CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 75-010 / S-001

***Name*:** Ibuprofen Tablets USP, 200 mg (Brown)

***Sponsor*:** LNK International, Inc.

***Approval Date*:** November 20, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

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Labeling Reviews	
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Statistical Review(s)	
Microbiology Review	
Administrative Documents	X
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

APPROVAL LETTER

7.1 D. Compliance

ANDA 75-010/S-001

PRIOR APPROVAL SUPPLEMENT

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

NOV 20 2000

Dear Sir:

This is in reference to your supplemental new drug application dated February 28, 2000 submitted pursuant to 505 (j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Ibuprofen Tablets USP, 200 mg.

Reference is also made to your amendment dated June 5, 2000 and September 8, 2000.

This supplemental application, submitted as a "Prior Approval Supplement" provides for the following:

A change in excipients used in the formulation.

We have completed the review of this supplemental application and it is approved.

We remind you that you must comply with the requirements for an approved abbreviated application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

11/19/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-010/S-001
Division File
Field Copy
HFD-92

Endorsements:

HFD-623/R. Bykadi, PHD, 10-31-00 R Bykadi 11-14-00
HFD-623/A. Mueller, PHD, 11-1-00 A Mueller 11-14-00
HFD-617/T. Ames, PM/11-1-00 T Ames 11/14/00
HFD-650/D. Conner
F/T by: gp/11-12-00

CHEMISTRY REVIEW - APPROVABLE

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APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

CHEMISTRY REVIEWS

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Ibuprofen Tablets USP, 200 mg

---

1. CHEMISTRY REVIEW #1

2. ANDA # 75-010/S-001

3. NAME AND ADDRESS OF APPLICANT

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

Tel: (516) 435-3500

4. LEGAL BASIS FOR SUBMISSION

Section 505 (j), FFD & CA

5. SUPPLEMENT(s) S-001 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Ibuprofen Tablets, USP, 200 mg(brown)

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-001 - A change in the excipients used in the formulation

9. AMENDMENTS AND OTHER DATES:

June 5, 2000	Gratuitous Amendment
April 4, 2000	CBE Denial
April 3, 2000	Bioequivalence review
February 28, 2000	Supplement Submission

10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC OTC
Analgesic and Antipyretic

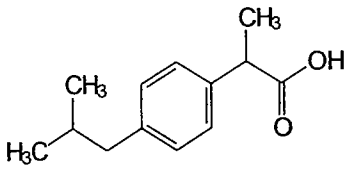
12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM Tablet (Brown) 14. POTENCY 200 mg

15. CHEMICAL NAME AND STRUCTURE

Ibuprofen. Benzeneacetic acid, □-methyl-4-(2-methylpropyl), (□)-.

$C_{13}H_{18}O_2$. 206.29. 15687-21-1, 58560-75-1.
Anti-inflammatory. USP 23, p785.



16. RECORDS AND REPORTS
N/A

17. COMMENTS

L N K International submitted this supplement as CBE supplement on February 28, 2000. The CBE was not granted since there is an addition of new excipient (Carnauba wax) in the formulation, and this amendment is treated as a level 3 change under Supac guidance.

18. CONCLUSIONS AND RECOMMENDATIONS
Not Approvable, **Minor**

19. REVIEWER: Raj Bykadi

DATE COMPLETED: August 8, 2000

Endorsements:

HFD-623/Raj Bykadi, PHD, /8/8/00 S. Bykadi 8-11-00
HFD-623/Albert Mueller, PHD, /8/8/00 A. Mueller 8-11-00

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confidential commercial

information from

CHEMISTRY REVIEW #1

23. RAW MATERIAL CONTROLS **N/A**

24. OTHER FIRM(s) **N/A**

25. MANUFACTURING AND PROCESSING **Not Satisfactory**
The firm did not manufacture an exhibit batch using the new formulation of coloring agent. An R&D batch (R&D lot963) was prepared for comparative dissolution studies. As this is a level 3 change we need documentation on the exhibit batch manufacture.

Deficiency: Please provide copies of exhibit batch documentation for the batch manufactured using the revised formulation ingredients.

26. CONTAINER **N/A**

27. PACKAGING AND LABELING **N/A**

28. LABORATORY CONTROLS (IN-PROCESS AND FINISHED DOSAGE FORM) **Not satisfactory**

We need the test results for IP and FP release. We have requested the batch record which should contain in-process and finished product release data.

28. STABILITY **Not satisfactory**

Stability data is submitted as an amendment to the supplement on July 5, 2000. The firm committed to send the stability data for the lot R&D 963 in the annual report. The stability data meet the stability specifications and the data are acceptable.

30. CONTROL NUMBERS **N/A**

31. SAMPLES AND RESULTS **N/A**

32. LABELING **N/A**

33. ESTABLISHMENT INSPECTION **N/A**

34. BIOEQUIVALENCY STATUS **Not Satisfactory**

Division of Bioequivalence reviewed the supplemental application. The division recommended that this supplement should be reviewed as level 3 Change under Supac Guidance. The firm should generate multi-point dissolution data on the old and new formulations. No new bioequivalence studies are required. (see review by N.L. Tran, 3/31/00)

Deficiency: Division of Bioequivalence has some additional comments on this supplemental application. Please respond to this deficiency/recommendation by Division of Bioequivalence separately.

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:
N/A

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes____X_____

If no, explain reason(s) below:

SPOT? Yes_____ No__X___

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA #75-010 N/A**

#	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

J. Bezdek 5-11-00
Reviewer Signature Date

TYPE OF LETTER: NOT APPROVALBEL - Minor

APPEARS THIS WAY
ON ORIGINAL

ANDA 75-010/S-001
Division File
DUP Jacket
Field Copy

Endorsements:

Endorsements:

HFD-623/R. Bykadi, PHD, 8/9/00
HFD-623/A. Mueller, PHD,8/9/00
HFD-617/B. McNeal, PM, 8/10/00

R. Bykadi 8-11-00
A. Mueller 8-11-00

F/T by: gp/8/11/00

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

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APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
ABBREVIATED NEW DRUG APPLICATION
CHEMISTRY, MANUFACTURING AND CONTROLS REVIEW

Ibuprofen Tablets USP, 200 mg

---

1. CHEMISTRY REVIEW #2

2. ANDA # 75-010/S-001

3. NAME AND ADDRESS OF APPLICANT

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

Tel: (631) 543-3787
Fax: (516) 543-2040

4. LEGAL BASIS FOR SUBMISSION

Section 505 (j), FFD & CA

5. SUPPLEMENT(s) S-001 6. PROPRIETARY NAME N/A

7. NONPROPRIETARY NAME
Ibuprofen Tablets, USP, 200 mg(brown)

8. SUPPLEMENT(s) PROVIDE(s) FOR:

S-001 - A change in the excipients used in the formulation

9. AMENDMENTS AND OTHER DATES:

February 28, 2000	Supplement Submission
April 3, 2000	Bioequivalence review
April 4, 2000	CBE Denial
June 5, 2000	Gratuitous Amendment
August 14,2000	Chemistry DL
September 8, 2000	Minor Amendment

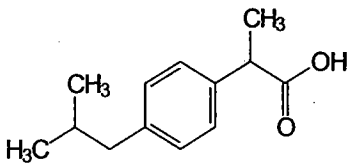
10. PHARMACOLOGICAL CATEGORY 11. Rx or OTC OTC
Analgesic and Antipyretic

12. RELATED IND/NDA/DMF(s)
N/A

13. DOSAGE FORM Tablet (Brown) 14. POTENCY 200 mg

15. CHEMICAL NAME AND STRUCTURE

Ibuprofen. Benzeneacetic acid, α-methyl-4-(2-methylpropyl), (±)-.
$C_{13}H_{18}O_2$. 206.28. 15687-21-1, 58560-75-1.
Anti-inflammatory. USP 24, p854.



16. RECORDS AND REPORTS
N/A

17. COMMENTS Chemistry and bioequivalence issues - satisfactory.

18. CONCLUSIONS AND RECOMMENDATIONS
Approvable

19. REVIEWER: Raj Bykadi
DATE COMPLETED: October 4, 2000

Endorsements:

HFD-623/Raj Bykadi, PHD, /10/4/00, 10/31/00 R Bykadi 11-14-00
HFD-623/Albert Mueller, PHD, /10/4/00, 10/31/00 11/1/00 A Mueller 11-14-00

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CHEMISTRY REVIEW #2

36. ORDER OF REVIEW:
The application submission(s) covered by this review was taken in the date order of receipt Yes____X_____

If no, explain reason(s) below:

SPOT? Yes_____ No__X___

If yes, complete a SPOT form.

APPEARS THIS WAY
ON ORIGINAL

37. **DMF CHECKLIST FOR ANDA #75-010 N/A**

F #	DMF TYPE/SUBJECT/HOLDER	ACTION CODE	RESULT OF REVIEW	DATE REVIEW COMPLETED

ACTION CODES: (1) DMF Reviewed. Other codes indicate why the DMF was not reviewed, as follows:

(2) Type 1 DMF;
(3) Reviewed previously and no revision since last review;
(4) Sufficient information in application;
(5) Authority to reference not granted;
(6) DMF not available;
(7) Other (explain under"Comments").

A Bykadi 11-14-00

Reviewer Signature Date

TYPE OF LETTER: APPROVALBEL

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

BIOEQUIVALENCE REVIEWS

Ibuprofen Tablets, USP
200 mg, Brown color
round and caplet shape
ANDA #75-010 /SCF001
Reviewer: Nhan L. Tran
File name: 75010D.200

LNK International
60 Arkay Drive
Hauppauge, NY
Submission Date:
Feb 28, 2000

REVIEW OF A CHEMISTRY CONSULT: A CHANGES BEING EFFECTED SUPPLEMENT (SUPAC-IR)

Background:

For ANDA 75-010, ibuprofen 200 mg, brown round shaped tablet and oval shaped caplet, LNK wants to change the color coating, [redacted] to [redacted] due to possible discontinuance of the original brown coating [redacted] by its maker, [redacted]. The firm requests that due to the apparent emergency nature of the change, and since this is not a change from one colorant to another, this supplement should be considered as a changes being effected supplement.

Formulation:

The formulation of the proposed and approved colors is shown below:

Component	Approved	Proposed
[redacted]		

Recommendation.

Based on the formulation above, this supplement does not meets SUPAC IR Level 1 for component and composition changes. A change in color, either in amount or from one color to another is a level 3 component and composition change. Hence, a change from one color (———— ————) to another color (————————) should be submitted as a prior approval supplement, not as a changes being effected supplement. This Level 3 change pertains mainly to the Chemistry, and for Bioequivalence documentation, no new Bioequivalence study is requested for Level 3 color change. However, comparative multi-point dissolution testing comparing the old and reformulated products and a request for waiver should be submitted.
The current SUPAC IR Guidance states that a biostudy is requested, however, a draft (revised) guidance under review mentions the eligibility of a waiver request, based on DBE's long-standing practice of not requesting a biostudy for a color change in approved solid oral dosage forms for both IR and MR.

The Chemistry Division should be informed of the recommendation.

Nhan L Tran, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 3/31/2000

Concur: _____ Date 4/3/00
Dale P. Conner, Pharm.D
Director
Division of Bioequivalence

BIOEQUIVALENCY DEFICIENCY

ANDA: 75-010/S[illegible]001 APPLICANT: LNK International

DRUG PRODUCT: Ibuprofen Tablets, USP, 200 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

This supplement does not meets SUPAC IR Level 1 for component and composition changes. A change in color, either in amount or from one color to another is a level 3 component and composition change. Hence, a change from one color ([redacted]) to another color ([redacted]) should be submitted as a prior approval supplement, not as a changes being effected supplement. This Level 3 change pertains mainly to the Chemistry, and for Bioequivalence documentation, no new Bioequivalence study is requested for Level 3 color change. However, comparative multi-point dissolution testing comparing the old and reformulated products and a request for waiver should be submitted.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-010/SCF001
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655 /N. Tran
HFD-655/S. NERURKAR 4/5/00
HFD-650/Dale Conner 4/10/00

BIOEQUIVALENCY - DEFICIENCIES Submission Date: 2/28/2000

1. ~~OTHER OPTIONS (less common)~~: Dissolution (DIS)
e.

Strengths: 200 mg
Study/Dissolution (STD)
Outcome: UN
UN - Unacceptable

Outcome Decisions:

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

Ibuprofen Tablets, USP
200 mg, Brown color
round and caplet shape
ANDA #75-010/SCF-001/AM
Reviewer: Nhan L. Tran
File name: 75010D.200

LNK International
60 Arkay Drive
Hauppauge, NY
Submission Date:
September 8, 2000

REVIEW OF A DEFICIENCY AMENDMENT

Background:

LNK has an approved ANDA 75-010 for ibuprofen 200 mg; brown round shaped tablet and oval shaped caplet. Now LNK wants to change the color coating from [redacted] to [redacted] due to a possible discontinuance of the original brown coating [redacted] by its maker, [redacted]. The firm requested on February 28, 2000, that due to the apparent emergency nature of the change, this supplement should be considered as a changes being effected supplement--SUPAC IR Level 1 for component and composition changes. The Division of Bioequivalence has denied the request, and concluded that this supplement should be viewed as a Prior Approval Supplement due to a change from one color to another color--SUPAC IR Level 3 change. For this, The Division requested that multipoint dissolution testing comparing the existing and the proposed formulations be conducted and data submitted to the Agency for evaluation (please see review by N. Tran, 4/23/2000). Dissolution data are submitted in this submission.

Review of the dissolution data:

The dissolution testing was conducted using the USP Method as shown in the following table:

I. Conditions for Dissolution Testing: USP Method
USP 24 Method II (Paddle) RPM: 50 No. Units Tested: 12 Medium: 900 ml; phosphate buffer pH 7.2 Specifications: NLT (Q) 80%/60 minutes

II. Results of In Vitro Dissolution Testing:

Sampling Times (Minutes)	Proposed Product Lot # R&D 963 Strength(mg): 200 mg			Current (approved) Product Lot # P13517B Strength(mg): 200 mg		
	Mean %	Range	%CV	Mean %	Range	%CV
15	98		2.5	99		2.4
30	102		2.1	103		2.8
45	97		1.7	100		1.8
60	95		2.3	101		1.6
F2 = 74.57						

Review of a waiver request

A waiver request is submitted based on 21 CFR 320.22(d)(4). The proposed drug product is a reformulated product that is identical, except for a different color to the approved product. Both formulations meet the approved in-vitro dissolution testing requirements.

Recommendations

1. The in vitro test results are acceptable. The dissolution testing should be incorporated into the firm's manufacturing controls and stability. The dissolution testing should be conducted in 900 mL of phosphate buffer, pH 7.2 at 37°C using USP 24 apparatus 2 (Paddle) at 50 rpm. The test should meet the following specifications:

Not less than 80% of the labeled amount of drug is dissolved in 60 minutes.

2. From the bioequivalence point of view, the firm has met the requirements for waiver of in vivo bioequivalence study, and the waiver for ibuprofen reformulated tablet, 200 mg is granted per 21 CFR 320.22(d)(4).

11/13

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED S.NERURKAR
FT INITIALED S.NERURKAR _____ Date 11/15/2000

Concur: _____ Date 11/29/00
for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence

cc: ANDA # 75-010 Supplement; HFD-655 (Tran, Nerurkar), Drug File, Division File.

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 75-010
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Team Leader

Endorsements: (Final with Dates)
HFD-655/Tran 11-13
HFD-655/ S. Nerurkar 11/15/00
for HFD-650/ D. Conner 11/20/00

BIOEQUIVALENCY - ACCEPTABLE submission date: **September 8, 2000**

1. **SUPPLEMENT/WAIVER** Strengths: **200mg Tablets & 200mg Caplets**

Outcome: AC

Outcome Decision: ✓ **AC** - Acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-010/S APPLICANT: LNK

DRUG PRODUCT: Ibuprofen Tablets USP, 200 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.
The dissolution data is acceptable. We acknowledge that the dissolution testing has been incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Barbara M Saint

for Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 75-010
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Reviewer
HFD-655/ Team Leader

Endorsements: (Final with Dates)
HFD-655/Tran 11-12
HFD-655/ S. Nerurkar 11/9/00
HFD-650/ D. Conner 11/29/00

BIOEQUIVALENCY - ACCEPTABLE submission date: **September 8, 2000**

1. **SUPPLEMENT/WAIVER** Strengths: **200mg Tablets & 200mg Caplets**

Outcome: AC

Outcome Decision: **AC** - Acceptable

WinBio Comments:

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

GENERIC NAME: Ibuprofen
SPONSOR: LNK
STRENGTH: 200 mg
TYPES OF STUDIES: N/A
CLINICAL STUDY SITE: N/A
ANALYTICAL SITE: N/A

ANDA #: 75-010/S
DOSAGE FORM: Tablet & Caplet

STUDY SUMMARY:

This supplement is for the change in the color. The waiver is granted.

DISSOLUTION: Acceptable

DSI INSPECTION STATUS

Inspection needed: NO	Inspection status:	Inspection results:
First Generic _No New facility _No___ For cause __No___ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: Nhan L. Tran, Ph.D.
INITIAL: _____
BRANCH: II
DATE: 11-13-00

TEAM LEADER: Shriniwas Nerurkar, Ph.D.
INITIAL: _____
BRANCH: II
DATE: 11/15/2000

for DIRECTOR, DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.
INITIAL: Barbara M Davit
DATE: 11/29/00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

ADMINISTRATIVE DOCUMENTS

SPECIAL

CBE- THIRTY (30) DAY SUPPLEMENT ROUTING FORM

This form is to accompany all CBE-30 Day Supplements. Upon completion, return to the OGD Document Room

I. To be completed by the OGD Document Room using information from the applicant Cover letter:

DATE PROCESSED: 3-1-00
APPLICATION # : 75010 SUPPLEMENT # : SCF001

II: To be determined by Chemistry Division Staff.

Date and initial appropriate category.

Division/Deputy Director decision is to be used for final classification:

Thirty (30) Day CBEs:

Chemistry Div. Staff	Qualifies as CBE-30 (GR)	Does Not Qualify. This is a CBE-0. (DC)	Does not Qualify. This is an Annual Report (DA)	Does not Qualify. This is a Prior Approval Supp. (DN)
Chemistry/Micro Project Manager(s)			B. McNeal 3-14-00	
Micro Team Leader (as needed)				
Chemistry Team Leader			3-13-00.	3-15-00
Chemistry Div. Dir. Or Deputy Dir.				3/15/00

COMMENTS: Deletion/partial deletion of ingredients intended to affect color - Level I. Issue-IR IIIA1a) & Addition of Carnauba Wax - Hence Carnauba Wax meets SUPAC-IR Level 1 (IIIA1b). Carnauba Wax in New formulation = ——— any, well w. this IVG guidelines

III. To Project Manager Chemistry Team I :

Prepare letter and notify applicnt by telephone when CBE is denied because it is a prior approval supplement.
DATE: 3/21/00 Notified Mr. Chudzik that this is a prior approval because ~~lead~~ addition of new excipient no matter how small is a prior approval. B. McNeal

Notify applicant by telephone that inappropriate CBE category used. DATE _____

Request that applicant withdraw supplement when CBE qualifies for submssion as an Annual Report DATE _____

IV. To Document Room

Record appropriate CBE Code DN Jack Jacobs Quantitation Supv.
File in archival submission

The addition of a new excipient or color (i.e. Carnauba Wax) not covered under Supac under levels 1 or 2. or in Level 3 no matter the amount added is considered a prior approval.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 75-010 / S-001

CORRESPONDENCE

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

ANDA 75-010 Ibuprofen USP 200mg Film Coated Brown Round & Capsule Shaped Tablets

February 28, 2000

Mr. Mark Anderson
Project Manager
Office of Generic Drugs
CDER, FDA
8700 Standish Place
Metro Park North II
Rockville, MD 20855-2773

NDA NO _____ REF NO. SCF001
NDA SUPP FOR formulation RW/AT

SUPAC-IR, Special Supplement, Changes Being Effected

Dear Mr. Anderson:

LNK requests a Special Supplement, Changes Being Effected on our Abbreviated New Drug Applications for **ANDA 75-010 Ibuprofen Tablets USP, 200 mg. (brown)** approved 3/1/99. **LNK** wants to change the [redacted] to [redacted]. [redacted] has informed LNK of the new formulation [redacted] of the same brown color. LNK would like to make the switch to this formulation before the possible discontinuance of the original brown coating, [redacted]. This supplement meets SUPAC IR Level 1 for changes to excipients where the change is unlikely to have a detectable impact on formulation quality and performance. Therefore, the appropriate form of a supplement might be in the annual report, except for the introduction of Carnauba wax in the new formulation. According to SUPAC IR., a change from one colorant to another would require a prior approval supplement, but this change is not a change in colorant, but a change in the colorants formulation. LNK is submitting this supplement because of the apparent emergency nature of the change (and the lack of specific SUPAC guidance) might allow a CBE with the following documentation.

[redacted]

ANDA 75-010 Ibuprofen USP 200mg Film Coated Brown Round & Capsule Shaped Tablets

Enclosed is a copy of letter from [redacted] (Exhibit 1), regarding the quantity of Carnauba Wax in this new formulation of [redacted] Brown. According to them, the purpose of Carnauba Wax in the formulation is as a [redacted]

Carnauba wax is used in many drug formulations. According to the most recent Inactive Ingredient Guide (IIG) dated 1996, there were 229 NDA that listed Carnauba Wax as part of an oral drug formulation, in a range of 0.1 mg to 200 mg. According to information from [redacted] the Carnauba wax is substituted as a [redacted] The amount of Carnauba wax in our formulation will be [redacted] mg per tablet. This is based on the current coating parameters, which will not be changed, of [redacted] / tablet and a coated tablet weight of [redacted] (current specification). Therefore, there does not appear to be any safety issues.

LNK is providing the documentation (Exhibit 2) on the two formulations from [redacted] LNK has performed the coating process with the [redacted]. All the required tests, including the profile dissolution were performed. Tabulated comparative dissolution results between lot R&D 963 and Bio-Study lot P13517B are attached (Exhibit 3). The lot is entered into 90 days accelerated and controlled room temperature stability program (to be submitted in Annual Report). LNK will place the first three production batches made, using the new [redacted] into controlled room temperature and 90 days accelerated stability program as per our approved stability protocol.

This change is not specifically covered by the SUPAC–IR examples, but LNK feels that the information and circumstances warrant a CBE supplement. This change will take effect May 2000. The two-month delay is intended to allow enough time to provide any additional information that the Agency may desire.

The LNK facility is in satisfactory GMP status based on an inspection performed June 10, 1999 through July 28, 1999.

LNK feels certain that the information is sufficient in order for your office to grant Changes Being Effected Supplement. If there is the need for additional information, please call me at (516) 543-3787.

Sincerely,

Pankaj S. Chadgar
Vice President

PSC/dju

ANDA 75-010/S-001

PRIOR APPROVAL SUPPLEMENT

LNK International Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, New York 11788

APR - 4 2000

Dear Sir:

This is in reference to your supplemental new drug application dated February 28, 2000, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Ibuprofen Tablets USP, 200 mg.

You noted that it is a "Supplement- Changes Being Effected".

This supplemental application provides for:

A change in excipients used in the formulation

The changes that you have described are not, in our opinion, the kind permitted by regulation to be put into effect in advance of approval of the supplement. Rather, this change is a major manufacturing change that requires approval of a supplement before a product made with the change can be distributed.

This letter is to notify you that an approved supplement is required for the proposed changes and that the supplement is under review. Please do not implement the proposed changes until you receive notification that the supplemental application is approved. Distribution of the drug is also subject to requirements for validation of the change.

Sincerely yours,

4/3/00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc:
ANDA 75-010/S-001
Div. File
Field Copy

Endorsements:
HFD-623 /R. Bykadi/3/23/00 R. Bykadi 3-27-00
HFD-623/A. Mueller/3/23/00 A. Mueller 3-27-00
HFD-617/B. McNeal/3/24/00 B. McNeal 3/29/00

Chemistry Review- CBE Denial

F/T by: gp/3/27/00

Filename: V:\FIRMSAM\LNK\LTRS&REV\75010S1CBEDENIED.DOC.DOT

APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

ANDA 75-010 / S-001
Ibuprofen 200mg Brown Round Tablets

June 5, 2000

Mr. Mark Anderson
Project Manager
Office of Generic Drugs
CDER, FDA
8700 Standish Place
Metro Park North II
Rockville, MD 20855-2773

NDA SUPPL AMENDMENT
SCF-001
AC

Amendment to Supplement
ANDA 75-010/S-001

Dear Mr. Anderson:

This is in reference to our chemistry Supplement (S-001) dated February 28, 2000 (Supac-IR - Special Supplement, changes being affected) and your letter dated April 4, 2000. In the initial supplement, LNK committed to submit the stability information for the lot (R&D 963) of **Ibuprofen 200 mg. Brown Round Tablets** in the annual report. Since OGD changed the supplement status, we are enclosing the stability data (90 days accelerated and three months ambient) for your review as an amendment.

We hope this information will be sufficient to grant LNK the approval of this supplement. If any other information is needed, please call me at 631-543-3787.

Sincerely,

Pankaj S. Chudgar
Vice President

PSC/dju
Enc.

Ibuprofn\amendltr.joe

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 06 2000
OGD

ANDA 75-010/S-001

PRIOR APPROVAL SUPPLEMENT

LNK International, Inc.
Attention: Pankaj S. Chudgar
60 Arkay Drive
Hauppauge, NY 11788

Dear Sir:

This is in reference to your supplemental new drug application dated February 28, 2000 submitted pursuant to 505 (j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Ibuprofen Tablets USP, 200 mg.

This supplemental application, submitted as a "Prior Approval Supplement" provides for the following:

A change in excipients used in the formulation

The supplemental application is deficient and, therefore not approvable under the section 505 of the Act for the following reasons.

Chemistry Deficiencies:

1 You provided in your cover letter a Table showing the differences in formulation of [redacted] and [redacted]. Comparison of these two formulations provided by [redacted] (Exhibit 2) showed that [redacted] and [redacted] are replaced by [redacted] and [redacted] in the new formulation. Please explain.

2. Please provide copies of exhibit batch documentation for the batch manufactured including all the in-process controls and finished product testing using the revised formulation ingredients.

For additional information we urge you to review the requirements of SUPAC-IR, section III.C for Level 3 changes of excipients in drug products.

Bioequivalence Deficiency:

The Division of Bioequivalence has completed its review of your submission of February 28, 2000. The following deficiency has been identified:

This supplement does not meet SUPAC IR Level 1 for component and composition changes. A change in color, either in amount or from one color to another is a level 3 component and composition change. Hence, a change from one color (————————) to another color (————————) must be reviewed as a Prior Approval Supplement. No new Bioequivalence study is requested for a Level 3 color change. However, comparative multi-point dissolution testing comparing the old and reformulated products and a request for a waiver should be submitted.

The file on this supplemental application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw this supplemental application. Your amendment should respond to all the deficiencies listed. Partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this letter will be considered as a MINOR amendment and should be so designated in your cover letter. If you have substantial disagreement with our reasons for not approving this supplemental application, you may request an opportunity for a hearing.

Sincerely yours,

8-11-00

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 75-010/S-001
Division File
DUP Jacket
Field Copy

Endorsements:

Endorsements:

HFD-623/R. Bykadi, PHD, 8/9/00 R. Bykadi 8-11-00
HFD-623/A. Mueller, PHD, 8/9/00 A. Mueller 8-11-00
HFD-617/B. McNeal, PM, 8/10/00 B. McNeal 8-11-00
HFD-655/N. Tran/N 8-14-00

F/T by: gp/8/11/00

CHEMISTRY REVIEW - NOT APPROVABLE - MINOR

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APPEARS THIS WAY
ON ORIGINAL

L N K INTERNATIONAL, INC.

OVER-THE-COUNTER PHARMACEUTICAL MANUFACTURERS

60 ARKAY DRIVE, HAUPPAUGE, LI, NY 11788 • (516) 435-3500

ANDA 75-010 Ibuprofen Tablets USP, 200 mg (brown)

September 8, 2000

Dr. Rashmikant Patel, Director
Division of Chemistry I
Office of Generic Drugs
CDER, FDA
8700 Standish Place
Metro Park North II
Rockville, Md 20855

SUPPL AMENDEMENT
SCF-001/AM

Minor Deficiency Amendment
SUPAC-IR Component and Composition Level 3
With In Vivo Bioequivalency Waiver Request

Dear Dr. Patel:

LNK is responding to a Minor Deficiency Letter dated August 14, 2000 to our supplement dated February 28, 2000 for LNK's Abbreviated New Drug Applications for **ANDA 75-010 Ibuprofen Tablets USP, 200 mg. (brown)**. LNK's response is formatted to repeat the FDA deficiencies in bolded type immediately followed by a response; additional information may be attached as referenced numbered exhibits.

Chemistry Deficiencies:

1. **You provide in your cover letter a Table showing the differences in formulation of ——— and ——— Comparison of these two formulations provided by ——— (Exhibit 2) showed that ——— and ——— are replaced by ——— and ——— in the new formulation. Please explain.**

LNK acknowledges the discrepancy. There was a misunderstanding based on the initial information provided by——— to LNK. ——— had originally identified only those changes in the table. LNK then requested the exhibits form ———. ——— did not feel the need to correct our table, which had been submitted to them for preview based on their understanding of change. ——— has provided a response (Exhibit 1) to our inquiry. ——— believed that the change in molecular weight/viscosity of the same component was not a change.. LNK will try to be more vigilant in future submissions; we assumed that they knew their information was acceptable with the FDA.

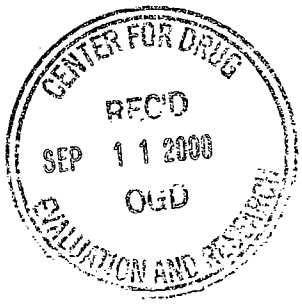

Table 1 – Revised comparison of approved and proposed [redacted] components

Component	[redacted] (Approved) *	[redacted] (Proposed)
[redacted]		

- X indicates an amount in the original formulation unknown to LNK, but verified for change in the new formulation with [redacted]
- Items in italics have been added to the previously submitted table.

2. **Please provide copies of exhibit batch documentation for the batch manufactured including all the in-process controls and finished product testing using the revised formulation ingredients.**

[redacted]

For additional information we urge you to review the requirement of SUPAC –IR, section III.C for Level 3 changes of excipients in drug products.

Bioequivalence Deficiency:

The Division of Bioequivalence has completed its review of your submission of February 28, 2000. The following deficiency has been identified:

This supplement does not meet SUPAC IR Level 1 for component and composition changes. A change in color, either in amount or from one color to another is a level 3 component and composition change. Hence, a change in from one color [redacted] to another color [redacted]) must be reviewed as a Prior Approval Supplement. No new Bioequivalence study is requested for a Level 3 color change. However, comparative multi-

point dissolution testing comparing the old and the reformulated products and a request for a waiver should be submitted.

LNK has reviewed the requirements for Component and Composition – Level 3 change. (C. Level 3 Changes; b. Dissolution Documentation; **Case B dissolution profile as described in Section III.B.2.b.)**

Case B:

Multi-point dissolution profile should be performed in the application/compendial medium at 15, 30, 45, 60 and 120 minutes or until an asymptote is reached. The dissolution profile of the proposed and currently used product formulations should be similar.

LNK had submitted this data in the initial filing without the 120-minute time point because the data had indicated maximum dissolution after 30 minutes. LNK resubmits the dissolution data (Exhibit 3). In addition we submit a Bioequivalence Waiver Request (Exhibit 4) as per your instruction.

LNK feels certain that the information is sufficient in order for your office to approve the supplement. If there is the need for additional information please call me at (516) 543-3787. Sincerely,

Sincerely,

Pankaj S. Chudgar
Vice President