CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-087

***Name*:** Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials

***Sponsor*:** Bedford Laboratories

***Approval Date*:** July 29, 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

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Administrative Documents	X
Correspondence	X

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

APPROVAL LETTER

ANDA 76-087

JUL 29 2004

Bedford Laboratories
Attention: Molly L. Rapp
300 Northfield Road
Bedford, OH 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to our Tentative Approval letters dated July 17, 2003, and April 9, 2004, and to your amendment dated May 11, 2004.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined your Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Diflucan® Injection, 2mg/mL, (in 0.9% Sodium Chloride Injection) of Pfizer, Inc.).

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

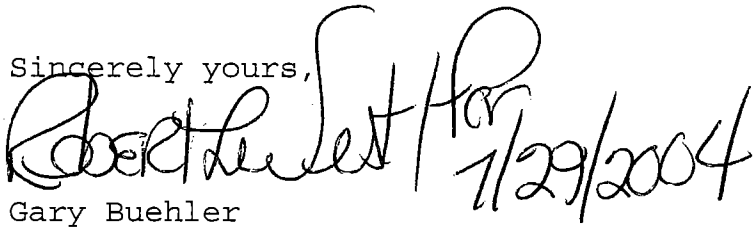
Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications, HFD-42
5600 Fishers Lane
Rockville, MD 20857

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,



Gary Buehler
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/A.Langowski/ A. Langowski 7/12/04
HFD-647/G.Smith/ 7/12/04
HFD-617/T.Palat/ 7/16/04
HFD-613/C.Park7/8/04/ 7/16/04
HFD-613/L.Golson/ 7/15/04
HFD-600/M.Stevens-Riley/ M. Stevens-Riley 7/20/04
HFD-600/N.Sweeney/ N. Sweeney 7.20.04

CMC OK
RAS 7/21/04

Robert Rivest
7/22/2004

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F/T by rad7/12/04

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

TENTATIVE APPROVAL LETTERS

ANDA 76-087

JUL 17 2003

Bedford Laboratories
Attention: Molly Rapp
300 Northfield Rd.
Bedford, Ohio 44146

Dear Madam:

This is in reference to your abbreviated new drug application dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Fluconazole Injection, 2 mg/mL, in 100 mL and 200 mL vials.

Reference is also made to your amendment dated January 21, 2003.

We have completed the review of this abbreviated application and have concluded that, based upon the information you have presented to date, the drug is safe and effective for use as recommended in the submitted labeling. Therefore, the application is **tentatively approved**. This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices of the facilities used in the manufacturing and testing of the drug product) and is therefore subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application is currently subject to a period of patent protection. Your application contains a Paragraph III Certification to each patent under Section 505(j)(2)(A)(vii)(III) of the Act stating that you will not market this drug product prior to the expiration of this patent. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until the period has expired, i.e., January 29, 2004.

Because the Agency is granting a tentative approval for this application, please submit an amendment at least 60 days (but not more than 90 days) prior to the date you believe your application will be eligible for final approval. This amendment

should identify changes, if any, in the conditions under which the product was tentatively approved, and should include updated information such as labeling, chemistry, manufacturing, and controls data as appropriate. An amendment should be submitted even if none of these changes were made. This submission should be designated clearly in your cover letter as a MINOR AMENDMENT. In addition to this amendment, the Agency may request at any time prior to the final date of approval that you submit an additional amendment containing the information described above.

Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made.

Please note that this drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the "Approved Drug Products with Therapeutic Equivalence Evaluations" list (the "Orange Book"), published by the Agency. Should you believe that there are grounds for issuing the final approval letter prior to January 29, 2004, you should amend your application accordingly.

At the time you submit any amendments, you should contact Ted Palat, PharmD, Project Manager, at 301-827-5849, for further instructions.

Sincerely yours,

Gary Buehler 7/17/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-610/Orange Book Staff

Endorsements:
HFD-645/A.Langowski/
HFD-647/G.Smith/
HFD-617/T.Palat/
HFD-600/M.Stevens-Riley/
HFD-600/N.Sweeney/
HFD-613/C.Park/6/23/03
HFD-613/L.Golson/

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F/T by rad6/23/03

TENTATIVE APPROVAL

conc satisfactory

ANDA 76-087

APR 9 2004

Bedford Laboratories
Attention: Molly L Rapp
300 Northfield Road
Bedford, Ohio 44146

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 21, 2000, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Fluconazole Injection, 2 mg/mL, (in 0.9% Sodium Chloride Injection) packaged in 200 mg/100 mL and 400 mg/200 mL single-dose vials.

Reference is also made to our letter dated July 17, 2003, granting tentative approval to this application, and to your amendments dated December 22, 2003, and February 9, 2004.

We have completed the review of this abbreviated application as amended, and based upon the information you have presented to date we have concluded that the drug remains safe and effective for use as recommended in the submitted labeling. However, final approval of your application is blocked at this time by a period of exclusivity granted to the NDA-holder, Pfizer, as discussed below. Thus, your application remains **tentatively approved.** This determination is based upon information available to the Agency at this time, (i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product). The determination is subject to change on the basis of new information that may come to our attention.

The reference listed drug product (RLD) upon which you have based your application, Diflucan® (in 0.9% Sodium Chloride Injection) of Pfizer Inc., was subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations,

the Orange Book, U.S. patent 4,404,216 (the '216 patent) expired on January 29, 2004.

However, as also noted in the Orange Book, the '216 patent has effectively been extended by an additional 6 months of marketing exclusivity under Section 111 of Title I of the Food and Drug Administration Modernization Act of 1997 (the Modernization Act). The Modernization Act created Section 505(A) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355a). Section 505(A) permits certain applications to obtain an additional six months of marketing exclusivity (pediatric exclusivity) if, in accordance with the requirements of the statute, the NDA sponsor submits requested information relating to the use of Fluconazole in the pediatric population. Pfizer, Inc. (Pfizer) has submitted such information to the Agency. The Agency determined that the information met the criteria stated in the statute and granted Pfizer 6-months of additional marketing exclusivity with respect to the '216 patent for its drug products containing Fluconazole. Therefore, final approval of your application may not be made effective pursuant to 21 U.S.C. 355(j)(5)(B)(ii) of the Act until this period of market exclusivity associated with the '216 patent has expired, i.e., July 29, 2004. The final approval date may be further extended if, upon review of the pediatric data submitted by Pfizer, the Agency decides that Pfizer is eligible for an additional period of Hatch-Waxman exclusivity.

In order to reactivate your application prior to final approval, please submit a "MINOR AMENDMENT - FINAL APPROVAL REQUESTED" 90 days prior to the date you believe that your application will be eligible for final approval. This amendment should provide the legal/regulatory basis for your request for final approval, and it should also identify changes, if any, in the conditions under which the product was tentatively approved, i.e., updated information such as final-printed labeling, chemistry, manufacturing, and controls data as appropriate. This amendment should be submitted even if none of these changes were made. This amendment should be designated clearly in your cover letter as a MINOR AMENDMENT - FINAL APPROVAL REQUESTED.

In addition to the amendment requested above, the agency may request at any time prior to the final date of approval that you submit an additional amendment containing the requested information. Failure to submit either or, if requested, both amendments may result in rescission of the tentative approval status of your application, or may result in a delay in the issuance of the final approval letter.

Any significant changes in the conditions outlined in this abbreviated application as well as changes in the status of the manufacturing and testing facilities' compliance with current good manufacturing practices (CGMPs) are subject to Agency review before final approval of the application will be made. Should you elect to amend your application to provide for such changes prior to approval, we request that the changes be categorized as representing either "major" or "minor" changes. The amendment will be reviewed according to OGD policy in effect at the time of receipt.

This drug product may not be marketed without final Agency approval under Section 505 of the Act. The introduction or delivery for introduction into interstate commerce of this drug product before the final approval date is prohibited under Section 501 of the Act and 21 U.S.C. 331(d). Also, until the Agency issues the final approval letter, this drug product will not be deemed approved for marketing under 21 U.S.C. 355 and will not be listed in the Orange Book. Should you believe that there are grounds for issuing the final approval letter prior to July 29, 2004, you should amend your application accordingly.

For further information on the status of this application, or upon submitting an amendment to the application, please contact Ted Palat, PharmD, Project Manager, (301) 827-5849.

Sincerely yours,

Gary Buehler 4/9/04
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-087
Division File
Field Copy
HFD-610/R. West
HFD-330
HFD-205
HFD-92

Endorsements:
HFD-645/A.Langowski/ 4/3/04
HFD-647/G.Smith/ 4/6/04
HFD-617/T.Palat/ 4/6/04
HFD-613/C.Park/ 4/7/04
HFD-613/L.Golson/ 4/7/04

20 CMC changes since TA dated 7/17/03

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F/T by rad4/2/04

Robert Radwat
4/9/2004

TENTATIVE APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

LABELING

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-087

LABELING REVIEWS

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-087 Date of Submission: December 21, 2000

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection

Labeling Deficiencies:

1. CONTAINER - 200 mg/100 mL

   The pictorial illustration on the hanging strip indicates that you will affix your label up side down. Please be advised that the statement of identity shall be in lines generally parallel to the base on which the package rests as it is designed to be displayed. We ask that you affix your label parallel to the orientation of your bottle and make revisions accordingly in terms of the location of the hanging strip. Please ensure that when the vial is hung, the calibration reflects actual volume of the solution remaining in the container.

2. INSERT

   a. DESCRIPTION – Last paragraph, first sentence:

      ... solution of fluconazole in a sodium chloride diluent.

   b. PRECAUTIONS (Pediatric Use) – Penultimate paragraph:

      ...for 1 to 1,616 days.... ["1,616" rather than "1.616"]

   c. ADVERSE REACTIONS (In Patients Multiple... Candidiasis, Hepatobiliary) – Second paragraph, first sentence:

      ...levels from a baseline value of 30 IU/L to ... [add "value"]

   d. DOSAGE AND ADMINISTRATION

      i. Dosage and Administration in Adults – Multiple Dose:

         A) Delete the sub-subsection heading " ——— ".

         B) Add the following text as the first sentence of the first paragraph.

            SINCE ORAL ABSORTION IS RAPID AND ALMOST COMPLETE, THE DAILY DOSE OF FLUCONAZOLE IS THE SAME FOR ORAL AND INTRAVENOUS ADMINISTRATION

         C) Esophageal candidiasis – Last sentence:

            ...minimum of three weeks and for at least...

ii. Dosage in Patients With Impaired Renal Function – First paragraph:

Delete the second sentence "[redacted]".

iii. Administration

A) First sentence – Revise to read:

Fluconazole injection is administered by intravenous infusion.

B) Add the following as the second paragraph.

Fluconazole injection in glass container is intended only for intravenous administration using sterile equipment.

e. HOW SUPPLIED – Second sentence:

..glass vials, each containing 200 mg of fluconazole in 100 mL of sodium chloride solution.

Please revise your labels and labeling, as instructed above, and submit 4 draft copies for a tentative approval or 12 final printed copies for a full approval of this application. If draft labeling is provided, please be advised that you will be required to submit 12 final printed copies of all labels and labeling at least 60 days prior to full approval of this application. In addition, you should be aware that color and other features (print size, prominence, etc) in final printed labeling could be found unacceptable and that further changes might be requested prior to approval.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-
http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

William Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

2. This drug product is not the subject of a USP monograph.

3. This ANDA appears to be the **FRIST GENERIC**.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 082 (Volume B.1.1).

5. Patent Data

019950	001	4404216	JAN 29,2004
019950	001	4416682	JUN 02,2001

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification III.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers
Seal: Flip-off Aluminum Seals [p.539, B.1.2)

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. **The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." In addition, majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"**

11. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the

established name for this product per Charlie's advice.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (20-090). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

Here are the answers from Don Hare and Yana Mille.

1. From Don Hare

I defer to more knowledgeable people on the Fluconazole Injection establish name issue but would like to explain how the listings in the Orange Book are determined. A drug product displayed in the Orange Book has a number of fields, among those are an active ingredient, dosage form, route of administration and trade name fields. We did not have an established name field per se. The example that you cited, Cimetidine in Sodium Chloride Injection is listed in the Orange Book as Cimetidine Hydrochloride - Active Ingredient

Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

As you can see we do not include the diluent in the Active ingredient field but it is part of the trade name.

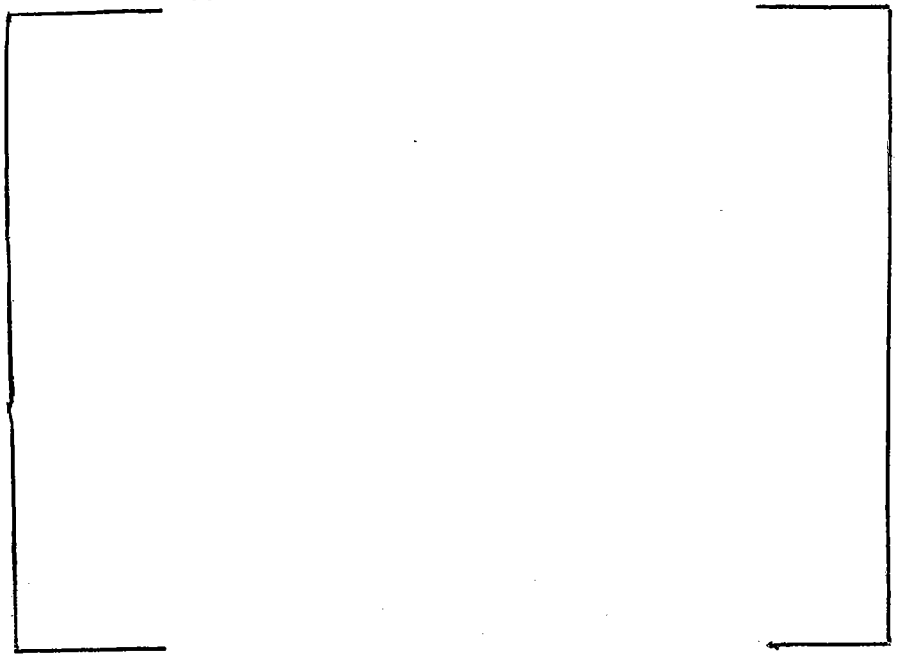
For the active ingredient name we use a hierarchy of (1) USP monograph, USAN, and lastly the active ingredient name in the labeling if not an official article or name.

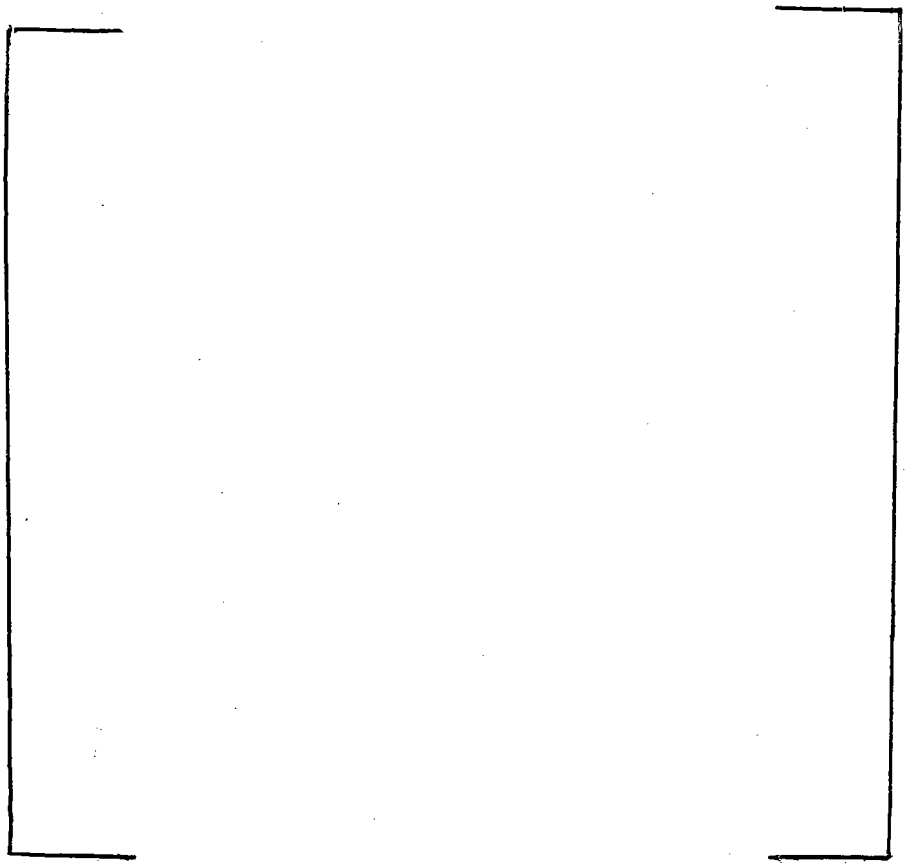
Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

2. From Yana Mille

Thanks for a copy of the labeling. Based on what I see I am now





Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question.

Date of Review: 2/6/01 **Date of Submission: 12/21/00**

Primary Reviewer: Chan Park **Date:** 2/16/01

Team Leader: **Date:** 2/20/01

cc:

ANDA: 76-087
DUP/DIVISION FILE
HFD-613/Cpark/CHoppes (no cc)
V:\FIRMSAM\BEDFORD\LTRS&REV\76087na1.LABELING Review

Maika Steiner-Riley A 2.1

(TENTATIVE APPROVAL SUMMARY)
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-087 Date of Submission: November 7, 2001

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

Submitted in DRAFT

CONTAINER LABELS - 200 mg/100 mL

Satisfactory in drat as of 11/7/01 submission

CARTON LABELING:

Satisfactory in draft as of 12/1/00 submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of 11/7/01 submission

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 11/26/01)

The firm claims that they will use silk-screened containers with pre-marked with calibration marks. Is this an accurate statement? I do not see the calibration marks in the sponsor's drawing of the proposed container.

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999.

2. This drug product is not the subject of a USP monograph.

3. This ANDA appears to be the **FRIST GENERIC**.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 082 (Volume B.1.1).

5. Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	001	4404216	JAN 29,2004	
019950	001	4416682	JUN 02,2001	

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification III.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 200 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers
Seal: Flip-off Aluminum Seals [p.539, B.1.2)

The firm claims that they will use silk-screened containers with pre-marked with calibration marks. We will have the chemist confirm this statement.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. **The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." In addition, majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"**

11. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product per Charlie's advice.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (20-090). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

Here are the answers from Don Hare and Yana Mille.

1. From Don Hare

I defer to more knowledgeable people on the Fluconazole Injection establish name issue but would like to explain how the listings in the Orange Book are determined. A drug product displayed in the Orange Book has a number of fields, among those are an active ingredient, dosage form, route of administration and trade name fields. We did not have an established name field per se. The example that you cited, Cimetidine in Sodium Chloride Injection is listed in the Orange Book as Cimetidine Hydrochloride - Active Ingredient

Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

As you can see we do not include the diluent in the Active ingredient field but it is part of the trade name.

For the active ingredient name we use a hierarchy of (1) USP monograph, USAN, and lastly the active ingredient name in the labeling if not an official article or name.

Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

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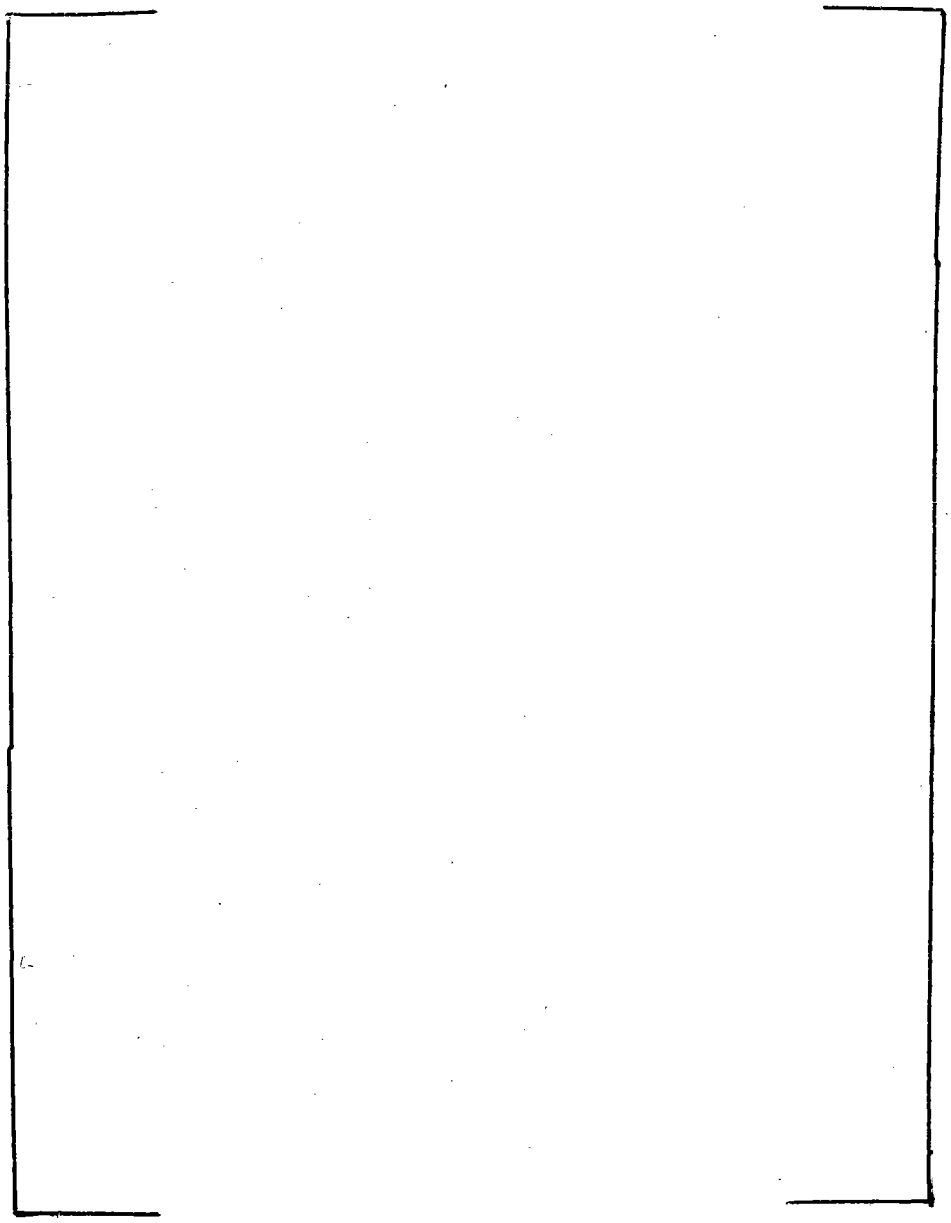
Thanks for a copy of the labeling. Based on what I see I am now



Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question. In the mean time, the storage temperature statement on the sponsor's labeling is identical to the one found on the innovator's labeling. We have not received any response from the new drug division or Glen Smith as of today. As indicated in Yana's e-mail, we may wait for the publication of guidance before we address this issue.

Date of Review: 11/16/01 **Date of Submission: 11/7/01**

Primary Reviewer: Chan Park C Park **Date:** 12/10/01

Team Leader: Date:

Linda Ogs 12/11/01

This TAP2 summary supersedes the TAP summary prepared 11/16/01.

(TENTATIVE APPROVAL SUMMARY)

REVIEW OF PROFESSIONAL LABELING

DIVISION OF LABELING AND PROGRAM SUPPORT

LABELING REVIEW BRANCH

ANDA Number: 76-087 Date of Submission: June 20, 2002

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection, 2 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? No

Submitted in DRAFT

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in draft as of 11/7/01 (100 mL) and 6/20/02 (200 mL) submission

CARTON LABELING:

Satisfactory in draft as of 12/1/00 (100 mL) and 6/20/02 (200 mL) submission

PROFESSIONAL PACKAGE INSERT LABELING:

Satisfactory in draft as of 11/7/01 (100 mL) and 6/20/02 (200 mL) submission

POST-APPROVAL REVISIONS

1. CONTAINER

   Increase the prominence of the expression of the unit strength (2 mg/mL).

2. INSERT

   a. Two separate insert labeling can be collapsed into one insert for both package sizes. We will inform this to the sponsor so that they may submit a revised insert labeling in FPL.

   b. 200 mL labeling:

      CLINICAL PHARMACOLOGY (Pharmacokinetics in Children) - Table:

      Include the N numbers in the last row, 3rd, 5th and last columns.

   The above comments have been forwarded to Molly Rapp of the firm on October 10, 2002 via a tele-conference.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22, 1999.

NDA Number: 19-950
NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 10/9/02)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. Is this an accurate statement? The firm adopted this method rather than having calibration on the container labels. However, I do not see the calibration marks in the sponsor's drawing of the proposed container.
Thanks, Chan

Answer: Yes its true! They are silk screening the volumetric calibration marks. You do not see it on the drawing because only physical engineering specifications are provided. The firm has been asked to provide validation data verifying the accuracy of the calibration marks. However, probably not that critical since this is an anti-fungal as opposed to a narcotic analgesic. Andrew (10/10/02)

FOR THE RECORD:

1. MODEL LABELING – Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22 1999. The innovator has a combined package insert labeling for injection, tablets and powder for oral suspension. S-034 approved 8/7/02 is specifically related to the approval of PPI for the 150 mg tablets.

2. This drug product is not the subject of a USP monograph.

3. This ANDA appears to be the **FRIST GENERIC**.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 082 (Volume B.1.1).

5. **Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Use Code
019950	**001**	**4404216**	**JAN 29,2004**	

Exclusivity Data

There is no unexpired exclusivity for this product.

440,4216 - 2-(2,4-Difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol and its pharmaceutically acceptable acid addition salts are disclosed. This particular bis-triazole derivative and its aforesaid salts are useful for treating fungal infections in animals, including humans. Methods for preparing these compounds from known starting materials are provided.

The sponsor's statements are accurate. The sponsor has filed Patent Certification III.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 400 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
ANDA – 200 mg/100 mL and 400 mg/200 mL (in sodium chloride in glass vial)

8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers (100 mL) & ——Stoppers (200 mL)
Seal: Flip-off Aluminum Seals [p.539, B.1.2 & p.513, B.3.2)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. See comment to/from the chemist above.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." In addition, majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"

11. I have sent the following e-mail to Yana Mille, Don Hare, Leo Chan, & Greg Davis regarding the established name for this product per Charlie's advice.

folks,

This is to make sure what is the established name for this product. Is the established name "Fluconazole Injection"?. The innovator markets both "Fluconazole in Sodium Chloride" and "Fluconazole in Dextrose" under the same application (20-090). I can't image having two established names for one product under one NDA if the diluents used for the premixing were a part of the established name. On the other hand, we find the diluent is a part of the established name for some premixed injection product in USP (e.g., Cimetidine in Sodium Chloride Injection). The orange book appears to list this product as "Fluconazole Injection". Please advise me as to "What is the official established name for this premixed fluconazole injection product?" Thanks for your help,

Chan

Here are the answers from Don Hare and Yana Mille.

1. From Don Hare

I defer to more knowledgeable people on the Fluconazole Injection establish name issue but would like to explain how the listings in the Orange Book are determined. A drug product displayed in the Orange Book has a number of fields, among those are an active ingredient, dosage form, route of administration and trade name fields. We did not have an established name field per se. The example that you cited, Cimetidine in Sodium Chloride Injection is listed in the Orange Book as Cimetidine Hydrochloride - Active Ingredient

Injectable: Injection - Dosage Form and R.O.A.
Cimetidine HCl in Sodium Chloride 0.9% - Trade Name

As you can see we do not include the diluent in the Active ingredient field but it is part of the trade name.

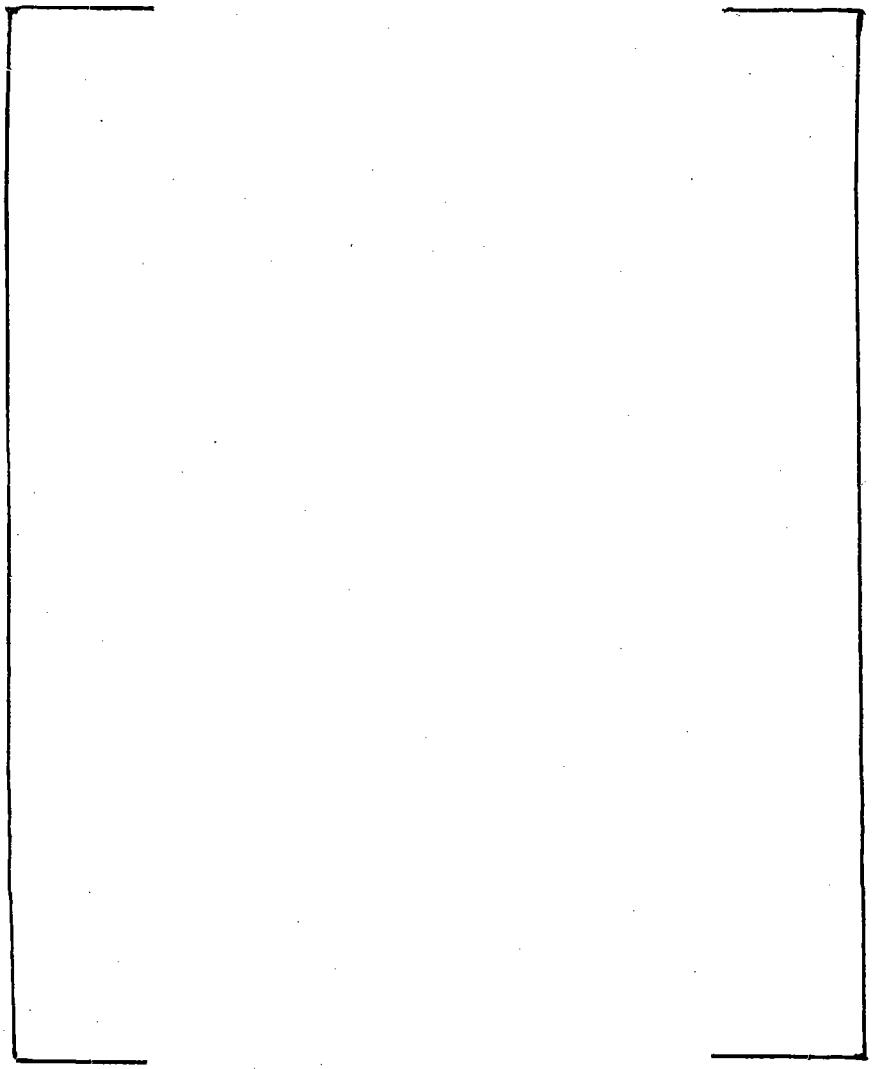
For the active ingredient name we use a hierarchy of (1) USP monograph, USAN, and lastly the active ingredient name in the labeling if not an official article or name.

Finally as you know the WH Act requires the labeling of the test drug to be the same as the RLD.

Don

2. From Yana Mille

Thanks for a copy of the labeling. Based on what I see I am now



Yana

12. We will make sure that the new drug division is aware of these potential issues as found above in Yana Mille's response. I forwarded Yana's e-mail to Glen Smith for the storage temperature question. In the mean time, the storage temperature statement on the sponsor's labeling is identical to the one found on the innovator's labeling. We have not received any response from the new drug division or Glen Smith as of today. As indicated in Yana's e-mail, we may wait for the publication of guidance before we address this issue.

13. The sponsor has filed another application for the same product, but for a different package size (200 mL) on June 20, 2002. However, the sponsor withdrew this application and made this as an amendment to ANDA 76-087 (originally filed for 100 mL) per Agency's recommendation. The sponsor markets both 100 mL and 200 mL package size.

Date of Review: 10/9/02 **Date of Submission: 6/20/02**

Primary Reviewer: Chan Park C Park **Date:** 10/15/02

Team Leader: J W Golson **Date:** 10/17/02

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ANDA: 76-087
DUP/DIVISION FILE
HFD-613/Cpark/LGolson (no cc)
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Review

(This TAP3 Summary supersedes the TAP2 summary prepared on 10/9/02)

(TENTATIVE APPROVAL SUMMARY)

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-087 Date of Submission: December 22, 2003

Applicant's Name: Bedford Laboratories

Established Name: Fluconazole Injection, 2 mg/mL

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

CONTAINER LABELS - 100 mL & 200 mL

Satisfactory in FPL as of 12/22/03 submission (A.4.1)

CARTON LABELING - 1 Vial x 100 mL & 1 Vial x 200 mL

Satisfactory in FPL as of 12/22/03 submission (A.4.1)

PROFESSIONAL PACKAGE INSERT LABELING

Satisfactory in FPL as of 12/22/03 submission (A.4.1, Rev. Jan, 04, Code # - FZC-P00)

POST-APPROVAL REVISIONS - CONTAINER:

Increase the prominence of the expression of the unit strength (2 mg/mL).

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Diflucan Injection (NDA 19-950/S-028) labeling approved on Feb 22, 1999.

NDA Number: 19-950

NDA Drug Name: Diflucan Injection

NDA Firm: Pfizer

Date of Approval of NDA Insert and supplement #:

S-028/approved 2/22/99

Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Other Comments:

1. This appears the FIRST GENERIC

2. See comment to chemist

3. The sponsor collapsed 2 separate package insert labeling (*i.e.,* one for the 100 mL & another one for 200 mL) into one as recommended by the Agency.

NOTE/QUESTION TO CHEMIST (This question was related to chemist via e-mail on 10/9/02)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. Is this an accurate statement? The firm adopted this method rather than having calibration on the container labels. However, I do not see the calibration marks in the sponsor's drawing of the proposed container.

Thanks, Chan

Answer: Yes it's true! They are silk screening the volumetric calibration marks. You do not see it on the drawing because only physical engineering specifications are provided. The firm has been asked to provide validation data verifying the accuracy of the calibration marks. However, probably not that critical since this is an anti-fungal as opposed to a narcotic analgesic. Andrew (10/10/02)

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2. This drug product is not the subject of a USP monograph.

3. This ANDA appears to be the **FIRST GENERIC**.

4. The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 082 (Volume B.1.1).

5. **Patent Data**

Appl No	Prod No	Patent No	Patent Expiration	Use Code	Patent Certification	Labeling Impact
019950	**001**	**4404216**	**JAN 29,2004**		III	None
019950	**001**	**4404216*PED**	**JUL 29,2004**		III	None

Exclusivity Data

There is no unexpired exclusivity for this product.

The sponsor's statements are accurate. The sponsor has filed Patent Certification III.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

Both RLD and the ANDA: Store between 5o to 30oC (41o to 86oF). Protect from freezing.

7. PACKAGING CONFIGURATIONS

RLD: 200 mg/100 mL & 400 mg/200 mL (in glass & Plastic; in Sodium Chloride & Dextrose)
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8. CONTAINER/CLOSURE

Container: Type I Flint Molded Vials
Closure: Gray Plug Stoppers (100 mL) & ——— Stoppers (200 mL)
Seal: Flip-off Aluminum Seals [p.539, B.1.2 & p.513, B.3.2)

The firm claims that their drug product will be silk-screened with ink to place the volumetric calibration marks on the containers. This is accurate. See comment to/from the chemist above.

9. This drug product is manufactured by Bedford Laboratories, Inc. (p.113, B.1.1)

10. The innovator has a combined package insert labeling for fluconazole tablet, oral solution and injection. The Pharmacokinetics and Metabolism of the CLINICAL PHARMACOLOGY section reads "The pharmacokinetic properties of fluconazole are similar following administration by the intravenous or oral routes. In normal volunteers, the bioavailability of orally administered fluconazole is over 90% compared with intravenous administration." In addition, majority of the information in this section is associated with the oral regimen. For these reasons, we will allow the generic sponsor retain all information for oral regimen. However, a single oral dose of fluconazole 150 mg is specifically for "Vaginal Candidiasis" only. Therefore, we will ask the generic sponsors to remove all information specifically associated with "Vaginal Candidiasis"

11. The sponsor has filed another application for the same product, but for a different package size (200 mL) on June 20, 2002. However, the sponsor withdrew this application and made this as an amendment to ANDA 76-087 (originally filed for 100 mL) per Agency's recommendation. The sponsor markets both 100 mL and 200 mL package size.

Date of Review: 1/29/04 **Date of Submission: 12/22/03**

Primary Reviewer: Chan Park C Park **Date:** 2/4/04

Team Leader: [signature] **Date:** 2/4/04

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cc:

ANDA: 76-087
DUP/DIVISION FILE
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Review