – Global Evaluation at Week 24
1=Worse, 2=NoChange, 3=Slightly Improved, 4=Improved, 5=Much Imp.
Overall Severity at Week 24
Improved from Baseline (0-9 scale with 9 being worse)
Overall Subject Self-Assessment at Week 24
1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

Secondary Endpoints –

Clinical Signs – FW (Fine Wrinkling)
MH (Mottled Hyperpigmentation)
Roughness
CW (Coarse Wrinkling)
Yellowing
Laxity

How measured –

Improvement = reduction from baseline to week 24 of one or more units on 0-9 scale.

Subject Self-Assessment - SW (Small Wrinkles)
Tone (pink/rosy tone)
Color (“brown spots”/blotchiness)
Texture
Tightness
Pores

How measured –

1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

Crow’s Feet Replicas

Reviewer’s Comments - Parameter definition not clear.

Cheek Replicas

Reviewer’s Comments - Parameter definition not clear.

Further review of the replicas and methods used is needed.

Pivotal Study #2: Protocol Number: J89-025
Location in NDA: Protocol: Study Report: Vol 1.25 p001-2954
Study Title: Double-Blind, Multi-Center, Vehicle-Controlled Study to
Evaluate the Safety and Efficacy of Tretinoin Emollient Cream (TEC-II)
0.02% in the Treatment of Photodamaged Skin.

Study design: Randomized (Y) Double Blind (Y) Placebo controlled (Y)
Multicentered (3) Caucasian (100%)

Indication: Photodamaged skin

Study arms (dosage, duration, treatment length for each arm):

TEC-II vs. vehicle

0.25 g per application q.h.s.

24 weeks

Efficacy endpoints (Primary and secondary):

Primary Endpoints – Global Evaluation at Week 24

1=Worse, 2=NoChange, 3=Slightly Improved, 4=Improved, 5=Much Imp.

Overall Severity at Week 24

Improved from Baseline (0-9 scale with 9 being worse)

Overall Subject Self-Assessment at Week 24

1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

Secondary Endpoints –

Clinical Signs –

FW (Fine Wrinkling)

MH (Mottled Hyperpigmentation)

Roughness

CW (Coarse Wrinkling)

Yellowing

Laxity

How measured –

Improvement = reduction from baseline to week 24 of one or more units on 0-9 scale.

Subject Self-Assessment -

SW (Small Wrinkles)

Tone (pink/rosy tone)

Color (“brown spots”/blotchiness)

Texture

Tightness

Pores

How measured –

1=Worse, 2=The Same, 3=Somewhat Improved, 4=Much Improved

Crow’s Feet Replicas

Reviewer’s Comments - Parameter definition not clear.

Cheek Replicas

Reviewer's Comments - Parameter definition not clear.

Potential Review Issue - The Applicant does not have any non-Caucasian subjects in either of the two pivotal studies. A separate study, L-91-026 was conducted enrolling only minorities. The applicant demonstrated that improvement was comparable or slightly less than that exhibited by subjects receiving vehicle. Thus, a demonstration may have been made that Renova 0.02% is not effective in a non-Caucasian population. If the Applicant had included a demographically heterogeneous population in its pivotal study this problem would not be as blatant.

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling? To be determined during NDA review process.

Proposed indication from sponsor's draft labeling:

"INDICATIONS AND USAGE:

(To understand fully the indication for this product, please read the entire INDICATIONS AND USAGE section of the labeling.)



As designed, could endpoints in pivotal trial #1 support labeling?
To be determined during NDA review.

As designed, could endpoints in pivotal trial #2 support labeling?
To be determined during NDA review.

7. Are all data sets for pivotal efficacy studies complete for all indications (indications) requested? (this is a stat question?)
Biostatistics to help determine.

8. Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?
To be determined during review.

PreIND Mtg: None held.

IND number/s: _____

PreIND Mtg Date: None held.

EP2 Meeting Date: None held.

Agency response to Phase 3 protocols: None were submitted and no responses are available.

PreNDA meeting date: May 5, 1997

Potential review issue: Both pivotal studies use a Dispensing Cap for dosing which may not appear in the to-be-marketed product.

Do endpoints as described by sponsor in pivotal Study 1 conform to previous agency commitments?

No previous commitments.

Do endpoints as described by sponsor in pivotal Study 2 conform to previous agency commitments?

No previous commitments.

- | | | |
|-----|---|--|
| 9. | Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division? | In Vols.
155 to 168.
Not included
in Clinical. |
| 10. | Has the application submitted a rationale for assuming the applicability of foreign data (disease specific microbiologic specific) in the submission to the US population? | N/A |
| 11. | Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? | N/A |
| 12. | Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division? | YES
N/A |
| 13. | Has the applicant presented a safety assessment based on all current world-wide knowledge regarding this product? | YES |
| 14. | Has the applicant submitted draft -labeling consistent with 21CFR 201.56 and 21CFR 201.57, current divisional policies, and the design of the development package (on its face)? | YES |
| 15. | Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? | Phase IV
commitments
from NDA
19-963 are
still not
fulfilled. |
| 16. | From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. | YES |

Reviewer's Comment - The Sponsor lacks a comparative study between Renova 0.05% (current marketed product) and Renova 0.02%. There is no evidence

based on cursory review that the new product is an improvement over the old product.

Information to be requested from Applicant:

- 1) What portions of this NDA are available in electronic format? If the Sponsor could provide these portions on a CD-ROM, this would facilitate timely review. Adobe Acrobat and Word formatted files are most convenient.
- 2) The Sponsor should provide any representative photographs (i.e., as contained in investigator teaching materials) to support the use of a 10-point scale for each of the proposed indications: the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin.
- 3) The Sponsor should provide any information regarding the difference between Renova 0.02% and Renova 0.05% in proposed clinical effect.

[/S/]
10/5/99

[/S/] 10/4/1999

Reviewing Medical Officer

[/S/]

Dermatology Team Leader

**APPEARS THIS WAY
ON ORIGINAL**

Olga Cintron, R.Ph.
Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V
Division of Dermatologic and Dental
Drug Products - HFD #540
9201 Corporate Blvd.
Rockville, Maryland 20850

CORRESPONDANCE

NDA 21-108
RENOVA® (tretinoin emollient cream) 0.02%



Dear Ms. Cintron:

Background

- Reference is made to our New Drug Application 21-108 submitted on September 1, 1999 for RENOVA (tretinoin emollient cream) 0.02%.
- On September 17, 1999 we received a facsimile transmission from you requesting additional information in preparation for the filing meeting.
- On September 17, 1999 Dr. Bill Timmer called me with a comment on the submission. The comment was to confirm the availability of tretinoin from _____ and clarification on the addresses of our manufacturing sites.

Purpose of Submission

- At this time we wish to provide the information requested by you and Dr. Timmer.

CM&C Responses

- The address and zip code of Ortho Pharmaceutical in Manati, Puerto Rico is listed correctly in NDA 21-108 in Volume 1.2 page 003 00028.
- The location of Ortho Biotech is listed in the NDA at 1000 Route 202 Raritan, NJ 08869 because this is location of the microbiological laboratories. The administrative office for Ortho Biotech is located at 700 Route 202 Raritan, NJ 08869.
- We have confirmed that _____ will continue to be a supplier of tretinoin for the foreseeable future.

History of Meetings

- On May 5, 1997 a Pre-NDA meeting was held with FDA at which the Agency reviewed our planned data package for this NDA. Comments provided at this meeting have been taken into account within the application.
- No other meetings have occurred with the Agency on this formulation.

Continued on next page

SEP 23 1999

**Foreign
Labeling**

- Foreign labeling is not available for this drug product because RENOVA 0.02% is not marketed anywhere in the world.

**Additional
Desk Copies**

- Four additional desk copies of volumes 1.1, 1.2, 1.18, 1.56 and 1.73 are included.

Questions

In the interim, should you have any questions, please contact me:

- Directly (908) 874-1239
- Our phone number dedicated for FDA use (908) 874-1700
- Fax (908) 904-3480
- E-mail pmanley@cpcus.jnj.com

Sincerely,

Kelly Johnson for

Paul F. Manley
Worldwide Director
Regulatory Affairs

Desk Copy: Dr. Bill Timmer, Chemist, Division of Dermatologic and Dental Products.

**APPEARS THIS WAY
ON ORIGINAL**

Division of Dermatologic and Dental Drug Products

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

FACSIMILE TRANSMISSION

DATE: September 17, 1999. Number of Pages (including cover sheet) 1
TO: Mr. Paul Manley, Worldwide Director, Regulatory Affairs
COMPANY: Johnson & Johnson Consumer Companies
NUMBER: 908-904-3480
MESSAGE: RE: NDA 21-108 Renova (tretinoin emollient cream), 0.02%

Please provide the following items in preparation for the filing meeting:

1. A history/list of all the meetings/telecons, including dates, between the Applicant and the Agency regarding the development of Renova 0.02%.
2. Submit translated copies of all foreign labeling for this drug product. *- not marked*
3. Submit additional 4 desk copies of Volume 1.1 and Volume 1.2.
4. Submit additional desk copies of volumes 18, 56, 73.
5. Please confirm the availability of tretinoin from _____ (per conversation with Dr. Timmer).

Thanks in advance for your help. The desk copies should be sent to my attention at 9201 Corporate Blvd., Room N-248, Rockville, MD 20850.

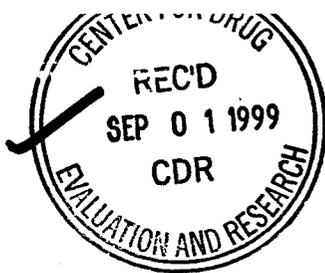
NOTE: We are providing the attached information via telefacsimile for your convenience. Please feel free to contact me if you have any questions regarding the contents of this transmission.

FROM: Olga Cintron, R.Ph.
TITLE: Project Manager
TELEPHONE: 301-827-2020

FAX NUMBER: 301-827-2075

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

*NDA 21-108
HFD 540/Div Files*



Johnson & Johnson
CONSUMER COMPANIES, INC.

AUG 31 1999

Jonathan Wilkin, M.D.
Food and Drug Administration
Center for Drug Evaluation and Research
Document and Records Section
12229 Wilkins Avenue
Rockville, Maryland 20852

NDA 21-108

RENOVA® (tretinoin emollient cream) 0.02%

RENOVA® (tretinoin emollient cream) 0.02%

Dear Dr. Wilkin:

Purpose of Submission

- Pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.50, we submit herewith a New Drug Application for RENOVA® (tretinoin emollient cream) 0.02%.
- RENOVA® (tretinoin emollient cream) 0.02% is indicated for the use in the mitigation (palliation) of fine _____ wrinkles, mottled hyperpigmentation, _____ and tactile roughness of facial skin.

Clinical Data

- RENOVA® (tretinoin emollient cream) 0.02% has been evaluated clinically under our IND _____
- Two adequate and well-controlled studies conducted in the United States demonstrate that RENOVA® (tretinoin emollient cream) 0.02% is safe and effective.
One foreign adequate and well-controlled study supports the safety and effectiveness of RENOVA® (tretinoin emollient cream) 0.02%. Patients completing this study were given the option of entering an open label study to evaluate the long-term effects of RENOVA® (tretinoin emollient cream) 0.02%.
- The histological effects of RENOVA® (tretinoin emollient cream) 0.02% have been evaluated in a clinical study.
- Safety and effectiveness of RENOVA® (tretinoin emollient cream) 0.02% in non-Caucasian subjects has been evaluated.
- As agreed at our May 5, 1997 pre-NDA meeting, an intent to treat analysis of the clinical data is included and the data have been evaluated stratifying by age. The SAS datasets will be provided to the FDA Project Manager under separate cover.



Continued on next page

RENOVA® (tretinoin emollient cream) 0.02%, Continued

-
- Preclinical Data**
- As agreed at our May 5, 1997 pre-NDA meeting, an integrated summary of non-clinical data is provided, cross-referencing information submitted previously to approved NDA 19-963 for RENOVA® (tretinoin emollient cream) 0.05%. Photocarcinogenicity data previously submitted to FDA are included in the NDA.
 - A summary of the segment I studies in rats is included in the preclinical section, and suggested labeling will be provided during the NDA review once final study results are available.
 - All preclinical safety calculations in the labeling are based on a human dose of 1 gram.
 - Johnson & Johnson Consumer Companies, Inc. was granted a waiver of a carcinogenicity study at the pre-NDA meeting.
-
- Human PK Data**
- Data on the percutaneous absorption of this formulation at the 0.05% concentration is provided. It was agreed at the pre-NDA meeting that this would be acceptable. Data comparing the in vitro release of the 0.05% and 0.02% formulations is included.
-
- Chemistry Data**
- The CMC section of the NDA cross-refers to NDA 19-963 for RENOVA® (tretinoin emollient cream) 0.05% as appropriate.
 - The application contains sufficient stability data to support an expiration date of ~~—~~ months stored at 25°C(77°F), excursions 15-30°C (59-86°F).
 - All manufacturing and testing sites in the application are ready for a pre-approval inspection.
-
- Labeling**
- The label proposed for RENOVA® (tretinoin emollient cream) 0.02% differs from the approved label for RENOVA® (tretinoin emollient cream) 0.05%.
 - Many of the items in the RENOVA® (tretinoin emollient cream) 0.05% label have been changed to present a more accurate description of the data.
 - Our proposed indication is not for use as adjunctive therapy. Improvement seen with RENOVA® (tretinoin emollient cream) 0.02% is statistically proven to be above and beyond that achieved by the vehicle group which used a comprehensive skin care and sun avoidance program including sunscreens, protective clothing, and emollient creams not containing tretinoin.
-

Continued on next page

AUG 31 1999

RENOVA® (tretinoin emollient cream) 0.02%, Continued

**Labeling
(continued)**

- The label continues to recommend that RENOVA® (tretinoin emollient cream) 0.02% should be used with a comprehensive skin care and sun avoidance program.
 - Data is included in the NDA justifying no age and patient population restrictions.
 - Clinical studies in this NDA and NDA 19-963 demonstrate that after stopping RENOVA® therapy, patients will lose some of the mitigating effects of RENOVA®, but most of the benefit is maintained.
 - Clinical data on patients using RENOVA® (tretinoin emollient cream) 0.02% for 76 weeks is provided. We view this as long-term data and therefore have omitted restrictions on long-term use of the product.
-

Other

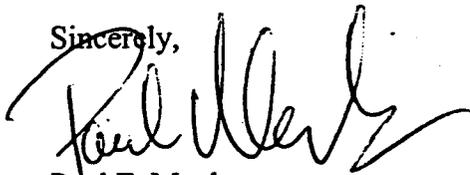
- Please note that throughout the NDA, RENOVA® (tretinoin emollient cream) 0.02% is referred to as TEC-II.
-

Questions

Should you have any questions, please contact me:

Directly (908) 874-1239
FDA phone number: (908) 874-1700
Fax (908) 904-3480
e-mail pmanley@cpcus.jnj.com

Sincerely,



Paul F. Manley
Worldwide Director
Regulatory Affairs

**APPEARS THIS WAY
ON ORIGINAL**

O (Division/Office) <i>FD-160 Peter Cooney</i>		FROM: <i>HFD-540 Olga Cintron</i>		
<i>7/3/99</i>	IND NO. -	NDA NO. <i>21-108</i>	TYPE OF DOCUMENT <i>new NDA</i>	DATE OF DOCUMENT <i>Aug-31-99</i>
NAME OF DRUG <i>Kenva (Ketorolac) 0.02%</i>		PRIORITY CONSIDERATION <i>3</i>	CLASSIFICATION OF DRUG <i>retroind</i>	DESIRED COMPLETION DATE -
NAME OF FIRM <i>Johnson & Johnson</i>				

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|---|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (Specify below) |
| <input type="checkbox"/> MEETING PLANNED BY _____ | | <i>New NDA</i> |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER |
| <input type="checkbox"/> OTHER | |

III. BIOPHARMACEUTICS

- | | |
|---|---|
| <input type="checkbox"/> SOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> AVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL- BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSEMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- CLINICAL PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS (Attach additional sheets if necessary)

Please review for feasibility. Please refer to attached new NDA announcement. A forward planning mtg will be scheduled and will advise microbiologist of the date/time of this meeting.

BEST POSSIBLE COPY

SIGNATURE OF REQUESTER <i>JS</i>	METHOD OF DELIVERY (Check one) <i>through Doc. Room</i> <input checked="" type="checkbox"/> MAIL <input type="checkbox"/> HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

WITHHOLD 1 PAGE (S)

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 page 2.

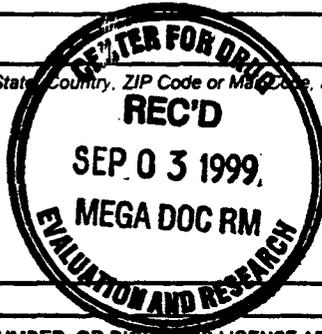
FOR FDA USE ONLY

APPLICATION NUMBER

21-108

APPLICANT INFORMATION

NAME OF APPLICANT Johnson & Johnson Consumer Companies, Inc.	DATE OF SUBMISSION AUG 31 1999
TELEPHONE NO. (Include Area Code) 908-874-1700	FACSIMILE (FAX) Number (Include Area Code) 908-874-1118
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 199 Grandview Road Skillman, NJ 08558	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE Paul Manley, Worldwide Director, Regulatory Affairs 199 Grandview Road Phone: 908-874-1239 Skillman, NJ 08558 FAX: 908-874-1118

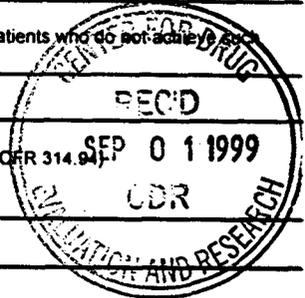


PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 21-108	
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) tretinoin	PROPRIETARY NAME (trade name) IF ANY RENOVA(R)
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any) all-trans-retinoic acid	CODE NAME (if any) RWJ 8203
DOSAGE FORM: cream	STRENGTHS: 0.02%
ROUTE OF ADMINISTRATION: topical	
(PROPOSED) INDICATION(S) FOR USE: adjunctive agent for use in the mitigation (palliation) of fine wrinkles, mottled hyperpigmentation, and tactile roughness of facial skin in patients who do not achieve such palliation using comprehensive skin care and sun avoidance programs alone	

APPLICATION INFORMATION

APPLICATION TYPE (check one)	<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE	<input checked="" type="checkbox"/> 505 (b) (1)	<input type="checkbox"/> 505 (b) (2)	<input type="checkbox"/> 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)	<input checked="" type="checkbox"/> ORIGINAL APPLICATION	<input type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION
	<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT
	<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT
			<input type="checkbox"/> SUPAC SUPPLEMENT
			<input type="checkbox"/> OTHER



REASON FOR SUBMISSION

Original NDA

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

NUMBER OF VOLUMES SUBMITTED 171 THIS APPLICATION IS PAPER PAPER AND ELECTRONIC ELECTRONIC

ESTABLISHMENT INFORMATION All Sites ready for inspection

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

NDA 19-963

This application contains the following items: (Check all that apply)	
X	1. Index
X	2. Labeling (check one) (X) Draft Labeling () Final Printed Labeling
X	3. Summary (21 CFR 314.50(c))
X	4. Chemistry Section
X	A. Chemistry, manufacturing, and control information (e.g. 21 CFR 314.50(d)(1), 21 CFR 601.2)
X	B. Samples (21 CFR 314.50(e)(1), 21 CFR 601.2(a)) (Submit only upon FDA's request)
X	C. Methods Validation Package (e.g. 21 CFR 314.50(e)(2)(i), 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50(d)(2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50(d)(3), 21 CFR 601.2)
X	7. Clinical Microbiology (e.g. 21 CFR 314.50(d)(4))
X	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)
X	10. Statistical section (e.g. 21 CFR 314.50(d)(6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50(f)(1), 21 CFR 601.2)
X	12. Case report forms (e.g. 21 CFR 314.50(f)(2), 21 CFR 601.2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
X	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)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.5(k)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify) - Financial Disclosure by Clinical Investigators

CERTIFICATION

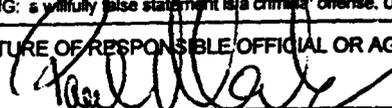
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as provided for by regulation or as requested 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, 810, 660 and/or 809.
4. In the case of a prescription drug product 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 Paul Manley, Worldwide Director, Regulatory Affairs	AUG 31 1999
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ADDRESS (Street, City, State, Zip Code) 199 Grandview Road Skillman, NJ 08858	TELEPHONE NO. (Include Area Code) (908) 874-1239
---	---

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 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.

ITEM 2

Reviewer's Guide to the Labeling Section

The Labeling section of this NDA was prepared in accordance with the FDA "Guideline on Formatting, Assembling, and Submitting New Drug and Antibiotic Applications" issued February 1987. We are placing the labeling in Item 2 as per Form FDA 356h as revised July 1997.

This section contains draft labeling for the proposed drug product, including the package inserts (both for the physician and the patient) and the various components of the packages (tube labels and carton and packer labels).

A fully annotated physician's insert is included in the NDA Application Summary (Item 3, Vol. 1.3). Annotation is provided both to the pertinent chapters of the Application Summary as well as to the corresponding technical sections of the NDA. The patient instruction sheet has not been annotated to avoid redundancy.

Four copies of the draft labeling have been included in this NDA, bound in Blue (Archival), Red (Chemistry), Yellow (Pharmacology), and Tan (Clinical) binders.

Please refer to the Overall NDA Reviewer's Guide located in Volume 1.1 of this application for additional information to facilitate review of this NDA.

**APPEARS THIS WAY
ON ORIGINAL**

002 00001

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

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

1. APPLICANT'S NAME AND ADDRESS

Johnson & Johnson Consumer Companies, Inc.
199 Grandview Road
Skillman, New Jersey 08558-9418

3. PRODUCT NAME

RENOVA(R) (tretinoin emollient cream) 0.02%

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?
IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE
AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

- THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.
 THE REQUIRED CLINICAL DATA ARE SUBMITTED BY
REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

2. TELEPHONE NUMBER (Include Area Code)

(908) 874-1700

5. USER FEE I.D. NUMBER

3668

6. LICENSE NUMBER / NDA NUMBER

N021108

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

- A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92
(Self Explanatory)
- THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)
- THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY
(Self Explanatory)
- A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE
(See item 7, reverse side before checking box.)
- THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act
(See item 7, reverse side before checking box.)
- FOR BIOLOGICAL PRODUCTS ONLY**
- WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION
- AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY
- BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92
- A CRUDE ALLERGENIC EXTRACT PRODUCT
- AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

YES NO

(See reverse side if answered YES)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

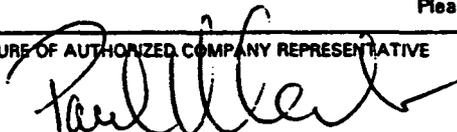
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DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0297)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

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SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE



TITLE

Paul F. Manley, Worldwide Director
Regulatory Affairs

DATE

AUG 31 1999