

Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Rockville MD 20857

CLINICAL INSPECTION SUMMARY

DATE: April 25, 2005

TO: Millie Wright, Regulatory Project Manager
Brenda Carr, Medical Officer
Division of Dermatologic and Dental Drug Products, HFD-540

THROUGH: Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 21-026

PROTOCOL(s): Protocol #BT100 USA/001 entitled: "A Double-blind, Randomized, Multi-center Study of 0.25% Miconazole-nitrate Ointment in the Treatment of Cutaneous Candidiasis Complicating Diaper Dermatitis"

SPONSOR: Barrier Therapeutics, Inc.

DRUG: Miconazole

INDICATION: Treatment of diaper dermatitis

CHEMICAL
CLASSIFICATION: 3

THERAPEUTIC
CLASSIFICATION: S

INSPECTION SUMMARY GOAL DATE: April 29, 2005

ACTION GOAL DATE: June 30, 2005

I. BACKGROUND:

In this NDA application, the sponsor included results of protocol BT100 USA/001 for the use of miconazole ointment in the treatment of diaper dermatitis.

The objective of the study was to assess the efficacy and tolerability of 0.25% miconazole nitrate ointment versus vehicle control in the treatment of cutaneous candidiasis complicating diaper dermatitis. Subjects were seen on an outpatient basis.

These inspections of the sites of Drs. Fling and Briones were requested by the reviewing division because the difference between success and non-success was greater than the overall cure rate for the study.

The goals of inspection included validation of submitted data and compliance of study activities with applicable statutes and federal regulations. Among the study elements reviewed for compliance were subject record accuracy, appropriate informed consent, appropriate use of inclusion/exclusion criteria, adherence to protocol, randomization procedures, documentation of serious adverse events, and accuracy of drug disposition records.

II. RESULTS (by site):

NAME	CITY	STATE/ COUNTRY	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION/FILE NUMBER
John Fling, M.D.	Fort Worth,	Texas	28 Feb 05	15 Apr 05	NAI/011471
Manuel Briones, M.D.	Guayaquil	Ecuador	7 Feb 05	25 Apr 05	NAI/011487

Site # 9

John Fling, M.D. (39 subjects)
855 Montgomery Street
Fort Worth, Texas

See **Overall Assessment and Recommendations**, below

- a. 39 subjects were enrolled in the study. Consent forms were present and signed appropriately for all subjects. Source documents for 20 of the enrolled subjects were reviewed in depth including, but not limited to, visit dates, test article administration, efficacy evaluations, concomitant medications, blinding and randomization, and adverse event reporting. No serious adverse events were reported.
- b. There were no limitations to the inspection.
- c. A Form 483 was not issued. No major objectionable conditions were noted.

Site #19

Manuel Briones, M.D. (41 subjects)

Francisco Bolona #610

Decima Oeste ler piso

Oficina 105

Ciudadela Kennedy

Guayaquil, Ecuador

See Overall Assessment and Recommendations, below

- a. 41 subjects were randomized to the study. 20 subjects were withdrawn from the study including five for a negative baseline culture and another 15 due to treatment failure. Consent forms were present and signed appropriately for all subjects. Source documents for 21 of the enrolled subjects were reviewed in depth including, but not limited to, visit dates, test article administration, efficacy evaluations, blinding, randomization, inclusion/exclusion criteria, and adverse event reporting. No serious adverse events were reported.

When questioned as to the possible reason for the greater treatment effect reported by his site, Dr. Briones hypothesized that as a dermatologist, he could distinguish between erythema induced by diaper irritation as compared to erythema induced by the test article. He suggested that pediatricians might not be as capable of a distinction between the two etiologies. It was noted that of the 23 study investigators in the US, 11 were dermatologists and twelve were pediatricians. The study was conducted at various US sites from April 3, 2003 to June 30, 2004. Latin American sites were added late to the study as the result of the approval of Amendment 4 to the protocol dated April 14, 2004, providing for the inclusion of Latin American sites to the study. The study monitor gave a presentation on the study to Dr. Briones's site on July 22, 2003. Dr. Briones began enrolling subjects into his study in September of 2003. Latin American investigators may not have had the opportunity to attend the initial pre-study meeting, and potential differences in study training may have also contributed to differences in treatment effect reporting.

- b. Limitations to the inspection: source documents were in Spanish.
- c. A Form 483 was not issued. No major objectionable conditions were noted.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the two clinical investigator sites inspected, there were sufficient documentation to assure that all audited subjects did exist, fulfill the eligibility criteria, received the study medication, and had the primary efficacy endpoint captured as specified in the protocol. The data submitted in support of this application by Drs. Fling and Briones appear adequate in support of the relevant submission.

Roy Blay, Ph.D.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

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Page 5 NDA 21-026, Clinical Inspection Summary

cc:

HFD-580/Doc. Rm. NDA 21-026

HFD-45/Program Management Staff (electronic copy)

HFD-46/RF

HFD-46/c/r/s

HFD-46/Blay

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/s/

Roy Blay
4/26/05 09:32:36 AM
CSO

Ni Aye Khin
4/26/05 03:28:57 PM
MEDICAL OFFICER

FDA Fax Memorandum

Date: April 25, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
CMC information request

Hi Isabel,

The chemistry reviewer has the following additional requests:

1. You cite two sources for the miconazole nitrate drug substance: Janssen N.V., and Noramco, Inc., both of which are owned by Johnson & Johnson, Inc., and both of which use the same manufacturing method. A Certificate of Analysis for a batch manufactured at the Janssen site in Belgium is provided in your submission. However, a Certificate of Analysis for a batch manufactured at the Noramco site is not provided.

1. Please submit a certificate of analysis of miconazole nitrate manufactured at the Noramco site in the U.S.A. Please also provide a chromatographic comparison (impurity profile) for miconazole nitrate from each site (to ascertain that there are no differences in the drug substance quality from the two sites).
2. The visual examination of the ointment for agglomerates is inadequate. Please include a microscopic test to assure that no agglomerates are present. Alternately, another test for homogeneity may be proposed.
3. All applications (e.g. NDAs, INDs) requesting agency action require the submission of an environmental assessment or a claim of categorical exclusion [21 CFR 25.15(a) and 21 CFR 314.101(d)(4)]. Please submit an environmental assessment or a claim of categorical exclusion.
4. Please provide a UV/VIS spectrum of the drug product.

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/s/

Mildred Wright
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April 22, 2005

REGULATORY AFFAIRS DEPARTMENT

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N-DDD(BC)

APR 25 2005

ORIG AMENDME

MEGA / CDER

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

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis complicated
by candidiasis

Response to Request for Chemistry,
Manufacturing and Control Information

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to facsimile transmissions of April 5, 2005 and April 12, 2005 from Ms. Millie Wright of your Division requesting additional Chemistry, Manufacturing, and Control Information.

At this time, we submit herewith our responses to the faxes of April 5 and April 12, 2005. We will address the April 12, 2005 fax first. In that document you requested the establishment registration number, contact person name, telephone number, and fax number for the facility. On Tuesday, April 19, 2005, Our Regulatory Associate, Donna Millisky sent this information to you via an e-mail message. I am again providing the following information as part of this submission:

b(4)

b(4)

is ready for inspection. We are not aware that they have an establishment registration number.

b(4)

In addition, we are providing the same information for our supplier of White Petrolatum:

b(4)

ORIGINAL

is ready for inspection.

In the April 12 Fax, you also requested the exact location in _____ for information on the aluminum tubes used to package Miconazole Nitrate USP 0.25% Ointment. We have been advised _____ our supplier of these packaging materials that DMF _____ pertains only to the materials used for our product. Therefore, the entire DMF _____ provides information on only these tubes. The most recent update to DMF _____ was submitted on January 5, 2005.

In that same information request you asked for information on the test for extractables from the tube's lining and indicated that the use of a food grade item does not automatically grant an exemption from this requirement. Please be advised that we are currently conducting extraction studies by applying the "PHYSIOCHEMICAL TESTS—PLASTICS" portion of USP <661> to the tube lining. We expect to have the results early next week and we will submit the results promptly in order to facilitate your review.

In regard to the fax of April 5, 2005, we also refer to a teleconference on April 19, 2005, between representatives of Barrier Therapeutics and your Agency where these issues were discussed. In response to your April 5, 2005 requests and the understandings reached during the teleconference, we are providing appropriately revised S-Sections containing more detailed information on the chemistry, manufacturing, and controls for Zinc Oxide and White Petrolatum. In order to facilitate your review and assist you in navigating through the revised sections, we are also providing you with a Reviewer's Guide.

We trust that we have satisfactorily responded to the requests made in the April 5 and April 12, 2005 faxes. This product is very important to Barrier and we are available to work with you should you have any questions and/or comments regarding this submission. Please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

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APR 15 2005

MEGA / CDER

BZ

N-000(stt)

ORIG AMENDMENT

**Barrier** Therapeutics, Inc.*A Vision for Innovative Medicine*

April 14, 2005

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

NDA 21-026**Miconazole Nitrate 0.25% Ointment****Indication: Diaper Dermatitis complicated
by candidiasis****Response to Request for Safety Update
Report and Med-Guide**

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to a telephone conversation on April 6 and 7, 2005 between Ms. Millie Wright of your Division and myself. During these telephone conversations Ms. Wright requested that we submit a Safety Update Report and that we convert the Patient Information Leaflet contained in our NDA Amendment to a Medication Guide.

At this time, we submit herewith our Safety Update Report and Medication Guide. Please be advised that all clinical studies of miconazole nitrate 0.25% ointment have been completed and all adverse event information was contained in our November 24, 2004 Amendment. There is no additional safety information to report from the United States. The only information we are including in this Safety Update Report is information from the Periodic Safety Update Report (PSUR) prepared by our colleagues in Europe and covering the period from August 2003 through August 2004.

Based on the information contained in the Safety Update Report, the worldwide post-marketing experience with miconazole nitrate resulted in an extremely low incidence of reported adverse events. It is therefore our position that no changes to the labeling submitted with our November 24, 2004 NDA Amendment are necessary at this time.

We have also provided a Medication Guide which has been prepared in conformance with 21CFR Part 208.

We trust that we have satisfactorily responded to the requests made to us by Ms. Millie Wright. Should you have any questions and/or comments regarding this submission, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel B. Drzewiecki

Global Head, Regulatory Operations

ORIGINAL

Enclosure: Form FDA 356h

FDA Fax Memorandum

Date: April 12, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
CMC information request

Hi Isabel,

The chemistry reviewer has the following request:

1. In the Agency's Information Request letter dated December 8, 2004, you were requested to include the establishment registration number, contact person name and phone number for all facilities and a statement that all the facilities are ready for inspection. You responded on December 13, 2004, with the requested information only for DSM, the drug product manufacturer. Please provide adequate contact information for _____ the manufacturer of the drug substance, zinc oxide, so that an inspection can be scheduled for this facility. Contact information should include a name, telephone, and fax number. The contact may be a US Agent or someone at the facility. b(4)
2. You provided a letter of authorization (LOA) in your NDA submission for the referenced Type 3 _____ . However, you did not include the exact location [in the DMF] of this packaging information. Please provide the exact location in DMF _____ of the referenced packaging information. Please note that a test of extractables is required to ascertain that your vehicle does not cause extractables to contaminate the drug product. This can be shown by including qualitative and quantitative extraction profiles of the container closure using the particular vehicle or an appropriate solvent. The information may also be provided in a referenced DMF. Please refer to Attachment C of the CDER Guidance for Industry "*Container Closure Systems for Packaging Human Drugs and Biologics*", which is available on the CDER website. The use of food grade items does not automatically grant an exemption from this requirement. b(4)

If you have questions, please call.

Respectfully,
Millie

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/s/

Mildred Wright

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CSO

FDA Fax Memorandum

Date: April 12, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
Micro information request

Hi Isabel,

The microbiology reviewer has the following request:

The Applicant is asked to provide miconazole nitrate MIC data for isolates of *C. albicans* or other *Candida* species obtained from clinical and therapeutic failures at test of cure (day 14) for both the miconazole nitrate treatment and the vehicle treatment groups. MIC results after 24 and 48 hours of incubation should be provided.

If you have questions, please call.

Respectfully,

Millie

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/s/

Mildred Wright
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CSO

FDA Fax Memorandum

Date: April 5, 2005

Subject: NDA 21-026/miconazole nitrate/amendment
CMC information request

Hi Isabel,

The chemistry reviewer has the following request:

You were informed in an "Information Request Letter" dated February 8, 2005, that the CMC information provided for zinc oxide and for white petrolatum in your submission, NDA 21-026(AZ), dated November 24, 2004, is not adequate for a drug substance. You were requested to either provide detailed manufacturing information and stability data, or to provide a reference to a Type II DMF. You responded in your submission NDA 21-026/N-000(BC), dated March 10, 2005, that there is no DMF for zinc oxide or for white petrolatum. You also stated that there are no trends of instability for either substance in the drug product, and that each of these drug substances is used in cosmetics and OTC applications. The fact that these compounds have been used in OTC products and in cosmetics has no bearing on the quality of the drug substance used in your drug product, and cannot take the place of the required CMC information (manufacturing controls needed to assure the quality and purity of the drug substance in question).

1. Please provide detailed chemistry, manufacturing, and controls information and stability data for zinc oxide and for white petrolatum. General descriptive information on the physical, chemical, and biological characteristics of the drug substances should be included. A flow diagram should be provided and should contain the chemical structures of the starting material(s), intermediates (either in situ or isolated), and, when feasible, significant side-products. A general step-by-step description of the synthesis and manufacturing processes, including the final isolation of the drug substance should be also provided. Relevant information should indicate the batch size (range), the relative ratios of reactants, catalyst, and reagents, process controls (brief description of the analytical procedures) and general operating conditions (time, temperature), controls of critical steps and intermediates, control of crystalline forms.

As stated in the CMC Information Request # 3 concerning "specifications" of zinc oxide and white petrolatum in the "Information Request Letter" dated February 8, 2005, a detailed listing of all the tests performed on the drug substance (e.g., description, identity, assay, loss on drying) should be provided. Acceptance criteria should be established for each test performed and should be submitted. A general description of the analytical

procedures should be provided that includes a citation to the specific USP monograph or general chapter or your standard test procedure number, as appropriate.

As you noted (on page 4 of your submission NDA 21-026/N-000(BC), dated March 10, 2005) in the quote from Section 3.1.2 of Q6A, you may provide alternative approaches. However, these alternative approaches should be adequately justified. You also note that "no mention of this as an issue was raised during the pre-NDA meeting of July 27, 2004". Please note that the Agency's response to your [only] CMC question is quoted below, and is found on page 54 of your submission NDA 21-026/N-000(BC), dated March 10, 2005):

"For a drug product containing more than one drug substance, the information requested for part S should be provided in its entirety for each drug substance." Consequently, each drug substance should have its own "S" section or each drug substance should be in its own DMF.

Please note that adequate CMC information of these two drug substance is required in order to complete a chemistry review of this NDA and the absence or inadequacy of such information is an approvability issue.

If you have questions, please call.

Respectfully,
Margo (for Millie)

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/s/

Margo Owens

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Faxed to sponsor 4/5/05.



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REGULATORY AFFAIRS DEPARTMENT

March 15, 2005

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MAR 16 2005

N-000(BZ)

MEGA / CDER

ORIG AMENDMENT

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

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by candidiasis

Partial Response to Information
Request Letter

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to an "Information Request Letter" of February 8, 2005 from Ms. Mary Jean Kozma Fornaro of your Division providing us comments on the Clinical, Statistical, Microbiology, Chemistry, Manufacturing and Controls sections and our proposed proprietary name, Zimycan™ of our submission.

At this time we are replying to the comments regarding the Clinical, Statistical, and Microbiological portions of the letter. Please find below the Agency's Information Requests in **bold text**, followed by Barrier's responses in plain text.

RESPONSES TO THE CLINICAL QUESTIONS

ORIGINAL

Information Request #1

Please identify the location in the amendment for the rationale for assuming the applicability of foreign data. Please submit the rationale if it was not submitted in the amendment.

It is our position that the data collected from these countries outside the US for this clinical trial is not "foreign data" but that it is data collected at "foreign sites". The studies that were done in the US and Latin American sites adhere to the same standards of clinical practice and GCPs. The following ten items document these similarities:

1. Investigator Meetings were conducted in the US and Latin America in order to initiate the clinical protocol.
2. The Principal Investigator (Dr. M. Spraker) attended all Investigator Meetings thus ensuring the continuity and integrity of the study.
3. The Principal Investigator was available throughout the study to give advice on trial related medical questions.
4. The medical doctors selected for all sites were professionally qualified.
5. The same Contract Research Organization () managed all study sites. **b(4)**
6. The same protocol and consent form was used with appropriate Ethics Committee approvals.
7. The same randomization plan was used and followed.
8. A Central Laboratory () was used for all study sites to determine the presence/absence of *Candida spp.* **b(4)**
9. GCP guidelines were followed at all study sites.
10. The same monitors conducted all required monitoring visits.

Furthermore, there is a significant overlap in ethnicity and race regarding the US and Latin America populations. This is evidenced by the current US population composition and continued immigration of residents of Latin America to the US. There is no scientific evidence to suggest that ethnic factors relating to genetic and/or physiologic and/or cultural and/or environmental characteristics of the Latin America populations would impact the outcome of the evaluation of the efficacy and safety of the trial.

The results of the clinical trial support the above statement in that the efficacy and safety results between study sites (US versus non-US) are comparable. Results of the overall cure rate at Study Day 14 were similar (Latin America 24% versus United States 22%) for the MITT population. *Candida spp.* were similar in both US and non-US sites.

Less than 16% of the subjects in each treatment group for the non-US sites reported adverse events as compared to 28% in the US sites. All of the adverse events were typical of the pediatric population suffering from illnesses other than cutaneous candidiasis complicating diaper dermatitis and were considered "unrelated" to the study medication.

Information Request #2

Please provide the summary safety results subgrouped by U.S. sites and non-U.S. sites. For the non-U.S. sites, please provide additional safety result analysis by each site.

Tables 14.3.1.1.1 and 14.3.1.1.2 present the analysis subgrouped by U.S. sites and non-U.S. sites, respectively. Tables 14.3.1.1.2.1 through 14.3.1.1.2.4

present the analysis of non-U.S. sites by individual investigator. All of the tables mentioned above can be found in Appendix 1.

Information Request #3

Please provide the summary safety results subgrouped by race and gender.

Tables 14.3.1.2.1 through 14.3.1.2.5 provide the summary safety results subgrouped by race.

Tables 14.3.1.3.1 through 14.3.1.3.2 provide the summary safety results subgrouped by gender.

All tables mentioned above can be found in Appendix 2.

Information Request #4

Please submit all Newly acquired safety information from world wide use since the submission dated November 24, 2004.

No additional safety information has been reported since the initial filing on November 24, 2004.

Information Request #5

Please provide a breakdown of the racial composition of Hispanic subjects, since the designation "Hispanic" may not necessarily reflect race, e.g. can be white, black, etc. This may be particularly true of some countries, such as the Dominican Republic.

Tables 14.1.4c, 14.1.5c and 14.1.6c provide the breakdown of the racial composition of Hispanic subjects for the intent-to-treat, modified intent-to-treat and per-protocol subjects, respectively, and can be found in Appendix 3. Hispanic races with a Fitzpatrick skin type of three or less are considered white, and a Fitzpatrick skin type of four or more are considered non-white.

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RESPONSES TO THE STATISTICAL QUESTIONS

Information Request #1

It is noted that the dropout rate on Day 14 in the vehicle group was 52%; the vehicle dropout rate is significantly greater than 13% dropout rate for the miconazole arm. Imputing missing data as a treatment failure, in this case, would favor the miconazole group. Please provide the rationale and analyses that would ensure the robustness of the efficacy results.

The rationale and analysis, followed by relevant listings, can be found in Appendix 4.

Information Request #2

Please provide details about treatment assignments to each study site and discuss any deviation that occurred during the study. Please submit the randomization list generated prior to the start of the study and give details of the block size, if any, which was used for generating the randomization list.

Listing 1.1 provides details about treatment assignments to each study site. This listing can be found in Appendix 5. No deviations were reported during the study.

The randomization list generated prior to the start of the study can be found in Appendix 5. The block size was 4.

Information Request #3

Please submit subgroup results by the type of diaper used during the study with respect to each of the overall cure rate and clinical cure rate.

Tables 14.2.3.1.1, 14.2.3.2.1, 14.2.3.3.1 and 14.2.3.4.1 present the subgroup results by the type of diaper used during the study with respect to each of the overall cure rate and clinical cure rate for the modified intent-to-treat and per-protocol subjects, respectively. The subgroup classification was based on the responses to question 4 of the baseline questionnaire.

The tables mentioned above can be found in Appendix 6.

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RESPONSES TO THE CLINICAL MICROBIOLOGY QUESTIONS

Information Request #1

Please provide a table that shows the clinical success and failure rates for the "Clinical Response", "Microbiologic Response", and "Therapeutic Response" without the presence of "Other Candida spp." in the 0.25% miconazole nitrate treatment group and the vehicle treatment group. Please include the P-value for the "Clinical Response" and "Therapeutic Response".

Table 14.2.1.2.1 provides the requested information and can be found in Appendix 7.

Information Request #2

Please provide a table that shows the clinical success and failure rates for the "Clinical Response", "Microbiologic Response", and "Therapeutic Response" without the presence of the "Missing" data and the "Other Candida spp." in the 0.25% miconazole nitrate treatment group and the vehicle treatment group. Please include the P-value for the "Clinical Response" and "Therapeutic Response" groups.

Table 14.2.1.2.2 provides the requested information and can be found in Appendix 8.

Information Request #3

Please provide the miconazole nitrate MICs for the *C. albicans* isolates for clinical success and failures in the "Clinical Response", "Microbiologic Response", and "Therapeutic Response" for both the 0.25% miconazole treatment group and the vehicle treatment group.

Listing 17.1 provides the MIC findings for *C. albicans* isolates at 24 hours in the Clinical Response by success and failure.

Listing 17.2 provides the MIC findings for *C. albicans* isolates at 48 hours in the Clinical Response by success and failure.

Listing 17.3 provides the MIC findings for *C. albicans* isolates at 24 hours in the Microbiologic Response by success and failure.

Listing 17.4 provides the MIC findings for *C. albicans* isolates at 48 hours in the Microbiologic Response by success and failure.

Listing 17.5 provides the MIC findings for *C. albicans* isolates at 24 hours in the Therapeutic Response by success and failure.

Listing 17.6 provides the MIC findings for *C. albicans* isolates at 48 hours in the Therapeutic Response by success and failure.

Listings can be found in Appendix 9.

Information Request #4

Please provide summaries of the miconazole nitrate MICs for the *Candida albicans* isolated during clinical trial BT100 USA/001 from both the active and placebo treatment groups. A separate summary should be done for the 0.25% miconazole treatment group and the placebo treatment group. A composite summary of the isolates from both groups should also be provided. The summary should include the mean, median, MIC₅₀ and MIC₉₀ of the isolates. The raw data from which the summaries were compiled should be provided.

Table 4.1 and 4.2 present the summary statistics for the *Candida albicans* isolates at 24 and 48 hours, respectively. A mean value was not computed since the majority of the values were less than or equal to 0.03.

The raw data from which the summaries were compiled are found in Listings 17.1 and 17.2 located in Appendix 9.

Table 4.1. MIC Findings for *Candida albicans* Isolates at 24 hours

	0.25% Miconazole Nitrate Ointment	Vehicle Control	Composite Summary
MIC	n (%)	n (%)	n (%)
≤ 0.03	95 (99.0)	100 (98.0)	195 (98.5)
0.06	0	2 (2.0)	2 (1.0)
1.00	1 (1.0)	0	1 (0.5)
Total	96	102	198
Median	≤ 0.03	≤ 0.03	≤ 0.03
MIC₅₀	≤ 0.03	≤ 0.03	≤ 0.03
MIC₉₀	≤ 0.03	≤ 0.03	≤ 0.03

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Table 4.2. MIC Findings for *Candida albicans* Isolates at 48 hours

	0.25% Miconazole Nitrate Ointment	Vehicle Control	Composite Summary
MIC	n (%)	n (%)	n (%)
≤0.03	87 (90.6)	93 (91.2)	180 (90.9)
0.06	8 (8.3)	8 (7.8)	16 (8.1)
0.25	0	1 (1.0)	1 (0.5)
1.00	1 (1.0)	0	1 (0.5)
Total	96	102	198
Median	≤ 0.03	≤ 0.03	≤ 0.03
MIC ₅₀	≤ 0.03	≤ 0.03	≤ 0.03
MIC ₉₀	≤ 0.03	≤ 0.03	≤ 0.03

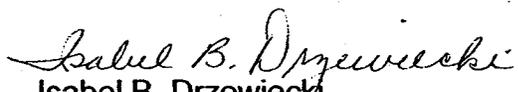
Information Request #5

Please provide a table of the KOH microscopic findings for the vehicle control groups by enrolled subject and their test-of-cure outcome.

Listing 18 provides the KOH microscopic findings for the vehicle control groups by enrolled subject and their test-of-cure outcome and can be found in Appendix 10.

With this submission, we have completed our responses to the Information Request Letter. The Chemistry, Manufacturing and Controls portion of the letter was addressed in our submission of March 10, 2005 and the portion of the letter concerning our chosen tradename was addressed in our submission dated February 15, 2005. We hope that the information provided is sufficient to continue with your evaluation of our NDA. Should you have any questions and/or comments regarding this submission, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,


Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

ORIGINAL

REGULATORY AFFAIRS DEPARTMENT



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

March 10, 2005

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MAR 11 2005

MEGA / CDER

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

ORIG AMENDMENT
N-000-(BC)

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis
complicated by candidiasis

Partial Response to Information
Request Letter

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to an "Information Request Letter" of February 8, 2005 from Ms. Mary Jean Kozma Fornaro of your Division providing us comments on the Clinical, Statistical, Microbiology, Chemistry, Manufacturing and Controls sections and our proposed proprietary name, Zimyca™ of our submission.

At this time we are replying to the comments regarding the Chemistry, Manufacturing and Controls portion of the letter. Please find below the Agency's Information Requests in **bold text**, followed by Barrier's responses in plain text.

Information Request #1

You identify zinc oxide as a drug substance. However, no manufacturing information or reference to a Type 2 DMF is provided. Furthermore, no stability data is provided. The information provided is adequate for an excipient, but is not adequate for a drug substance. Please either provide detailed manufacturing information and stability data, including expiration dating, or change the designation of zinc oxide from drug substance to excipient.

b(4)

There is no Type 2 DMF available for zinc oxide. However, the supplier's COA indicates that it is "Pharma Grade". Regarding the manufacturing and stability of zinc oxide, please refer to the latest Merck Index monograph for Zinc Oxide. There are two major methods for manufacturing zinc oxide: vaporization of metallic zinc, followed by oxidation with preheated air, and roasting of zinc sulfide. Either way produces high-purity ZnO which meets all requirements

of the USP monograph and is tested for additional trace heavy metals by the supplier. Note that the COA submitted in Appendix 4 of the March 3, 2004 submission to IND 21,542 reports this test. Zinc oxide is practically insoluble in water, but is soluble in dilute acids or bases (i.e. typical behavior for an amphoteric metal oxide). It is not subject to further oxidation, and the only likely reaction would be conversion to zinc sulfide if it were exposed to hydrogen sulfide gas. There are no reported hydrates and no phase changes.

Zinc oxide is assayed in the finished product and has been assayed in all stability testing of the finished drug product. There are no trends or indication of instability. At the July 27, 2004 pre-NDA meeting, there was a conversational agreement with Dr. Norman Schmuff that this section would have minimal content due to its widespread acceptance in OTC formulations. Based on this explanation, it is our opinion that adequate CMC information is available on the manufacturing and stability of zinc oxide and no further information is necessary.

Consistent with Q7A, the designation of a "retest date" rather than an "expiration date" is appropriate for a drug substance. Will the Agency accept the designation of a "retest date" rather than an "expiration date" for zinc oxide?

Please refer to your records of the guidance meeting of September 3, 2003 and the follow-up office-level teleconference on December 18, 2003, at which the Agency stated their belief that "the zinc oxide and petrolatum are active". Re-designation of zinc oxide as an excipient would be contrary to the FDA determination stated in the December 18, 2003 teleconference. Copies of all pertinent correspondence between the Agency and Barrier Therapeutics will be found in chronological order in Attachment 1 to this letter. The minutes of the July 27, 2004 pre-NDA Meeting, the minutes of September 3, 2003 Guidance Meeting, and the December 18, 2003 teleconference minutes are contained in this attachment.

It should be noted, however, that up until that point in time, the sponsor had considered Zinc Oxide to be an excipient.

Information Request #2

You identify white petrolatum as a drug substance. However, no manufacturing information or reference to a Type 2 DMF is provided. Furthermore, no stability data is provided. The information provided is adequate for an excipient, but is not adequate for a drug substance. Please either provide detailed manufacturing information and stability data, including expiration dating, or change the designation of white petrolatum from drug substance to excipient.

There is no Type 2 DMF available for white petrolatum. Petrolatum is a mixture of hydrocarbons, primarily branched-chain solid hydrocarbons and high-boiling liquid

hydrocarbons. The compendial standards (USP 28) do not provide for a true assay of this component. Apart from establishing a "fingerprint" range of physical properties, it is unclear what additional quality attributes might be examined in stability testing.

At the July 27, 2004 pre-NDA meeting, there was a conversational agreement with Dr. Norman Schmuft that this section would have minimal content due to its widespread acceptance in OTC and cosmetic formulations. Based on this explanation, it is our opinion that adequate CMC information is available on the manufacturing and stability of white petrolatum and no further information is necessary.

Consistent with Q7A, the designation of a "retest date" rather than an "expiration date" is appropriate for a drug substance. Will the Agency accept the designation of a "retest date" rather than an "expiration date" for white petrolatum?

Please refer to your records of the guidance meeting of September 3, 2003 and the follow-up office-level teleconference on December 18, 2003, at which the Agency stated their belief that "the zinc oxide and petrolatum are active". Re-designation of white petrolatum as an excipient would be contrary to the FDA determination stated in the December 18, 2003 teleconference. Copies of all pertinent correspondence between the Agency and Barrier Therapeutics will again be found in chronological order in the attachment described in Item 1 (Attachment 1). The minutes of the July 27, 2004 pre-NDA Meeting, the minutes of September 3, 2003 Guidance Meeting, and the December 18, 2003 teleconference minutes are contained in this attachment.

It should be noted that up until that point in time the sponsor had considered White Petrolatum to be an excipient.

Information Request #3

Please also note that if white petrolatum and zinc oxide are considered drug substances, the specification of the drug product (3.2.P.5 Table I) is deficient. The specification of any drug product should include an identification test and assay of all drug substances. Hence, if white petrolatum and zinc oxide were to be deemed drug substances, an identification test and assay of these two components should be included in the specification of the drug product.

We agree with the concepts of what should be included in the specification for a drug product, as described in Q6A. The current drug product release and stability specifications include testing for the identification and assay of zinc oxide.

As stated above, petrolatum is not a single molecular species and an assay in the usual sense is not possible. Furthermore, petrolatum constitutes more than 83%

of the product. If it were an excipient, it would likely be considered to be a vehicle with the composition stated as "q.s. ad 100%". It is difficult to see what added value would result from an assay in this case, even if it were technically feasible.

We also believe that little enhancement to the quality and safety of the drug product will result from an application of section 3.2.2.(c) of the Q6A Guidance to require an assay of petrolatum, a component that makes up well over half of the drug product. We note that Section 3.1.2 of Q6A states in part:

"Approaches other than those set forth in this guidance may be applicable and acceptable. The applicant should justify alternative approaches. Such justification should be based on data derived from the new drug substance synthesis and/or the new drug product manufacturing process. This justification may consider theoretical tolerances for a given procedure or acceptance criterion, but the actual results obtained should form the primary basis for whatever approach is taken."

We have used this drug product in our clinical trials for which there was no assay for the amount of petrolatum and for which the manufacturing controls provided adequate control of the amount of petrolatum in the drug product. We believe that this provides an acceptable alternative approach to the traditional quality attribute of a chemical assay.

Please note that no mention of this as an issue was raised during the pre-NDA meeting of July 27, 2004.

Information Request #4

You state under "Specifications-Trihydroxystearin" in 3.2.P.4.4, that the "specification and analytical procedures for testing trihydroxystearin are those in the USP monograph for hydrogenated castor oil".. However, the quality standard for trihydroxystearin is listed in 3.2.P.3, Table 1 and in 3.2.P.1, Table 1 as "In-house Standard". Please confirm that the excipient "Trihydroxystearin" is compendial, and resubmit the composition Table 1, with the excipient listed as Trihydroxystearin, NF or otherwise clearly state, in a footnote to Table 1 that trihydroxystearin Trihydroxystearin meets compendial requirements.

The trihydroxystearin of this application meets all of the test requirements of Hydrogenated Castor Oil, NF. However, it is not during the manufacturing process and therefore does not comply with all of the requirements presented in the "Description" portion of the monograph.

We will add the following information to the trihydroxystearin portion of 3.2.P.2.1.2 for clarification:

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Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

February 16, 2005

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N-000(S)

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FEB 17 2005

ORIGINAL AMENDMENT

MEGA / CDER

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

NDA 21-026
Miconazole Nitrate 0.25% Ointment

Indication: Diaper Dermatitis complicated by candidiasis

Partial Response to Information Request Letter

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for Miconazole Nitrate, 0.25% Ointment and specifically to our amendment to this NDA of November 24, 2004, in which we provided a complete response to the non-approvable letter of July 24, 2000. We also refer to an "Information Request Letter" of February 8, 2005 from Ms. Mary Jean Kozma Fomaro of your Division providing us comments on the Clinical, Statistical, Microbiology, Chemistry, Manufacturing and Controls sections and our proposed proprietary name, Zimycan™ of our submission.

At this time we are replying to the comments provided by the Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS) regarding our proposed proprietary name, Zimycan™. The letter advises that DMETS does not recommend the proprietary name Zimycan™ due to its potential to look similar to Lumigan.

We respectfully request reconsideration of the proprietary name Zimycan™ (pronounced "Zye-mi-can"). There are important product profile differences between Zimycan™ and Lumigan, which significantly reduce the possibility of a medication error to occur. In this regard, we requested two independent companies to provide us with a safety evaluation of the name Zimycan™.

b(4)

These two companies worked totally independent of each other and arrived at similar conclusions to support the use of the name Zimycan™. We have attached their reports for your information and review.

The two reports found that in reviewing the post-marketing experience in the U.S., there were no reports of medication errors between an ophthalmic solution and a topical ointment. There is also a lack of orthographic and phonetic similarity between the product names as measured by the Computerized Orthographic and Phonologic Analysis (COPA).

In addition, one of the companies did a direct side by side comparison of Zimycan™ vs. Lumigan which demonstrates that there are a significant number of differences in the clinical characteristics of the two products which decreases the risk of confusion. This comparison is contained in the report.

The trademark Zimyca™ is very important to Barrier Therapeutics and, based on the information in these two independent reports and the measurements taken, we most certainly believe that Zimyca™ and Lumigan can safely coexist in the market place.

We respectfully request expedited review of this important information that we are presenting in support of our trade name Zimyca™ in order to plan our production and packaging schedules, order the necessary components and meet our PDUFA date of May 24, 2005.

Should you have any questions and/or comments regarding this submission, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,



Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

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REGULATORY AFFAIRS DEPARTMENT



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

February 15, 2005

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FEB 16 2005

MEGA / CDER

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

ORIG AMENDMENT

N-000(BZ)

NDA 21-026

Miconazole Nitrate 0.25% Ointment

**Indication: Diaper Dermatitis complicated
by candidiasis**

Response to Clinical Information Request

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for 0.25% Miconazole Nitrate, zinc oxide/white petrolatum ointment and specifically to our amendment to this NDA of November 24, 2004 which contained a complete response to the non-approvable letter of July 24, 2000. We also refer to a facsimile transmission from Ms. Millie Wright of your Division, received on February 14, 2005. In that fax, we were requested to provide an index for the subject Data Listings located in Volumes 8-13 of our NDA amendment submission.

At this time, we submit herewith a Table of Contents for the Subject Data Listings contained in Volumes 8-13 of the amendment. In this Table of Contents we have included the Listing, Title of the Listing, NDA Volume and Page Numbers. We hope it is helpful and satisfactory for the medical reviewer's needs.

Should you have any questions and/or comments regarding this Table of Contents, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel Drzewiecki

Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

Recode (N-000) BZ
PER pm 2-18-05



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

INFORMATION REQUEST LETTER

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operations
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

Please refer to your November 24, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for miconazole nitrate ointment, 0.25%.

We are reviewing the Clinical, Statistical, Microbiology, Chemistry, Manufacturing and Controls sections and your proposed proprietary name, Zimykan, of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Clinical:

1. Please identify the location in the amendment for the rationale for assuming the applicability of foreign data. Please submit the rationale if it was not submitted in the amendment.
2. Please provide the summary safety results subgrouped by U.S. sites and non-U.S. sites. For the non-U.S. sites, please provide additional safety result analysis by each site.
3. Please provide the summary safety results subgrouped by race and gender.
4. Please submit all Newly acquired safety information from world wide use since the submission dated November 24, 2004.
5. Please provide a breakdown of the racial composition of Hispanic subjects, since the designation "Hispanic" may not necessarily reflect race, e.g. can be white, black, etc. This may be particularly true of some countries, such as the Dominican Republic.

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Statistical:

1. It is noted that the dropout rate on Day 14 in the vehicle group was 52%; the vehicle dropout rate is significantly greater than 13% dropout rate for the miconazole arm. Imputing missing data as a treatment failure, in this case, would favor the miconazole group. Please provide the rationale and analyses that would ensure the robustness of the efficacy results.
2. Please provide details about treatment assignments to each study site and discuss any deviation that occurred during the study. Please submit the randomization list generated prior to the start of the study and give details on the block size, if any, which was used for generating the randomization list.
3. Please submit subgroup results by the type of diaper used during the study with respect to each of the overall cure rate and clinical cure rate.

Clinical Microbiology:

The following requests relate to clinical trial BT100 USA/001.

1. Please provide a table that shows the clinical success and failure rates for the "Clinical Response", "Microbiologic Response", and "Therapeutic Response" without the presence of "Other *Candida* spp." in the 0.25% miconazole nitrate treatment group and the vehicle treatment group. Please include the P-value for the "Clinical Response" and "Therapeutic Response".
2. Please provide a table that shows the clinical success and failure rates for the "Clinical Response", "Microbiologic Response" and "Therapeutic Response" without the presence of the "Missing" data and the "Other *Candida* spp." in the 0.25% miconazole nitrate treatment group and the vehicle treatment group. Please include the P-values for the "Clinical Response" and "Therapeutic Response" groups.
3. Please provide the miconazole nitrate MICs for the *C. albicans* isolates for clinical successes and failures in the "Clinical Response", "Microbiologic Response", and "Therapeutic Response" for both the 0.25% miconazole treatment group and the vehicle treatment group.
4. Please provide summaries of the miconazole nitrate MICs for the *Candida albicans* isolated during clinical trial BT100 USA/001 from both the active and placebo treatment groups. A separate summary should be done for the 0.25% miconazole treatment group and the placebo treatment group. A composite summary of the isolates from both groups should also be provided. The summary should include the mean, median, MIC₅₀ and MIC₉₀ of the isolates. The raw data from which the summaries were compiled should be provided.
5. Please provide a table of the KOH microscopic findings for the vehicle control groups by enrolled subject and their test of cure outcome.

Chemistry, Manufacturing and Controls:

Please clarify the following:

1. You identify zinc oxide as a drug substance. However, no manufacturing information or reference to a Type 2 DMF is provided. Furthermore, no stability data is provided. The information provided is adequate for an excipient, but is not adequate for a drug substance. Please either provide detailed manufacturing information and stability data, including expiration dating, or change the designation of zinc oxide from drug substance to excipient.
2. You identify white petrolatum as a drug substance. However, no manufacturing information or reference to a Type 2 DMF is provided. The information provided is adequate for an excipient, but is not adequate for a drug substance. Please either provide detailed manufacturing information and stability data, including expiration dating, or change the designation of white petrolatum from drug substance to excipient.
3. Please also note that if white petrolatum and zinc oxide are considered drug substances, the specification of the drug product (3.2.P.5 Table 1) is deficient. The specification of any drug product should include an identification test and assay of all drug substances. Hence, if white petrolatum and zinc oxide were to be deemed drug substances, an identification test and assay of these two components should be included in the specification of the drug product.
4. You state under "Specifications-Trihydroxystearin" in 3.2.P.4.4, that the "specification and analytical procedures for testing trihydroxystearin are those in the USP monograph for hydrogenated castor oil".. However, the quality standard for trihydroxystearin is listed in 3.2.P.3, Table 1 and in 3.2.P.1, Table 1 as "In-house Standard". Please confirm that the excipient "Trihydroxystearin" is compendial, and resubmit the composition Table 1, with the excipient listed as Trihydroxystearin, NF, or otherwise clearly state, in a footnote to Table 1 that trihydroxystearinTrihydroxystearin meets compendial requirements.
5. Is formula F100 identical to formula F114? If formula NP0426 is the same as formula NP0425, why do they have different formula numbers? How do these two formulas, NP0426 and NP0425, relate to formulas F100 and F114?
6. Please note that the primary stability data on the tube are not directly applicable to the tube, and could not be used in lieu of a primary stability study on the tubes. Contrary to your assertion in 3.2.P.8.1.2.1 "Stability Batches", the difference of size between the two tubes is not considered insignificant by the Agency. You have provided no primary stability data on the tube.
7. Your proposal to use the results of a study of the 3 production batches manufactured at Janssen as supportive stability data is acceptable, but it cannot be used instead of primary stability data to determine the expiration date. Only primary stability data (and appropriate statistical analysis, if provided) may be used to determine shelf life.

b(4)

8. Are there any CMC changes in the current NDA submission from those provided in the original submission by Johnson and Johnson? Please provide a tabulated list and details of such changes, if any.
9. Please state which batches/formulas were used in the pre-clinical trials and which batches/formulas were used in the clinical trials. Please specify if there are any differences between those batches/formulas.

Office of Drug Safety, Division of Medication Errors and Technical Support (DMETS):

DMETS does not recommend the use of the proprietary name Zimykan due to its potential to look similar to Lumigan. Lumigan (Bimatoprost) is an ophthalmic solution indicated for reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension who are intolerant of other IOP-lowering agents or insufficiently responsive to other IOP-lowering medications. Lumigan is available in 8 mL containers and the usual adult dose is one drop in affected eye daily in the evening. The latter portion of the names '-MIGAN' of Lumigan and '-MYCAN' of Zimykan could potentially look-alike when scripted. Additionally, the first letters of each name ('Lu-' vs. 'Zi-') could also look-alike as well depending on how they are scripted (see below). Moreover, to compound the potential for confusion between the two drug names, both products are available only in one strength and thus the strength may be omitted on a prescription. Additionally, it is not unlikely to see a prescription for ophthalmic products and topical products written with an instruction of "Use as directed. Dispense #1" which may add to the confusion with Lumigan and Zimykan. Although it is likely that a caregiver or the patient will recognize the product differences between the two products, a transcription error may occur in the pharmacy or on the nursing floor when transcribing to the Medication Administration Record (MAR) and subsequently a wrong product may be dispensed to the patient. Although Lumigan was identified to have look-alike potential with Zimykan in EPD, the verbal prescription study showed that three participants misinterpreted the name as Lisimican, Lusimican and Lusimitan which sounds similar to Lumigan. Thus, the look-alike and sound-alike similarities with the two product names coupled with similar general direction of use compounds the potential for name confusion resulting in medication errors involving Lumigan and Zimykan.

We recommend that you promptly submit another proprietary name to the Agency for review.

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

May Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic & Dental Drug Products,
HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
2/8/05 12:47:19 PM

DSI CONSULT: Request for Clinical Inspections

Date: February 2, 2005

To: Ni A. Khin, M.D., Branch Chief
Good Clinical Practice Branch I
DSI, HFD-46

Through: Joanne L. Rhoads, M.D., M.P.H., Director, DSI, HFD-45
Stanka Kukich, M.D., Deputy Division Director, HFD-540

CC: Roy Blay, Ph.D.
Good Clinical Practice Branch I
Division of Scientific Investigations
HFD-46

From: Millie Wright., Project Manager, HFD-540

Subject: **Request for Clinical Inspections**
NDA 21-026
Barrier Therapeutic, Inc.
miconazole nitrate ointment, 0.25%

Protocol/Site Identification:

As discussed with you, the following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

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Indication	Protocol #	Site (Name and Address)	Number of Subjects
Diaper dermatitis complicated by candidiasis	BT100/USA/001	Site 19 Manuel Briones, M.D./PI Address: Francisco Bolona #610 Decima Oeste ler piso Oficina 105 Cuidadela Kennedy Guayaquil, Ecuador *See below	41 subject
Same as above	Same as above	Site 9**See below John Fling, M.D.PI Address: University of North Texas Health Science at Forth Worth 1 st Floor Pediatric Depart. 855 Montgomery St. Fort Worth, TX 76107 *See below	39 subjects

*We do not have telephone numbers for the investigators and did not want to alert the sponsor that we were requesting an inspection until we knew for certain if they were to be initiated. The contact information for my contact at Barrier is as follows:
Isabel Drzewieck, Global Head, Regulatory Operations, Phone # (609) 945-1247.
You can either contact her directly, or let me know the status and I will be happy to call her.

**Rationale for requesting site inspection at site 9: This site had a delta between success and non-success that was wider than the overall cure rate for the study.

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-026

Barrier Therapeutics, Inc.
Attention: Isabel Drzewiecki
Global Head, Regulatory Operations
600 College Road East, Suite 3200
Princeton, New Jersey 08540

Dear Ms. Drzewiecki:

We acknowledge receipt on November 24, 2004 of your November 24, 2004 resubmission to your new drug application for miconazole nitrate ointment, 0.25%.

We consider this a complete, class 2 response to our July 24, 2000 action letter. Therefore, the user fee goal date is May 24, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any question, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Mary Jean Kozma-Fornaro
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mary Jean Kozma Fornaro
2/1/05 11:18:23 AM



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

January 5, 2005

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REGULATORY AFFAIRS DEPARTMENT

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JAN 06 2005

MEGA / CDER

N-000(BC)
ORIG AMENDMENT

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

NDA 21-026

Miconazole Nitrate 0.25% Ointment

**Indication: Diaper Dermatitis complicated
by candidiasis**

**Addendum to the Amendment to
Unapproved New Drug Application**

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for ZIMYCAN™ (0.25% miconazole nitrate zinc oxide/white petrolatum) Ointment. The original sponsor of this NDA was Johnson & Johnson Consumer Products Worldwide. Ownership was transferred to Barrier Therapeutics, Inc. on June 21, 2002. At the time of ownership transfer, this NDA was subject to a non-approvable letter dated July 24, 2000. Since assuming ownership, Barrier Therapeutics has been committed to submitting an amendment containing a complete response to this July 24, 2000 action letter.

On November 24, 2004, we submitted the amendment to NDA 21-026 to respond to the deficiency cited in the Agency's "not approvable" action letter of July 24, 2000.

In reviewing the Chemistry, Manufacturing and Control Section of our November 24, 2004 amendment, we found that we had inadvertently omitted some information. We request that the attached addendum containing "Section 3.2.P.2.3.5 In-Vitro Studies" be included in our November 24, 2004 Amendment submission. In preparing the Chemistry, Manufacturing and Control Section of the amendment we used our amendment (Serial No. 046) of March 3, 2004, to our IND 21,542 for Miconazole Nitrate Ointment as the starting document. At that time we had not yet conducted the in-vitro study using Miconazole Nitrate Ointment 0.25% produced at Janssen Pharmaceutica and Miconazole Ointment 0.25% produced at DSM Pharmaceuticals, Inc. The in-vitro study was completed as we were completing the NDA amendment process and was inadvertently not added to the already completed Chemistry Manufacturing and Control Section. We apologize for this oversight and regret any inconvenience this may have caused your Division and especially the Chemistry Reviewer.

We trust that this addendum adequately completes our November 24, 2004 Amendment. Should you have any questions and/or comments regarding this submission, please contact me directly at (609) 945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

Isabel Drzewiecki

Isabel B. Drzewiecki
Global Head, Regulatory Operations

Enclosure: Form FDA 356h

IBD/ma

600 College Road East

Princeton, NJ 08540

Telephone 609.945.1200

Facsimile 609.945.1216

234



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

December 13, 2004

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DEC 14 2004 N-000(CBC)

MEGA/CDER
ORIG AMENDMENT

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

NDA 21-026
Miconazole Nitrate 0.25% Ointment

**Indication: Diaper dermatitis
complicated by candidiasis**

**General Correspondence: Response
to CMC Information Request**

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for ZIMYCAN™ (miconazole nitrate 0.25% zinc oxide/white petrolatum) Ointment and specifically to our amendment to this unapproved New Drug Application dated November 24, 2004. We also refer to a fax transmission dated December 8, 2004 received from Millie Wright, Project Manager for this NDA in your Division.

The December 8, 2004 fax indicated that the chemistry reviewer requested that we provide a table with the complete address, function, establishment registration number, contact person name, and phone number for each manufacturing, packaging, and testing facility and a statement that all facilities are ready for inspection. Please be advised that the drug product is manufactured, packaged, and tested by DSM Pharmaceuticals, Inc. in Greenville, NC. Attached is a copy of a letter from DSM to Barrier Therapeutics containing a table which includes all of the requested information.

We have been advised by our suppliers of the active pharmaceutical ingredient, miconazole nitrate, Janssen Pharmaceutica, N.V., Janssen Pharmaceutica Laan 3, B-2440 Geel BELGIUM and Normaco, Inc., 1440 Olympic Drive, Athens, GA 30601 that the requested information is available in the Drug Master File (DMF) b(4) They have also advised us that they are ready for inspection.

Should you have any questions and/or comments regarding this submission, please contact me directly at 609-945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,

ORIGINAL

Isabel Drzewiecki
Isabel Drzewiecki
Global Head, Regulatory Operations

International Inspections:

We have requested inspections because (please check appropriate statements):

- There are insufficient domestic data
- Only foreign data are submitted to support an application
- Domestic and foreign data show conflicting results pertinent to decision-making
- There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- Other: SPECIFY
Site #19 stands out as a concern based on our assessment of the overall and clinical cure rates. This site had a 33% overall cure rate for active vs. 0% for vehicle. It had a 67% clinical cure rate for active vs. 0% for vehicle. The overall cure rates for U.S. and foreign sites combined were 23% for active vs. 10% for vehicle and a 38% clinical cure rate for active and 11% for vehicle.

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by April 29, 2005. We intend to issue an action letter on this application by May 24, 2005. (Please note that this is a 6 month review cycle. We plan on having the labeling meeting May 1, 2005. If you can not meet the requested April 29, 2005 target date, please inform the Division.) Thank you.

Should you require any additional information, please contact Millie Wright.

Concurrence: (if necessary)

Dr. Stanka Kukich, Deputy Division Director

Cc: Medical Team Leader, Dr. Markham C. Luke
Cc: Medical Reviewer, Dr. Brenda Carr

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On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Stanka Kukich
2/2/05 05:43:19 PM

FDA Fax Memorandum

Date: December 8, 2004

Subject: NDA 21-026/miconazole nitrate/amendment
CMC information request

Hi Isabel,

The chemistry reviewer has the following request:

Please provide a table with complete address, the function, establishment registration number, contact person name and phone number for each manufacturing, packaging and testing facility and a statement that all the facilities are ready for inspection.

If you have questions, please call.

Respectfully,
Millie

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this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
12/9/04 11:06:54 AM
CSO

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
(Division/Office): Fran LeSane, SCSO/Fred Marsik, Micro TL rFD-520/9201 Corporate Blvd.		FROM: Division of Dermatologic and Dental Drug Products/HFD-540, Millie Wright, PM		
DATE: December 6, 2004	IND NO.	NDA NO. 21-026	TYPE OF DOCUMENT: AL	DATE OF DOCUMENT: November 24, 2004
NAME OF DRUG: miconazole nitrate	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: PDFA due date is May 24, 2005	
NAME OF FIRM: Barrier Therapeutics, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): Sponsor mtg				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input checked="" type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS Please review the clinical micro section of the NDA. You should have received Vols. 15.1-15.2, 15.7-15.18-15.40 & 15.43. If you have not received the volumes, please let me know. We will be scheduling a team mtg around the 45 th day to identify any IR needs and to make sure it is a complete response. If you have questions, please call Millie Wright/7-2084 or e-mail Wrightm.				
SIGNATURE OF REQUESTER Millie Wright, PM		METHOD OF DELIVERY (Check one) x <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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/s/

Frances LeSane
12/6/04 05:42:09 PM



Barrier Therapeutics, Inc.

A Vision for Innovative Medicine

November 24, 2004

RECEIVED

NOV 24 2004

MEGA/CDER

AZ
N-000(A2)

ORIG AMENDME

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

NDA 21-026
Miconazole Nitrate 0.25% Ointment

**Indication: Diaper dermatitis
complicated by candidiasis**

**Amendment to Unapproved
New Drug Application**

Dear Dr. Wilkin,

Reference is made to New Drug Application 21-026 for ZIMYCAN™ (0.25% miconazole nitrate zinc oxide/white petrolatum) Ointment. The original sponsor of this NDA was Johnson & Johnson Consumer Products Worldwide. Ownership was transferred to Barrier Therapeutics, Inc. on June 21, 2002. At the time of ownership transfer, this NDA was the subject of a non-approvable letter dated July 24, 2000. Since assuming ownership, Barrier Therapeutics has been committed to submitting an amendment containing a complete response to this July 24, 2000 action letter.

At this time, in accordance with the provisions of 21 CFR 314.60, Barrier Therapeutics submits herewith an amendment to NDA 21-026 to respond to the deficiency cited in the Agency's "not approvable" action letter of July 24, 2000. The primary deficiency in order to make the application approvable was that an adequate and well-controlled clinical trial needed to be conducted in which the severity of the diaper dermatitis was to be adequately defined and the involvement of *Candida albicans* was to be proven. Barrier Therapeutics conducted a Phase 3, randomized, double-blind, vehicle controlled clinical study, BT100USA/001 which is considered to be the pivotal clinical study for this indication to fulfill this requirement. The results of this study demonstrate the efficacy and safety of ZIMYCAN™ Ointment for the indication of Diaper dermatitis complicated by *Candida*. The protocol for this clinical study was also the subject of a Special Protocol Assessment.

In addition, as agreed to at a meeting on October 7, 2002 between representatives of your Agency and Barrier Therapeutics and confirmed at the Guidance Meeting held with your Agency on July 27, 2004, we committed to submitting a completely new Chemistry, Manufacturing and Controls Section in this amendment. This Section is included in this amendment and is in the ICH Common Technical Document (CTD) format.

ORIGINAL

Barrier Therapeutics has chosen the trade name of ZIMYCAN™ for our product and we requested approval of this trade name in our amendment (S-048) to our IND 21,542 on April 26, 2004. We trust that this trade name is acceptable.

At this time we wish to advise you that [redacted] will be a distributor of this product and they are included in this NDA. We have included labeling for [redacted] cartons, tubes, and package insert in Section 2.0 of this application. These labels and labeling are identical to the Barrier Therapeutics labels and labeling with the exception of the trade name. [redacted] has chosen the trade name [redacted] and we are also requesting approval of this trade name as part of this NDA amendment. Please note that the Physician's Package Insert is identical to the Barrier one except for the trade name, therefore we have not annotated it. Since [redacted] will be distributing the drug to hospitalized patients only, we have not included the proposed Patient Leaflet with this labeling. b(4)

Since clinical study BT100USA/001 was required to be conducted to fulfill the requirements for approval of this New Drug Application, we respectfully request that three years of Exclusivity be granted for the indication, "Diaper dermatitis complicated by candidiasis".

We also wish to advise you that, as agreed to at our July 27, 2004 Guidance Meeting and reflected in the minutes of that meeting dated August 25, 2004 and confirmed in your facsimile transmission of October 28, 2004, we are not including Item 10.0 (Statistical Data Section) in the amendment because it is an exact duplicate of Item 8.0 (Clinical Data Section) and will be cross-referenced to Item 8. However, we are providing a "desk copy" of Item 8 for the statistical reviewers' use. You will find it bound in black acco folders. We have also included the electronic copies in the front of the first black acco jacket. Appendices 16.2 (Subject Data Listings) and 16.3 (Case Report Forms) are contained in the clinical trial report. Instead of duplicating these subject data listings in NDA Amendment Item 11.0 and the Case Report Forms in NDA Amendment Item 12.0, we have cross-referenced these two sections back to the respective appendices. Again, we have provided "desk copies" of Appendices 16.2 and 16.3 for the Statistical reviewers' use. They are also bound in black acco folders with the electronic copies in the front of the first black jackets. The SAS data sets are also being provided electronically. These include a "Read Me" file that describes the content of the CD. Certification that the enclosed electronic media has been scanned and has been found to be virus-free is included.

Also included in this amendment to assist in your review are an Overall NDA Amendment Reviewer's Guide, a Reviewer's Guide for the Chemistry, Manufacturing and Control Section, and a Reviewer's Guide for the Clinical/Statistical Section. You will find the Overall Guide immediately following the Table of Contents in Volume 2.1. The Chemistry, Manufacturing and Controls Reviewer's Guide and the Clinical/Statistical Reviewer's Guide will be found

immediately behind the Volume Table of Contents in the first volume of Item 4 and immediately behind the Volume Table of Contents in the first volume of Item 8.

We trust that this amendment adequately responds to all of the Agency's concerns and will permit approval of the New Drug Application. Should you have any questions and/or comments regarding this submission, please contact me directly at 609-945-1247 or at idrzewiecki@barriertherapeutics.com.

Sincerely,



Isabel Drzewiecki

Global Head , Regulatory Operations

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NDA 21-026

Barrier Therapeutics, Inc.
Attention: Geert Cauwenbergh, Ph.D.
100 Overlook Center, 2nd Floor
Princeton, NJ 08540

Dear Dr. Cauwenbergh:

We acknowledge receipt on June 24, 2002, of your June 21, 2002 correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: miconazole nitrate, 0.25%

NDA Number: 21-026

Name of New Applicant: Barrier Therapeutics, Inc.

Name of Previous Applicant: Johnson & Johnson Consumer Companies, Inc.

You are responsible for any correspondence outstanding as of the effective date of the transfer.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal Service:

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

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug
Products, HFD-540
9201 Corporate Blvd.
Rockville, Maryland 20850-3202

NDA 21-026

Page 2

If you have any questions, call Millie Wright, Regulatory Project Manager, at (301) 827-2020

Sincerely,

{See appended electronic signature page}

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

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/s/

Mary Jean Kozma Fornaro
7/11/02 08:52:30 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

NDA 21-026

Food and Drug Administration
Rockville MD 20857

Johnson & Johnson Consumer Companies, Inc.
Attention: Paul F. Manley
Director, Drug Regulatory Affairs
199 Grandview Road
Skillman, New Jersey 08558-9418

JUL 24 2000

Dear Mr. Manley:

Please refer to your new drug application (NDA) dated January 21, 2000, received January 24, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for miconazole nitrate ointment, 0.25%.

We acknowledge receipt of your submissions dated February 1, March 17 and 28, May 10 and 22, and June 26, 2000. Your submission of January 21, 2000, constituted a complete response to our June 28, 1999, action letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiency may be summarized as follows:

You need an adequate and well controlled clinical trial, in which the severity of disease is adequately defined and *Candida albicans* involvement adequately documented, that demonstrates the effectiveness and safety of miconazole nitrate ointment, 0.25%, and the contribution of each of its active components (21 CFR 300.50), in those clinical subsets that correspond to your proposed indication. Any planned clinical trial should have sufficient representation from both genders and from minorities. Prolonged treatment beyond 7 days, repeated usage for relapse, and development of antifungal resistance should be addressed.

Although not the basis for the non approval of this application, please note the following:

CMC Microbiology

1. Please revise your microbial limits to include separate Total Aerobic Microbial Count and Total Combined Yeasts and Molds acceptance criteria. Acceptable limits for Total Aerobic Microbial Count and Total Combined Yeasts and Molds would be ≤ 100 cfu/g and ≤ 50 cfu/g, respectively.

2. Your microbial limits test methodology is not designed to detect all "harmful" microorganisms. Therefore, the "Shall contain no detectable harmful microorganisms" acceptance criteria is not appropriate. Please establish acceptance criteria for each individual or class of pathogenic indicator microorganism (e.g., *Staphylococcus aureus*, Pseudomonaceae, *Candida albicans*, *E. coli*, Enterobacteriaceae) enumerated by the test.

CLINICAL MICROBIOLOGY

1. Since the activity of miconazole may be decreased at either extreme of alkaline or acidic pH, and because there is the potential for this topical ointment to be used in an alkaline environment, the activity of the miconazole at the concentration of 0.25% should be determined *in vitro* under alkaline conditions against *Candida albicans*.
2. There are no recognized susceptibility testing interpretive criteria for miconazole nitrate. You will need to validate any criteria that you use for interpreting microbiology and clinical outcome data.

In addition, please note that the tradename, Pediastat, was found unacceptable, since there are other similar appearing and similar sounding approved tradenames.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with this division to discuss what further steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Millie Wright, Project Manager at (301) 827-2020.

Sincerely,



Jonathan K. Wilkin, M.D.

Director

Division of Dermatologic and Dental
Drug Products

Office of Evaluation V

Center for Drug Evaluation and Research

68

JUN 26 2000

~~BT~~
GC

VIA OVERNIGHT MAIL
Dr. Jonathan Wilkin
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room – Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA 21-026

PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment

**Amendment to a pending
application**

MICs of *Candida albicans* Isolates

Dear Sir or Madam:



Purpose The purpose of this document is to provide you with recent information on the minimum inhibitory concentrations (MICs) of 448 isolates of vaginal *C. albicans*.

Background The MICs of isolates of vaginal *Candida albicans* were determined as part of a study of a new treatment regimen for vulvovaginal yeast infection. The women from whom the organisms were isolated were from across the U.S. Baseline cultures were obtained and the isolates submitted to a reference laboratory to determine the MICs; 448 isolates were taken and measured.

The study has been completed but has not yet been reported.

The graph enclosed represents the results of the MIC evaluations.

Continued on next page

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ORIGINAL

MICs of *Candida albicans* Isolates, Continued

Discussion

This graph indicates that over 70% of the isolates have an MIC of 0.05 mcg/mL or less. Ninety five percent have MIC values of 1.6 mcg/mL or less; the highest MIC measured was 6.25 mcg/mL.

Questions / Comments

If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl

Regulatory Affairs Manager

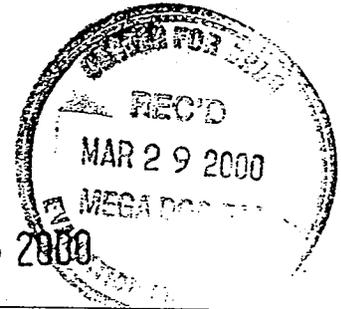
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Johnson & Johnson
CONSUMER COMPANIES, INC.

NDA 21-026 AMENDMENT

BL



MAR 28 2000

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA 21-026
PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment
**Amendment to a pending
application - Labeling**

Electronic and Hard Copy of Revised Product Insert

Dear Sir or Madam:

Purpose

The purpose of this document is to provide you with electronic and hard copies of the proposed product insert for PEDIASTAT™ (Miconazole Nitrate, USP 0.25%) Diaper Rash Ointment.

Background

NDA 21-026 was submitted on August 25, 1998. On June 28, 1999 a not approvable letter was issued by the agency. July 1, 1999, Johnson & Johnson Consumer Companies, Inc. responded that with our intent to submit an amendment to answer the not-approvable issues. On January 21, 2000, a full response to the not-approvable letter was submitted to the agency. On March 10, 2000, a request was made for a hard and electronic copy of the proposed product insert updated to match the newly stated indication.

Continued on next page

ORIGINAL

MAR 28 2000

Electronic and Hard Copy of Revised Product Insert,
Continued

**This
Submission**

This submission includes the following:

- A hard copy of the draft of the proposed product insert and
- A 3.5" disk containing the same document

**To be
Submitted**

On March 24, 2000, a request was made for a safety update. This work is being done and will be submitted as soon as it is completed.

**Questions /
Comments**

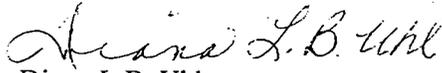
If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl
Regulatory Affairs Manager

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52

Johnson & Johnson
CONSUMER COMPANIES, INC.

May 22, 2000



Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic and
Dental Drug Products
Office of Drug Evaluation V
HFD-540
Center for Drug Evaluation
And Research
Document Control Room N-115
Food and Drug Administration
9201 Corporate Boulevard
Rockville, MD 20850

NDA No. 21-026
PEDIASTAT™
(miconazole nitrate, USP 0.25%)
Diaper Rash Ointment

NEW CORRESP

NC

GENERAL CORRESPONDENCE:
Copies of the Advisory Committee
Briefing Book

Dear Dr. Wilkin:

Reference is made to the Dermatologic Drugs Advisory Committee Meeting which is scheduled for June 30, 2000, in order to discuss the PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment, NDA No. 21-026. Johnson & Johnson Consumer Companies, Inc. (JJCCI) would like to inform the Division that fourteen copies of the PEDIASTAT Diaper Rash Ointment briefing book were sent directly to Ms. Mille Wright, Project Manager. Under a separate cover letter, fourteen copies of the briefing book were also sent to Ms. Tracy Riley, secretary for the Advisory Committee Meeting. The briefing book is clearly marked in uppercase, bolded script "AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION."

The Advisory Committee Meeting is quickly approaching and we would like to remind the Division that we have not yet received the questions which will be proposed to the advisory committee members. JJCCI would appreciate if the Division could communicate these questions to us as early as possible or the possibility of having a teleconference in order to discuss what the Division may be planning to ask at this meeting so that we can plan accordingly.

5/25/00
Reviewers have
described to
reviewer
NAT
[Signature]

We would appreciate the Division's cooperation with this matter. If there are any comments or questions, please contact me at (908) 874-1402, FDA direct line (908) 874-1700, or fax number (908) 874-1118.

Sincerely,

A handwritten signature in cursive script, appearing to read "Diana Uhl", with a stylized flourish or initial at the end.

Diana Uhl
Manager,
Regulatory Affairs

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Cc: Fourteen copies of the briefing book and this cover letter were sent to Ms. Mille Wright, Project Manager, Division of Dermatologic and Dental Drug Products

421

Johnson & Johnson
CONSUMER COMPANIES, INC.

MAR 17 2000

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room – Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA 21-026

PEDIASTAT™ (miconazole nitrate,
USP 0.25%) Diaper Rash Ointment

**Amendment to a pending
application**

Copies of Tube and Cartons for NDA 21-026

BL

Dear Sir or Madam:

NDA ORIG AMENDMENT

Purpose

The purpose of this document is to provide you with copies of the preliminary proposed tubes and cartons for PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment.

Background

NDA 21-026 was submitted on August 25, 1998. On June 28, 1999 a not approvable letter was issued by the agency. July 1, 1999, Johnson & Johnson Consumer Companies, Inc. responded that with our intent to submit an amendment to answer the not-approvable issues. On January 21, 2000, a full response to the not-approvable letter was submitted to the agency. On February 23, 2000, a request was made to submit mock-up labeling from the carton and tube to the NDA.

Continued on next page

ORIGINAL

C:\WINDOWS\TEMP\Copies of tube carton.doc
Last printed 03/17/00 10:33 AM
Page 1 of 2



MAR 17 2000

Copies of Tube and Cartons for NDA 21-026, Continued

**This
Submission**

This submission includes the following:

- Color copies or photocopies of the tube and carton labeling* for all sizes to be marketed and samples:
 - 5g samples
 - 30g marketed
 - 60g marketed

* This is a mock-up of the labeling. The not approvable letter indicated that the name PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment may not be acceptable so the design of the carton and tube was not completed. The mock up; was completed by inserting the PEDIASTAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment name.

**To be
Submitted**

On March 10, 2000, a request was made for a hard and electronic copy of the product insert updated to match the newly stated indication. The insert is being revised and is expected to be submitted on or before March 24, 2000.

**Questions /
Comments**

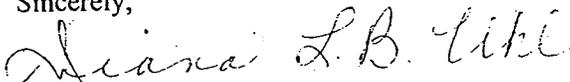
If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: dthl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl
Regulatory Affairs Manager

44

Johnson & Johnson
CONSUMER COMPANIES, INC.

NDA SUPPLEMENT

MAY 10 2000

VIA OVERNIGHT MAIL
Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental
Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA No. 21-026
Name of Product PEDIASAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment
Type of Submission Safety Update

54

Dear Dr. Wilkin,

Purpose The purpose of this document is to provide the updated safety information that you requested.

Background The original NDA 21-026 for PEDIASAT™ (miconazole nitrate, USP 0.25%) Diaper Rash Ointment was filed October 24, 1998. The first Safety Update was submitted on January 24, 1999. On March 24, 2000, the agency requested an update for final review.

Safety Update

- No clinical studies are currently ongoing nor have any new studies been initiated in the United States or Europe.
- No new or additional safety data is available in the United States or Europe, including no pertinent animal data, no demonstrated or potential adverse effects of the product, no clinically significant drug drug interactions or no other safety considerations such as data from epidemiological studies of related drugs.
- No serious adverse events have been reported in the United States or Europe.

Status of Requests By our records, this completes all open requests from the agency for this NDA.

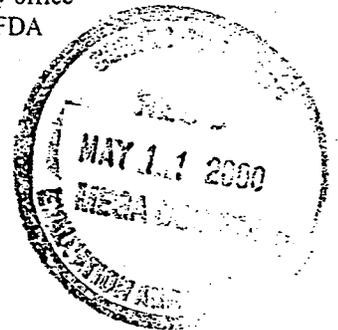
Questions If you have questions or comments about this submission, please contact me:

Phone: (908) 874-1402 direct line into my office
Phone: (908) 874-1700 line reserved for FDA
FAX: (908) 874-1118
e-mail: duhl@cpcus.jnj.com

Sincerely,

Diana L.B. Uhl

Diana L.B. Uhl
Manager, Regulatory Affairs



ORIGINAL



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFD-540 / Wright M.

NDA 21-026

Food and Drug Administration
Rockville MD 20857

MAR 16 2000

Johnson & Johnson Consumer Companies, Inc.
Attention: Paul F. Manely
Director, Drug Regulatory Affairs
199 Grandview Road
Skillman, New Jersey 08558-9418

Dear Mr. Manely:

We acknowledge receipt on January 24, 2000 of your January 21, 2000 resubmission to your new drug application (NDA) for Pediasat Diaper Rash Ointment (miconazole nitrate), 0.25%.

This resubmission contains additional clinical and chemistry submitted in response to our June 28, 1999 action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is July 24, 2000.

If you have any questions, call Millie Wright, Project Manager, at (301) 827-2020.

Sincerely,

MJE 3/16/00

Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff
Division of Dermatologic and
Dental Drug Products, HFD-540
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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NDA 21-026

CC:

NDA 21-026
HFD-540/Div File
HFD-540/Wright
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Ko
HFD-540/DeCamp
HFD-540/Timmer
HFD-540/Jacobs
HFD-540/Nostrandt
HFD-540/Bashaw
HFD-540/Tandon
HFD-540/AI-Osh
HFD-520/Sheldon

DISTRICT OFFICE

Drafted by: MAW/February 13, 2000
Initialed by: MJK/March 15, 2000
Final: MAW/March 15, 2000
Filename N21026rs (word)

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)
(DDR: Update the user fee goal date based on the class of resubmission)

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FEB 1 2000

VIA OVERNIGHT MAIL
Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA No. 21-026

**PEDIASTAT™ (miconazole
nitrate) Diaper Rash
Ointment, 0.25%**

**AMENDMENT to an
Unapproved Application**

AMENDMENT to NDA 21-026 - Correction to the Response to the Not Approvable Letter

- Purpose** The purpose of this document is to provide the agency with corrected information to the January 21, 2000 submission in response to the not approvable letter issued June 28, 1999 for NDA 21-026.
- Background** On August 24, 1998, NDA 21-026 was submitted to the agency for review. Ultimately, a not-approvable letter was issued on June 28, 1999. On July 1, 1999, a response was made to the agency indicating that we would be submitting an amendment. On January 21, 2000 a response was submitted to the not-approvable letter.
- Submission**
- This submission includes Page 000 00095, which was inadvertently left out of Attachment 4.
 - The paragraph in the cover letter titled "New Information" currently reads ... Finished Product Specification ... Report . This should read "The revised Finished Product Specification with a maximum of the associated impurity and a maximum of all impurities and Specification Report .. (Attachment 4)" **b(4)**
 - Also enclosed is a revised Table of Contents showing the correct Specification number for Attachment 4.

199 GRANDVIEW ROAD, SKILLMAN, NJ 08558-9418 (908) 874-1000

JOHNSON & JOHNSON CONSUMER PRODUCTS COMPANY • JOHNSON & JOHNSON CONSUMER PRODUCTS WORLDWIDE
PERSONAL PRODUCTS COMPANY • PERSONAL PRODUCTS WORLDWIDE
JOHNSON & JOHNSON WORLDWIDE ABSORBENT PRODUCTS AND MATERIALS RESEARCH

FEB 1 2000

Conclusion We apologize for the errors and believe the enclosed information completes the response to the the agency's concerns regarding this NDA. A copy of this submission has been sent to the Newark, NJ, FDA Field Office.

Questions If you have questions or comments regarding this submission, please contact me:

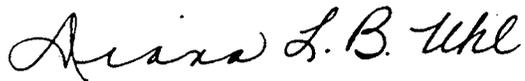
Phone: (908) 874-1700 (line reserved for FDA)

Phone: (908) 874-1402 (direct line to my office)

FAX: (908) 874-1118

e-Mail: duhl@cpcus.jnj.com

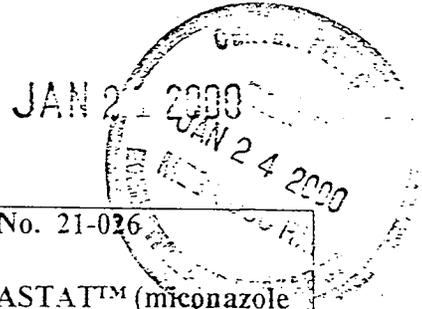
Sincerely,



Diana L.B. Uhl, Manager, Regulatory Affairs

Appears This Way
On Original

Johnson & Johnson
CONSUMER COMPANIES, INC.
NDA AMENDMENT



VIA OVERNIGHT MAIL
Jonathan Wilkin, MD, Director
Division of Dermatologic and Dental Products
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA No. 21-026
PEDIASTAT™ (miconazole nitrate) Diaper Rash Ointment, 0.25%
AMENDMENT to an Unapproved Application

AMENDMENT to NDA 21-026 - Response to the Not Approvable Letter

Purpose The purpose of this document is to provide the agency with information in response to the not approvable letter issued June 28, 1999 for NDA 21-026. The issues cited relate to the Clinical and Chemistry sections of the NDA.

Background On August 24, 1998, NDA 21-026 was submitted to the agency for review. Ultimately, a not-approvable letter was issued on June 28, 1999. On July 1, 1999, a response was made to the agency indicating that we would be submitting an amendment.

Submission This submission includes a full response to the not-approvable issues and the request for information.

Reviewer's notes

- Each issue is listed below in the same order as in the June 28, 1999 letter. The agency's description of the issue is *italicized*; our response is in normal font.
- A Table of Contents is provided.
- Replacement pages for the NDA are included, where necessary.
- For your convenience, the references cited are included and cited by first author and year. References are in alphabetical order.

New Information An HPLC peak in the finished product has now been identified as a BHT-related impurity as a consequence of production transfer to the Beerse, Belgium site. This is not a new peak but a peak for which better resolution has enabled identification and quantitation. BHT is a low-level component of the U.S.-manufactured petrolatum. The levels in the finished product will be controlled by adding a maximum BHT level to the petrolatum specification and a maximum impurity level for this impurity to the finished product specification.

b(4)

ORIGINAL

4

JAN 21 2000

**New
Information**

See Attachments for:

- The revised White petrolatum specification with a maximum of BHT allowed. (Attachment 11) with **b(4)**
- Test Method (BHT in Petrolatum) and Justification for (Attachment 11)
- The revised Finished Product Specification with a maximum of of the associated impurity and a maximum of all impurities and Specification Report. (Attachment 4)
- Test Method (Degradation Products of Miconazole Nitrate in ZOOM Topical Ointment), Protocol for additional Method Validation for Amendment to the "Protocol for Additional Method Validation" for and Addendum to August 5, 1999, Challenge Stress Study Report for testing the level of the associated impurity in the finished product. (Attachment 12) **b(4)**

Conclusions

We believe the enclosed information comprehensively answers the agency's concerns regarding this NDA. We are happy to answer any additional points of issue you may have, and are open to discussing the merits of this product at an Advisory Committee if you feel this is necessary.

Questions

If you have questions or comments regarding this submission, please contact me:

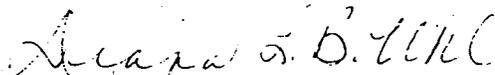
Phone: (908) 874-1700 (line reserved for FDA)

Phone: (908) 874-1402 (direct line to my office)

FAX: (908) 874-1118

e-Mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl, Manager, Regulatory Affairs

Appears This Way
On Original

JUN 28 1999

NDA 21-026

Johnson & Johnson Consumer companies, Inc.
Attention: Paul F. Manley
Director, Drug Regulatory Affairs
199 Grandview Road
Skillman, New Jersey 08558-9418

Dear Mr. Manley:

Please refer to your new drug application (NDA) dated August 24, 1998, received August 24, 1998, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Pediastat (miconazole nitrate) Diaper Rash Ointment, 0.25%.

We acknowledge receipt of your submissions dated October 6, November 18, and November 20, 1998; January 7, March 1, March 30, and May 25, 1999.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

CLINICAL:

1. The indication requires clear-cut definition so that the product may be recommended for a target population who can receive the clinical benefit without introducing the risk of drug resistance through indiscriminate use. An indication for the treatment of moderate or severe diaper dermatitis in association with *C. albicans* infection in infants may be acceptable, if a clinical trial, in which the severity of disease is properly defined and *C. albicans* infection is demonstrated both by wet mount examination of pseudohyphae and by culture, shows superiority of miconazole nitrate, 0.25% ointment over the ointment base.
2. Any planned clinical trial should have sufficient representation from both sexes and from minorities to permit proper subset analysis.
3. The possibility of adverse effect by the ointment base should be addressed in a 3-arm study which includes a treatment group not exposed to the ointment base.
4. The relevance of the dermal safety studies should be addressed, especially with respect to (i) target population being infants and not adults, (ii) test sites not in diaper area, and (iii) appropriateness of using UVA alone in phototoxicity testing and in the challenge phase of the photoallergenicity study.

CHEMISTRY:

1. During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.
2. The release testing program is unacceptable in that:
 - a. degradation testing must be included in the release testing program,
 - b. the Appearance, Odor, and Weight tests, as well as the ZnO ID and assay tests, must should be part of the release testing program,
 - c. the ID test for miconazole nitrate should be changed to USP <197> or <201>,
 - d. the batch sampling plan is unacceptable. Every batch lot must meet its analytical specifications via testing (c.f., 21 CFR 211.165).
3. Please verify that no reprocessing of the drug product will occur under any circumstances.

Although not the basis for the non approval of this application, the following information is requested:

1. The procedure to determine the free fatty acids in trihydroxystearin lacks detail. Please submit the exact test method or SOP to measure free fatty acids. Alternately, the compendial method may be used.
2. The nature of the internal coating of the container /closure system is not specified; it is, however, stated that the coating is acceptable for food-contact use. More information about the internal coating is required, specifically, its chemical composition.
3. You have not specified the humidity at which the accelerated stability data were obtained. Also, storage conditions were stated to be below 30°C, but should probably be restated to indicate: Store at room temperature.
4. The tradename, Pediastat, was found unacceptable. The principal reason was that the suffix "stat" implied fast-acting.
5. If an OTC Final Monograph for Diaper Rash that includes zinc oxide as active ingredient is published, contribution of therapeutic effect by zinc oxide may need to be demonstrated.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment

should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,



Jonathan K. Wilkin, M.D., Director
Division of Dermatologic and Dental Drug
Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

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cc:

Archival NDA 21-026
HFD-540/Div. Files
HFD-540/M. Wright
HFD-540/Kozma-Fornaro
HFD-540/Wilkin
HFD-540/Walker
HFD-540/Ko
HFD-540/Jacobs
HFD-540/Nostrandt
HFD-540/DeCamp
HFD-540/Timmer
HFD-540/Srinivasan
HFD-540/Gao
HFD-880/Bashaw
HFD-880/Tandon
HFD-520/King
HFD-002/ORM
HFD-105/ADRA
HFD-95/DDMS
HFD-830/DNDC Division Director
DISTRICT OFFICE

Concurrence:

HFD-540/Walker
HFD-540/DeCamp
HFD-540/Jacobs
HFD-540/Bashaw
HFD-540/Srinivasan
HFD-540/Kozma-Fornaro

Drafted by: maw/June 23, 1999

Initialed by:

final:

filename: N21026NA.WPD

NOT APPROVABLE (NA)

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189

Johnson & Johnson
CONSUMER COMPANIES, INC.

ORIGINAL

MAY 25 1999

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA 21-026
PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment
**Amendment to a pending
application**

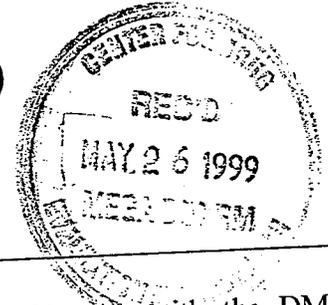
ORIG AMENDMENT

BC

May 25, 1999

Corrected DMF Letter -

b(4)



Dear Sir or Madam:

Purpose

The purpose of this document is to provide you with the DMF information from which you requested on April 23, 1999.

b(4)

Background

NDA 21-026 was submitted on August 25, 1998. Subsequent to the filing, the agency requested a change in the DMF letter provided by which was found on page 004 00089 of the NDA. The letter of authorization incorrectly listed instead of the name and address of Johnson & Johnson Consumer Companies, Inc.

b(4)

On May 6, 1999 sent a corrected letter to the agency. This formal submission is to ensure that the letter is submitted to the NDA.

Continued on next page

MAY 25 1999

Corrected DMF Letter -

Continued b(4)

This
Submission

This submission includes the following:

- The corrected authorization letter from 00089 in NDA 21-026.

to replace page 004 b(4)

To be
Submitted

By our records, we have no unanswered requests related to this NDA.

Questions /
Comments

If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,

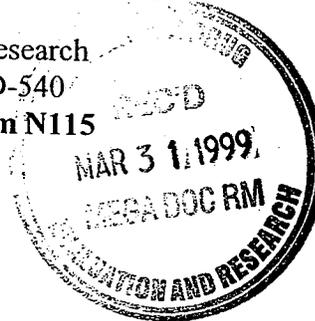


Diana L.B. Uhl
Regulatory Affairs Manager

NDA ORIG AMENDMENT

MAR 30 1999

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850



NDA 21-026
PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment
Amendment to a pending
application

March 22, 1999

Response to Requests for Information

Dear Sir or Madam:

Purpose

The purpose of this document is to provide you with the information that has been requested recently by phone and fax and to update you on the status of all requests to date.

Background

NDA 21-026 was submitted on August 25, 1998. Subsequent to the filing, the agency requested information related to the filing. The status of these requests follow:

Date of Request	Status	Comments
9/14/98	Complete	Request for more desk copies of volume 1.1
10/5/98	Complete	Request for information on and subsequent request for specifications and test procedures for

b(4)

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Response to Requests for Information, Continued

Background (continued)

Date of Request	Status	Comments	Location
10/20/98	Complete	Various requests from a teleconference held 10/20/98 for which the last submission was made 3/1/99	N/A
About 3/1/99	Faxed and enclosed	<ul style="list-style-type: none">• A missing page from the 83-129 study• Explanation of the difference between Chemoderm 1001 and 1001B fragrances• UV absorbance spectrum of the active ingredient miconazole nitrate	Attachment 1 2 3
3/9/99	Enclosed	<ul style="list-style-type: none">• Various requests listed in FDA Fax Memo of March 9, 1999	Attachment 4A - 4G
3/12/99	Enclosed	Request for quantitative formulation for the test samples used in the <i>in vitro</i> zinc permeation study	Attachment 5

b(4)

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Response to Requests for Information, Continued

**This
Submission**

- Page 6 of the final report for 83-129 is included as **b(4)** Attachment 1. It is numbered as page 008 00088A of the NDA.
- Attachment 2 is a fax (March 4, 1999) containing the information on the Chemoderms (1001 and 1001B).
- Attachment 3 is a fax (March 5, 1999) and the UV absorbance spectrum of the active ingredient miconazole nitrate.
- Attachments 4A - 4G are the narrative and documents that are the responses to the FDA Fax Memo of March 9, 1999 (including a copy of the original fax).
- Attachment 5. are the formulae for the test samples used in the *in vitro* permeation (of zinc) study.

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Response to Requests for Information, Continued

(continued)
**Status of all
responses**

According to our records, we have now completed all the requests to date.

**Questions /
Comments**

If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl
Regulatory Affairs Manager

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All pages are accounted for in this document.
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FDA Fax Memo

Date: March 9, 1999

Subject: NDA 21-026/Pediastat/Information request

Hi Diana,

Could you please provide us with the following additional information:

1. Vol 1.19 page 008 001657. Please provide English translation.
2. Vol 1.15 page 008 000399. Appendix C.8.6. The title says this Table concerns subjects with or without Candida at rash site at baseline. However, the first row of the Table has the wording "at the anal site" twice. Is this a wrong Table? Please provide correct data on those analyzed using stratification with *C. albicans* at rash site.
3. The stratified data submitted on 11/18/98 states there are 22 patients treated with active drug and 26 with ointment base within the *C. albicans*+ group, and 26 treated with active drug and 23 with ointment base within the *C. albicans*- group. Please give I.D. numbers of these patients.
4. a) Please provide the ethnic distribution of the two Australian studies.
b) Skin types in the Australian studies: fair, medium and dark - how were they defined?
5. Study 83-129. CRFs of the 3 discontinuations due to AE have not been submitted. Have they previously received waiver not to have the CRFs submitted? If unavailable, what is the rationale? They must supply details of those 3 cases satisfactorily. **b(4)**
6. Study MIC-BEL-1, Case 11. Please supply a narrative in English with details of her moniliasis, including outcome, and use of the test medication.

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FDA Fax Memo

Date: March 9, 1999

Subject: NDA 21-026/Pediastat/Information request (Cont.)

7. The Norway letter - is it ready? When ready, please give a complete version from beginning to end.

If you have questions, please call.

Respectfully,

Millie

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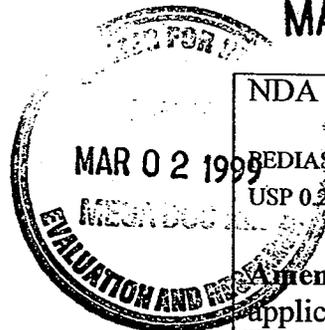
143

Johnson & Johnson
CONSUMER PRODUCTS WORLDWIDE

ORIGINAL

MAR 1 1999

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room - Room N115
9201 Corporate Boulevard
Rockville MD 20850



NDA 21-026
BEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment
Amendment to a pending
application

February 19, 1999

Final Response to October 20, 1998 Teleconference

Dear Sir or Madam:

ORIG AMENDMENT
BIB

Purpose The purpose of this document is to provide you with the final information requested during the teleconference of October 20, 1998. The information finishing out these requests is the results of an *in vitro* permeation (elemental zinc) study.

Background NDA 21-026 was submitted on August 25, 1998. Subsequent to the filing, the agency requested a teleconference to discuss some issues related to the filing.

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Last printed February 19, 1999 4:12 PM
Page 1 of 5

Division of Johnson & Johnson Consumer Companies, Inc.

199 Grandview Road, Skillman, NJ 08558-9418 (908) 874-1000

Final Response to October 20, 1998 Teleconference, Continued

Background

In a November 18, 1998 submission were the following:

- A 3.5" computer disk with a WORD 97 file of the proposed labeling
- 2-3.5" computer disks and documents associated with the SAS files for the clinical studies.
- An explanation of the difference between the two formulas 610-58 and 610-73.

On November 20, 1998, the following was submitted:

- Foreign labeling and translations except for the Portuguese translation of the labeling for DAKTOZIN diaper rash ointment.
- A timeline estimate for submitting results of Franz Cell method for zinc permeation.
- Data from the stratification by severity by *Candida* (+) or (-).
- A discussion of an adequate number of subjects relative to the ICH Guideline E1A.
- A discussion of the merits of the use of an active control in the pivotal studies.
- A discussion of microbial colonization vs. microbial infection

In a January 7, 1999 submission, the following was submitted:

- Portuguese translation of the package insert for the DAKTOZIN diaper rash ointment product.
- The four-month safety update.

Continued on next page

Final Response to October 20, 1998 Teleconference, Continued

**This
Submission**

This submission includes the following:

- The *in vitro* permeation assay results to detect elemental zinc in the recovery fluid when product is applied to human cadaver skin.

**To be
Submitted**

By our records, the questions posed in the October 20, 1998 teleconference have been answered.

**For Your
Information**

Penetration of zinc into the skin strata:

Dr. Bashaw, who requested that the *in vitro* permeation test for elemental zinc be performed, also suggested that penetration of the zinc into the skin strata, "would be nice, if appropriate." These data were not collected. Time did not allow for the development of validated procedures for washing the ointment off the cadaver skin, and the recovery and quantitation of elemental zinc in the epidermis and dermis.

**Questions /
Comments**

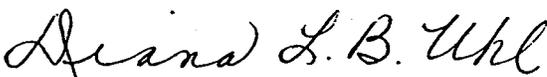
If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl

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102

Su, BM

Johnson & Johnson
CONSUMER COMPANIES, INC.

JAN 7 1999

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-540
Document Control Room – Room N115
9201 Corporate Boulevard
Rockville MD 20850

NDA 21-026

PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment

**Amendment to a pending
application**

January 6, 1999

Partial Response to October 20, 1998 Teleconference

Dear Sir or Madam:



Purpose

The purpose of this document is to provide you with part of the information requested during the teleconference of October 20, 1998 and the four (4)-month safety update.

Background

NDA 21-026 was submitted on August 25, 1998. Subsequent to the filing, the agency requested a teleconference to discuss some issues related to the filing.

This Submission

This submission includes the following:

- Portuguese translation of the package insert for the DAKTOZIN diaper rash ointment product.
- The four-month safety update.

Continued on next page

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Partial Response to October 20, 1998 Teleconference, Continued

Previously Submitted

On November 18, 1998, the following items were submitted:

- A 3.5" computer disk with a WORD 97 file of the proposed labeling
- 2-3.5" computer disks and documents associated with the SAS files for the clinical studies.
- An explanation of the difference between the two formulas 610-58 and 610-73.

On November 20, 1998, the following was submitted:

- Foreign labeling and translations except for the Portuguese translation of the labeling for DAKTOZIN diaper rash ointment.
- A timeline estimate for submitting results of Franz Cell method for zinc permeation.
- Data from the stratification by severity by *Candida* (+) or (-).
- A discussion of an adequate number of subjects relative to the ICH Guideline E1A.
- A discussion of the merits of the use of an active control in the pivotal studies.
- A discussion of microbial colonization vs. microbial infection

To be Submitted

By our records, the following will be outstanding upon your receipt of this submission:

- The results of the zinc oxide permeation test.

If this is incorrect, please contact me.

Continued on next page

Partial Response to October 20, 1998 Teleconference,
Continued

**Questions /
Comments**

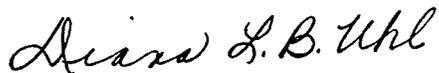
If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl
Regulatory Affairs Manager

ORIGINAL

Johnson & Johnson
CONSUMER COMPANIES, INC.

ORIG AMENDMENT

BZ

NOV 18 1998

VIA OVERNIGHT MAIL
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation V, HFD-54
Document Control Room - Room 545
9201 Corporate Boulevard
Rockville MD 20850



NDA 21-026
PEDIASTAT™ (Miconazole Nitrate,
USP 0.25%) Diaper Rash Ointment
Amendment to a pending
application

November 18, 1998

Partial Response to October 20, 1998 Teleconference

Dear Sir or Madam:

Purpose

The purpose of this document is to provide you with part of the information requested during the teleconference of October 20, 1998.

Enclosures

Enclosed per your request are the following:

- A 3.5" computer disk with a WORD 97 file of the proposed labeling.
- 2- 3.5" computer disks and documents associated with the SAS files for the clinical studies
- An explanation of the difference between the two formulas 610-58 and 610-73.

Continued on next page

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Last printed November 17, 1998 10:51 AM
Page 1 of 3

Partial Response to October 20, 1998 Teleconference, Continued

Formulations

The following table indicates the make up of the two formulations.

Note:

- Chemoderm 1001
was reported to be a possible sensitizer. **b(4)**
- Chemoderm 1001/B is the same fragrance without the
fraction.

Table 1: Differences between formulas 610-58 and 610-73

Ingredient	Formula 610-58 %w/w	Formula 610-73 %w/w
Miconazole Nitrate, USP	0.25	0.25
Trihydroxystearin		
Zinc Oxide, USP	15.00	15.00
Chemoderm 1001		
Chemoderm 1001/B		
White Petrolatum, USP	81.35	81.35

b(4)

Remaining Questions

The remaining information requested at the teleconference or a
timeline to completion will be sent to the agency this week.

Continued on next page

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**Partial Response to October 20, 1998 Teleconference,
Continued**

**Questions /
Comments**

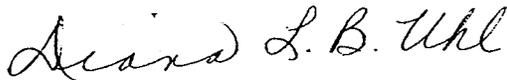
If you have any questions about this information, please contact me:

Phone: (908) 874-1700 (line reserved for FDA)

FAX: (908) 874-1118

e-mail: duhl@cpcus.jnj.com

Sincerely,



Diana L.B. Uhl
Regulatory Affairs Manager

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On Original**

45-Day Forward Planning Meeting

OCT 13 1998

NDA 21-026: Pedistat™ Diaper Rash Ointment 0.25% Miconazole Nitrate Diaper Rash Ointment

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:

Type II: _____
Type III: _____
Type IV: _____

b(4)

DMF Number	Date of LOA	Date of Last Amendment	Date of Last Deficiency Letter	Date of Last Review	Completion Date
	-----	-----	-----	10/98*	10/98
	11/12/96	NA	NA	NA	5/99
	8/12/98	NA	NA	6/14/95	5/99

b(4)

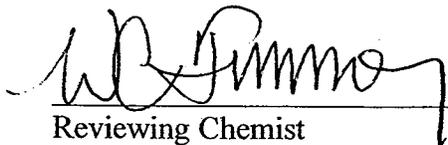
*This DMF for the drug substance has been reviewed in HFD-590; it is waiting for the TL's signature; there were no deficiencies.

4. A trademark consult for **PEDISTAT** will be submitted to the L&N Committee.
5. The sponsor states that all facilities are ready for inspection.
6. The EER request was submitted in 9/98 for two facilities. Janssen Pharmaceutica in Belgium is both the drug substance and drug product manufacturer, and J & J in NJ is a secondary tester, Janssen (drug substance) is ACCEPTABLE, Janssen (drug product) has been assigned an inspection; J&J is ACCEPTABLE.
7. The sponsor is claiming a categorical exclusion to the environmental assessment.
8. The estimated date of completion of the DMFs and NDA is May 1999.

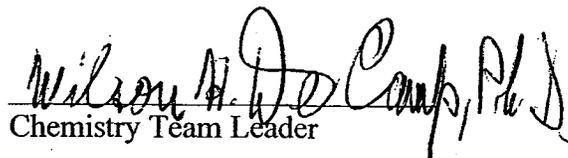
CMC SECTION CHECKLIST:

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-



Reviewing Chemist



Chemistry Team Leader

Forward Planning Meeting Summary

Date: October 13, 1998

Participants from the FDA:

HFD-540

Jonathan Wilkin, M.D., Division Director

Hon-Sum Ko, M.D., Medical Reviewer

Amy Nostrandt, Ph.D., Pharmacology/Toxicology Reviewer

Abby Jacobs, Ph.D., Pharmacology/Toxicology Team Leader

Millie Wright, R.N., M.S.N, Project Manager

HFD-725

R.Srinivasan, Ph.D., Biostatistics Team Leader

Ping Gao, Ph.D., Biostatistics Reviewer

HFD-880

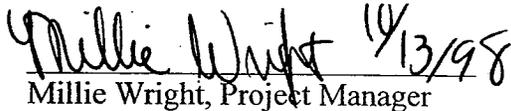
Dennis Bashaw, PharmD., Biopharmaceutic Team Leader

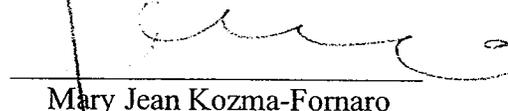
OCT 13 1998

SUBJECT: NDA 21-026 Pediastat™ (miconazole nitrate) 0.25% Ointment

OBJECTIVE: To determine the fileability of NDA 21-026

The meeting was convened to determine the adequacy of NDA 21-026 for filing. All sections of the New Drug Application (NDA) were evaluated in terms of the general content and format requirements. The application was deemed fileable.


Millie Wright, Project Manager


Mary Jean Kozma-Fornaro
Supervisor, Project Management Staff

Attachments (7 checklists)

CC:

Orig NDA 21-026

Div File

HFD-540/Wright

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Filability Checklist:

45 DAY MEETING CHECKLIST

FILEABILITY:

OCT 13 1999

On initial overview of the NDA application:

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)? NO

Study Number:

Study Title:

Sample Size:

Arms:

NDA Volume:

Pages:

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) (2) (Y/N) Reference drug: **Not applicable**

Identification of pivotal trials:

Pivotal Study #1: Protocol Number: **12966.37A**

Location in NDA: Protocol: **vol1.16** Study Report: **vol 1.16**

Study Title: **An evaluation of the efficacy of BPC formula #610-73 in the treatment of acute diaper dermatitis in infants and prevention of onset of severe diaper dermatitis**

Study design: Randomized (Y/N) Double Blind (Y/N) Placebo controlled (Y/N)
Multicentered (Y/N) **This study is of parallel group comparison.**

Indication: **acute diaper dermatitis in infants**

Study arms (dosage, duration, treatment length for each arm): **0.25% miconazole nitrate vs ointment base applied at every diaper change for 7 days**

Pivotal Study #2: Protocol Number: **12966.37B**

Location in NDA: Protocol: **vol1.17** Study Report: **vol 1.17**

Study Title: **An evaluation of the efficacy of BPC formula #610-73 in the treatment of acute diaper dermatitis in infants and prevention of onset of severe diaper dermatitis**

Study design: Randomized (Y/N) Double Blind (Y/N) Placebo controlled (Y/N)
Multicentered (Y/N) **This study is of parallel group comparison.**

Indication: **acute diaper dermatitis in infants**

Study arms (dosage, duration, treatment length for each arm): **0.25% miconazole nitrate vs ointment base applied at every diaper change for 7 days**

6. Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?

Yes for 12966.37A
No for 13966.37B

Proposed indication from sponsor's draft labeling: **treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor**

Endpoint in pivotal trial #1: **Rash site evaluation (numbers and sum of scores), global, overall rating by investigator, microbiological status**

Endpoint in pivotal trial #2: **Rash site evaluation (numbers and sum of scores), global, overall rating by investigator**

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

To be answered by Stat Reviewer

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?

No policy or agreement

PreIND Mtg: (Y/N)

IND number/s: **21,542**

PreIND Mtg Date: **N/A**

EP2 Meeting Date: **N/A**

Agency response to Phase 3 protocols: **N/A**

PreNDA meeting date: 1/9/97

Do endpoints in pivotal Study 1 conform to previous agency commitments? (~~Y/N~~/No previous commitment)

Do endpoints in pivotal Study 2 conform to previous agency commitments? (~~Y/N~~/No previous commitments)

9. Has the applicant submitted line listings in a format to allow reasonable review of the patient data? **YES**
Has the applicant submitted line listings in the format agreed to previously by the Division? **No prev. agreement**
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? **NO**
11. Has the applicant submitted all additional required case record forms (beyond deaths and drop-outs) previously requested by the Division? **Not applicable**
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**
However, it should be recognized that there are only 252 subjects in all three phase 3 trials (199 in the two pivotal trials) who have used the current formulation proposed for marketing for 7 days.
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? **YES**
15. Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions with the Sponsor? **YES**
16. From a clinical perspective, is this NDA fileable? If "no", please state below why it is not. **YES**

If certain claims are not fileable please state which claims they are and why they are not fileable.

Concerns to be Conveyed to Applicant

1. Although claims are generally not issues for filing, it is noted that the indication requested is controversial and ambiguous (treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor). In the pre-NDA meeting, the Applicant has been advised of the requirements for an indication with and one without *Candida* in the claim (see minutes of 1/9/97 meeting). The Applicant is now using three phase 3 studies to support the proposed indication. However, one study has been shown to be a failure in a previous NDA submission. The two pivotal trials were done in Australia, and one did not collect microbiological data. Therefore, the indication in **b(4)**

this NDA will be supported by ONE single-centered study (12966.37A), if that study is found to be successful and if the proposed indication is regarded as acceptable.

No dose-ranging studies have been performed.

3. The total number of patients exposed to the formulation to be marketed for its intended use has been only 252, and these patients were exposed for 7 days, whereas actual clinical use in diaper dermatitis in infants may involve repeat episodes of varying time span.

H-S Ko 10-13-98
Reviewing Medical Officer (Hon-Sum Ko, M.D.)

SW 10/13/98
Dermatology Team Leader (Susan Walker, M.D.)

Appears This Way
On Original

OCT 9 1998

FORWARD PLANNING MEETING CHECKLIST

October 13, 1998

NDA 21-026 Pediastat (miconazole nitrate ointment) Diaper Rash Ointment, 0.25%

Indication: The treatment of moderate to severe diaper dermatitis where *Candida albicans* may be contributing factor.

Sponsor: Johnson & Johnson Consumer Companies, Inc.

Type: 3S

Filing Date: October 23, 1998.

User Fee Date: August 24, 1998

Regulatory Due Date: February 20, 1999.

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, Microbiology, 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 REQUESTING CATEGORICAL EXCLUSION.

VOLUME 1.3, PAGE 004 00605

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

YES. INTEGRATED SUMMARY OF EFFECTIVENESS IS LOCATED IN VOLUME 1.20, page 008 02022 AND THE INTEGRATED SUMMARY OF SAFETY IS LOCATED IN VOLUME 1.20, page 008 02157 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?

Yes. Based on Sponsor's indication, no additional studies are needed. If the Sponsor had chosen as part of their indication, "diaper dermatitis without Candida, they would have needed the 3-arm studies discussed at the Pre NDA meeting.

- (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?

YES. Statement located in Vol. 1.5, page 005 00011

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

NO. CARCINOGENICITY STUDIES WERE NOT REQUIRED.

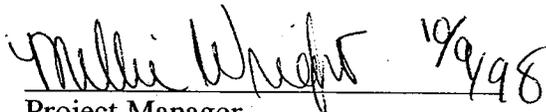
- (k) On its face, does the application contain at least two adequate and well-controlled clinical trials?

YES. (10833/10842.33; 12966.37A; 12966.37B)

- (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 VOLUME 1.15, PAGE 008 00208.
- (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, PAGE 016 00001.
- (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?
NO. THE SPONSOR PROVIDED A TABLE, VOLUME 1.1, PAGE 003 00014, COMPARING THE LABELING OF THE DRUGS MARKETED IN FOREIGN COUNTRIES AND THE PROPOSED U.S. LABELING.
- (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 SPONSOR SUPPLIES A LISTING OF ALL SAFETY DATA FROM COMPLETED CLINICAL STUDIES (DOMESTIC AND FOREIGN), AS WELL AS SAFETY DATA FROM WORLDWIDE POSTMARKETING SURVEILLANCE. ADVERSE EXPERIENCES UP TO AND INCLUDING SEPTEMBER 1997 FOR THE ALREADY MARKETED 0.25% MICONAZOLE NITRATE FORMULATION FOR THE INDICATION OF DIAPER DERMATITIS ARE LISTED IN TABLE 10 IN VOLUME 1.20. ADDITIONALLY, ADVERSE EXPERIENCES REPORTED TO JANSSEN RESEARCH FOUNDATION THROUGH SEPTEMBER 28, 1989 FOR VARIOUS TOPICAL FORMULATIONS OF MICONAZOLE NITRATE ARE LISTED IN TABLE 8, VOLUME 1.20. ADVERSE EXPERIENCES REPORTED TO JANSSEN RESEARCH FOUNDATION, PHARMACOVIGILANCE DEPARTMENT FOR ANY TOPICAL DERMATOLOGICAL FORMULATIONS OF MICONAZOLE NITRATE AND INCLUDED IN THEIR SECOND CIOMS SAFETY UPDATE ARE PRESENTED IN TABLE 9 IN VOLUME 1.20.

(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?
NO APPLICABLE.

(3) From a project management perspective, is this NDA fileable? If "no". please state on the
reverse why it is not.
**THIS APPLICATION IS FILEABLE FROM A PROJECT MANAGEMENT
PERSPECTIVE.**


Project Manager


Supervisory Project Manager

cc:
Orig NDA 21-026
Div. File
HFD-540/Wright

**Appears This Way
On Original**

ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: NDA 21026/000
Stamp: 24-AUG-1998 Regulatory Due: 24-AUG-1999
Applicant: JOHNSON AND JOHNSON

Priority: 3S
Action Goal:
District Goal: 25-APR-1999

Brand Name: PEDIASTAT (MICONAZOLE
NITRATE)OINT 0.25%

Established Name:
Generic Name: MICONAZOLE NITRATE
Dosage Form: ONT (OINTMENT)
Strength: 0.25%

FDA Contacts: M. WRIGHT (HFD-540) 301-827-2084 , Project Manager
W. TIMMER (HFD-540) 301-827-2048 , Review Chemist
W. DECAMP II (HFD-540) 301-827-2041 , Team Leader

Overall Recommendation:

Establishment: 9610028
JANSSEN PHARMACEUTICA NV
TURNHOUTSEBAAN 30, B-2340
BEERSE, , BE

DMF No:
AADA No:

Profile: CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 22-SEP-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION
Profile: OIN OAI Status: NONE
Last Milestone: ASSIGNED INSPECTION TO IB
Milestone Date: 22-SEP-1998

Responsibilities: DRUG SUBSTANCE
MANUFACTURER
FINISHED DOSAGE
MANUFACTURER

Establishment: 2243656
JOHNSON AND JOHNSON
GRANDVIEW RD
SKILLMAN, NJ 08558

DMF No:
AADA No:

Profile: CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 05-OCT-1998
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Responsibilities: FINISHED DOSAGE OTHER TESTER

Appears This Way
On Original

OCT 6 1998

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

NDA 21-026

**PEDIASTAT™ Diaper Rash Ointment
0.25% miconazole nitrate**

CHEMISTRY AMENDMENT

Dear Dr. Wilkin:

Purpose of Amendment

The purpose of this amendment is to correct information that was in the original submission and to replace that information with documents that will allow a full review of the Chemistry, Manufacturing, and Control section.

Information to be deleted or ignored

Page numbers 004 00077 and 00078 in volume 1.2 refer to a drug master file number 49 for Subsequent contact with determined that this information was inaccurate and that the drug master file referred to in their authorization letter did not, in fact, exist.

b(4)

Correct Information

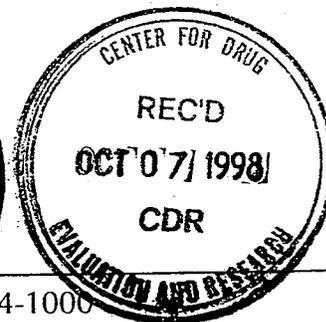
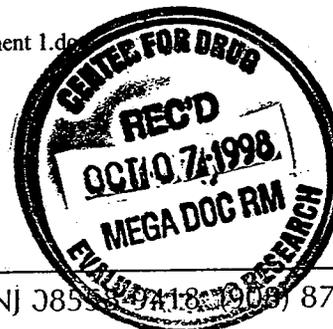
In this package, there are copies of the following:

- A new list of DMF documents to replace the page attached to the original FDA 356H form.
- The product specification and analytical test methods for Trihydroxystearin
 - Product Specification b(4)
 - Test Methods:
 - Hydroxyl Value
 - Iodine Value
 - Saponification Value
 - Particle Size
 - Melting Point
 - Acid Value

b(4)

Continued on next page

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Last printed October 6, 1998 2:46 PM
Page 1 of 3



**Agency
communications**

On October 5, 1998, a conversation took place between Ms. Wright, Project Manager; Dr. DeCamp, CMC; and Dr. Timmer, Reviewer and myself.

A discussion of the situation at _____ ensued with the final agreement that the submission of the specifications and the test methods for the excipient would avert the CMC group's recommendation for a refusal to file due to the lack of a DMF. **b(4)**

The final decision of the fileability of the submission was being made Tuesday, October 13, 1998 so that this information must arrive on or before Thursday, October 8 in order to be reviewed in time for the meeting.

Copies

The following copies were prepared and sent or faxed:

- CMC Desk copies Faxed and mailed Directly to
Ms. Wright
 - FDA Archive Copy Mailed to Document Center
 - FDA CMC Review Copy Mailed to Document Center
 - FDA(true) field copy Mailed to Newark District
Office
-

Contacts

If you have any questions about this information, please contact:
Diana L.B. Uhl, Manager, Regulatory Affairs or
Paul F. Manley, Director, Regulatory Affairs.

Our phone number reserved for the FDA is (908) 874-1700.

Sincerely,



Diana L.B. Uhl,
Regulatory Affairs Manager

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Johnson & Johnson

CONSUMER COMPANIES

AUG 24 1998

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

NDA 21-026 User Fee No. 3509

PEDIASTAT™ Diaper Rash Ointment
0.25% miconazole nitrate

COVER LETTER

Dear Dr. Wilkin:

Proposed product

This submission provides a full New Drug Application (NDA) as prescribed in 21 CFR 314, for PEDIASTAT™ (0.25% miconazole nitrate) Diaper Rash Ointment as a prescription drug for the treatment of moderate to severe diaper dermatitis where *Candida albicans* may be a contributing factor.

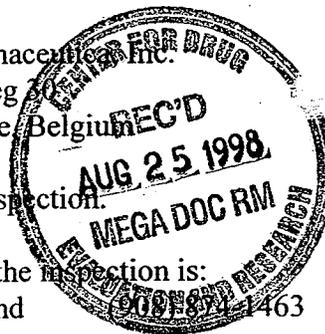
Proposed Manufacturer

The proposed manufacturer of the 0.25% miconazole nitrate diaper rash ointment is:

Janssen Pharmaceutics Inc.
Turnhoutseweg 30
B-2340 Beerse, Belgium

They are ready for inspection.

The U.S. contact for the inspection is:
James Haviland



Samples

Samples which are required will be submitted upon request.

Submission

This submission consists of 30 volumes, labeled 1.1 through 1.29, with one volume labeled 1.4A, plus three copies of the methods validation package. These volumes are detailed in the overall reviewers' guide.

Continued on next page

199 GRANDVIEW ROAD, SKILLMAN, NJ 08558-9418 (908) 874-1000

JOHNSON & JOHNSON CONSUMER PRODUCTS COMPANY • JOHNSON & JOHNSON CONSUMER PRODUCTS WORLDWIDE
PERSONAL PRODUCTS COMPANY • PERSONAL PRODUCTS WORLDWIDE
JOHNSON & JOHNSON WORLDWIDE ABSORBENT PRODUCTS AND MATERIALS RESEARCH,

AUG 24 1998

Submission (continued)

One archival copy and one review copy have been sent to the document control room. One copy of the Chemistry, Manufacturing and Controls information, as required, was sent to the Newark District Office, as indicated in the Field Copy Certification.

User Fee

The user fee of \$256,846 (user fee no. 3509) has been sent to:
Mellon Bank
3 Mellon Bank Center
27th Floor
(FDA360909)
Pittsburgh PA 15259-0001

Safety Update

Safety updates will be made as required by 21 CFR 314.50(5)(b).

**History June
1985 – April
1986**

This NDA builds upon the OTC NDA which was submitted June 20, 1985 and was determined to be not approvable on April 28, 1986. The deficiencies noted were:

b(4)

Deficiencies

- The agency did not feel that it was appropriate to market this product OTC.
- The clinical studies failed to establish statistically significant superiority of the active drug over the placebo.

**Subsequent
Meeting June,
1986**

A meeting with FDA on June 2, 1986 was held to discuss what was needed to approve this product. The answer from the agency was:

- One or more additional clinical studies
 - A study to look for blood levels of the active and adverse effects in about 20 infants.
-

Continued on next page

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AUG 24 1998

**Pre-NDA
Meeting
January, 1997**

The decisions from this meeting were:

- No bioequivalence studies would need to be performed to submit this NDA.
- An *in vitro* release test should be performed to show the equivalence of the manufacturing processes.
- No additional nonclinical studies would be required.
- No additional systemic safety studies would be required.
- The age range for patients should reflect the patient population in the clinical studies with a minimum age of 3 months.
- An FDA suggestion that if the indication were for "the treatment of diaper dermatitis where *Candida* spp may be a contributing factor", then data would have to support more than *Candida albicans*.
- Discussion in the NDA should cover microbial resistance.
- Clinical data should be provided in a SAS transport file (SAS 6.11 preferred) accompanied by a data dictionary.

***In vitro* Release
- May, 1998**

A teleconference was held regarding the adequacy of the *in vitro* work done to compare the manufacturing sites.

The decisions in the meeting were:

- The data are acceptable with the following comments:
 - The CMC section of the original manufacturer, must be reviewed by the agency with the CMC of the proposed manufacturer, Janssen Pharmaceutica, NV. The CMC would be reviewed according to the most recent CMC requirements.

b(4)

Continued on next page

AUG 24 1998

In vitro Release – May, 1998 (continued)

- The CMC sections must support the briefing package in the conclusion that there have been no significant changes between the two sites.

NDA 21-026

To the best of our knowledge and belief each of these items have been addressed in this NDA. The SAS transport files will be provided upon request.

Contacts

The following people may be contacted with questions regarding this NDA:

Paul F. Manley, Director, Drug Regulatory Affairs

Diana L.B. Uhl, Manager, Drug Regulatory Affairs

Phone Either may be reached on the phone line reserved for FDA use:

(908) 874-1700

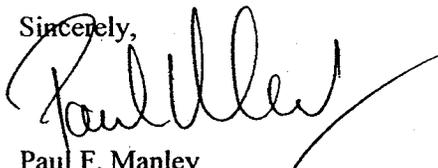
FAX Mr. Manley: (908) 874-1253

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Sincerely,



Paul F. Manley
Director, Drug Regulatory Affairs

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NDA REGULATORY FILING REVIEW
Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications

NDA #: 21-026 **TRADENAME (0.25% miconazole nitrate, 15% zinc oxide and 81.35% white petrolatum ointment/ user fee date 5/24/05)**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s):
3. The purpose of this and the questions below (questions 3 to 5) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval and that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," skip to question 4. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical equivalent(s) should be cited as the listed drug(s).)

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007)? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

4. (a) Is there a pharmaceutical alternative(s) already approved? YES NO

(Pharmaceutical alternatives are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," skip to question 5. Otherwise, answer part (b).

- (b) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES NO
(The approved pharmaceutical alternative(s) should be cited as the listed drug(s).)

NOTE: If there is more than one pharmaceutical alternative approved, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (ORP) (HFD-007) to determine if the appropriate pharmaceutical alternatives are referenced.

If "Yes," skip to question 6. Otherwise, answer part (c).

- (c) Have you conferred with the Director, Division of Regulatory Policy II, ORP? YES NO

If "No," please contact the Director, Division of Regulatory Policy II, ORP. Proceed to question 6.

5. (a) Is there an approved drug product that does not meet the definition of "pharmaceutical equivalent" or "pharmaceutical alternative," as provided in questions 3(a) and 4(a), above, but that is otherwise very similar to the proposed product? YES NO

If "No," skip to question 6.

If "Yes," please describe how the approved drug product is similar to the proposed one and answer part (b) of this question. Please also contact the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007), to further discuss.

- (b) Is the approved drug product cited as the listed drug? YES NO

6. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This is not applicable. This is a new indication for "...treatment of diaper dermatitis only when complicated by candidiasis, as documented by microscopic evidence....." This is a new combination product, the ingredients are 0.25% miconazole nitrate, 15% zinc oxide and 81.35% white petrolatum ointment.. A search by the Division located no patents involved. The applicant referenced published literature.

7. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)).) YES NO
8. Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 21 CFR 314.101(d)(9)). YES NO
9. Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application should be refused for filing under 21 CFR 314.101(d)(9). YES NO
10. Are there certifications for each of the patents listed for the listed drug(s)? YES NO

11. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

- 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):
- 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: *IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)].*

- 21 CFR 314.50(i)(1)(ii): No relevant patents.
- 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)
Patent number(s):
- 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):
- Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

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12. Did the applicant:

- Identify which parts of the application rely on information (e.g. literature, prior approval of another sponsor's application) that the applicant does not own or to which the applicant does not have a right of reference?
YES NO
- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?
YES NO
- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?
N/A YES NO
- Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?
N/A YES NO

13. If the (b)(2) applicant is requesting 3-year exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

- Certification that at least one of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).
YES NO
- A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.
Sponsor provided some published study reports, but no list. YES NO

• EITHER

The number of the applicant's IND under which the studies essential to approval were conducted.

IND# 21,542 NO

OR

A certification that the NDA sponsor provided substantial support for the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

YES NO

14. Has the Associate Director for Regulatory Affairs, OND, been notified of the existence of the (b)(2) application?

YES NO

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Mildred Wright
5/19/05 02:07:54 PM
CSO

Mildred Wright
5/19/05 02:10:53 PM
CSO