

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER      74464**

**ADMINISTRATIVE DOCUMENTS**

ANDA APPROVAL SUMMARY

ANDA: 74-464

DRUG PRODUCT: Indomethacin Extended Release Capsules USP

FIRM: Eon Laboratories

DOSAGE FORM: capsules STRENGTH: 75 mg

CGMP STATEMENT/EIR UPDATE STATUS: acceptable, 06-09-97

BIO STUDY: approval, letter sent 07-05-96

VALIDATION: DS and DP are compendial

STABILITY: The specified market containers are used in stability.

Expiration: 24 months

Finished Product Tests and Specifications:

1. Description: #2 gelatin capsule, green cap, clear body containing white and green pellets, with "E270" imprinted in black ink on both cap and body.

LABELING: approve, per review dated 04-06-98

STERILIZATION VALIDATION: N/A

SIZE OF BIOBATCH: - ADEQUATE, per review dated 12-15-97

SIZE OF STABILITY BATCHES: capsules (lot 930301)  
Proposed production batches

CHEMIST: 4-29-98

TEAM LEADER:

April 29, 1998

Y:\NEW\FIRMSAM\EON\LTRS&REV\74464AP.498

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER      74464

CORRESPONDENCE

NEW CORRESP

NC

April 13, 1998

Mr. Peter Rickman  
Branch Chief  
Regulatory Affairs  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**RE: General Correspondence  
ANDA 74-464  
Indomethacin Extended-Release Capsules, USP 75 mg**

---

Dear Mr. Rickman,

In reference to our earlier telephone conversation regarding Indomethacin Extended-Release Capsules USP, 75 mg, we are submitting a copy of Merck's letter regarding their patent No. 4173626. The letter confirms that we are not infringing their patent. Unfortunately, we have been unable to locate the return receipt of the notification letter sent to Merck.

In lieu of the signed receipt, we hope that Merck's letter acknowledging non-infringement will satisfy the conditions outlined in 21 CFR 314.95. In addition we certify that we were not sued by Merck within the 45 day statutory period for the Notice of Patent Certification letter issued on February 2, 1994.

If you need further clarification or information, please do not hesitate to call me at (718) 276-8607 ext. 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



Zohra Lomri  
Sr. Regulatory Affairs Associate

**RECEIVED**

**APR 14 1998**

**GENERIC DRUGS**



Eon Labs  
A Health Care Company

Eon Labs Manufacturing, Inc.  
227-15 N. Conduit Avenue  
Laurelton, NY 11413  
Telephone 718 276-8600  
Fax 718 949-3120

April 6, 1998

Chan Park  
Division of Labeling and Program Support  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room, Metro Park North II  
7500 Standish Place, Room 150  
Rockville, MD 20855-2773

**NEW CORRESP**

NC

**RE: FACSIMILE MINOR AMENDMENT  
ANDA 74-464  
Indomethacin Extended-release Capsules, USP 75 mg**

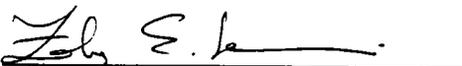
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Dear Mr. Park,

In reference to our earlier telephone conversation regarding Indomethacin Extended-Release Capsules USP, 75 mg, we are submitting our facsimile amendment to update our Patent Certification.

We hope that our response satisfactorily address the deficiencies noted in your facsimile. If you need further clarification or information, please do not hesitate to call me at (718) 276-8607 ext. 393.

Sincerely,  
Eon Labs Manufacturing, Inc.

  
\_\_\_\_\_  
Zohra Lomri  
Sr. Regulatory Affairs Associate

**RECEIVED**

**APR 10 1998**

**GENERIC DRUGS**

March 4, 1998

Douglas Sporn  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20857

ORIGINAL AMENDMENT

N/AM

Re: **MINOR AMENDMENT**  
**Indomethacin Extended Release Capsules, USP, 75 mg**  
**ANDA 74-464**

---

We refer to Dr. Rashmikant M. Patel's letter of January 13, 1998 regarding the above referenced abbreviated new drug application. The following are our responses to the deficiency noted in the letter.

1. Comment:

The [redacted] that you reference for the drug substance, Indomethacin USP, was reviewed and found to be deficient. The DMF holder has been notified of the status. Please do not respond to this letter until you have received confirmation from the DMF holder that the deficiencies have been addressed.

Response:

We have been advised by our active drug substance DMF holder [redacted] that they have addressed the deficiencies referred to above.

2. Comment:

Please revise your specification for [redacted] for the [redacted] on release and stability to more accurately represent the actual data.

Response:

The specification for [redacted] on release and stability have been revised from [redacted] more accurately represent the actual data. As a consequence the following documents are being submitted reflecting the revised specifications:

D. Sporn

March 4, 1998

RECEIVED

Page 1 of 3  
MAR 05 1998

GENERIC DRUGS

85-0-2

- Product Monograph, QC I001 (**ATTACHMENT 1**).
- QC Finished Capsule Specification & Report Form (**ATTACHMENT 2**).
- Post Approval Stability Commitment for Indomethacin 75 mg E.R. Capsules (**ATTACHMENT 3**).

**3. Comment:**

**Please revise your stability commitment to specify that the extension of the expiration date will be based on three lots of product.**

**Response:**

See response to Comment 4.

**4. Comment:**

**Please revise your stability commitment to specify that yearly thereafter, one lot of each size and each container closure system will be placed on stability.**

**Response:**

The Post Approval Stability Commitment filed in the original ANDA already states that the extension of the expiration date will be based on three lots of product: we refer you to the first paragraph of the stability commitment document which provides for "The first three production lots of the product will be packed for stability testing...The data obtained from these stability studies will be used to extend the expiration date as permitted by 21 CFR 314.70(d)(5)...". Additionally, it states "...Yearly, thereafter, at least one production batch shall be added to the stability program..." packaged in the smallest and largest package size within a container/closure system. This statement represents the smallest and largest package size within a stability bracket. In accordance with current stability guidelines, bracketing is an acceptable approach for monitoring the product shelf life of solid oral dosage forms. By using a stability bracket, it is not required to perform individual stability studies on each intermittent bottle size.

Although the Post Approval Stability Commitment filed in the original ANDA was in accordance with the stability regulations, a revised Post Approval Stability Commitment using the same language described above has been submitted in response to comment 2 as **ATTACHMENT 3**.

**5. Comment:**

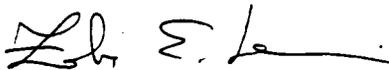
**The specifications for the description on stability should be the same as that the specification for description at release.**

**Response:**

The specifications for the description on stability have been revised to match the specifications for the description at release. A Stability Protocol for Indomethacin Extended-Release Capsules USP, 75 mg (Intermediate) and a Stability Specification Summary are provided, **(ATTACHMENT 4)**.

We hope the responses satisfactorily address the deficiencies noted in your letter. If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



---

Zohra E. Lomri  
Sr. Regulatory Affairs Associate

November 20, 1997

Douglas Sporn  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20857

FDA CRIO AMENDMENT

**Re: MINOR AMENDMENT  
Indomethacin Extended Release Capsules, USP, 75 mg  
ANDA 74-464**

---

We refer to Dr. Rashmikant M. Patel's letter of October 23, 1997 regarding the above referenced abbreviated new drug application, and to the conference call of October 28, 1997 with the Division of Chemistry I.

We hope our responses to the deficiency letter satisfactorily address the outstanding issues that have appeared repeatedly in the numerous deficiency letters for the Indomethacin application. The conference call of October 28, 1997, between OGD and Eon Lab's, was instrumental in clarifying FDA's concerns with regards to the manufacturing controls for the finished product, and provided guidance as to the agency's position on approval for a sustained release product where complicated manufacturing parameters are involved.

In an effort to clarify any confusion associated with previous deficiency letter responses, we have strived to submit this minor amendment addressing all deficiencies as completely as possible and to be in conformance with the discussions of the October 28, 1997 conference call. Pending review of our amendment, should there remain outstanding issues that cannot be resolved, we will officially request a meeting with the OGD and the appropriate personnel from the Division of Chemistry I in an effort to reach an understanding and/or agreement to satisfy the remaining concerns.

**A. Chemistry Deficiencies:**

PAGES 2-5  
CMC DEFICIENCIES

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D. Sporn

November 20, 1997

RECEIVED Page 1 of 7

NOV 24 1997

GENERIC DRUGS

**Labeling Deficiencies:**

**1. GENERAL COMMENTS**

**Please note the patent of the reference listed drug "Indocin® SR" expires December 11, 1998. We refer you to the 17th edition "Orange Book". As discussed over the telephone between Chan Park of the Agency and Zohra Lomri of your firm on October 21, 1997, please submit an update Patent Certification.**

**Response:**

The Patent Certification you are referring to was submitted in the original application and in correspondence dated 3/18/94.

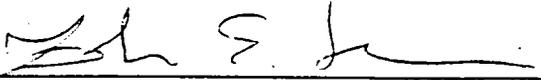
**2. INSERT**

**We acknowledge the receipt of your revised package insert labeling submitted on August 20, 1997. As Chan Park of the Agency have informed over the telephone to Zohra Lomri and Sadie Ciganek of your firm on October 21, 1997, you revised package insert labeling was modeled after an approved innovator's labeling (Issued August, 1995). Please note that the innovator's labeling you had used for side-by-side comparison for your April 8, 1996 submission is still the last approved labeling. The final printed package insert labeling you had submitted on April 8, 1996 appears to be satisfactory. Therefore, we ask you to submit a commitment statement that you will not use the revised package of August 20, 1997 submission for your drug product.**

We commit to not using the revised package insert submitted August 20, 1997. Instead, we will be using the 2/96 revision submitted April 8, 1996.

We hope the responses satisfactorily address the deficiencies noted in your letter. If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



---

Zohra E. Lomri  
Sr. Regulatory Affairs Associate



Eon Labs  
The Pharmacy Drug Company

Eon Labs Manufacturing, Inc.  
227-15 N. Conduit Avenue  
Laurelton, NY 11413  
Telephone 718 276-8600  
Fax 718 949-3120

## FIELD COPY CERTIFICATION

I certify that a true copy of a Minor Amendment for Eon Labs Manufacturing, Inc's., Indomethacin Extended Release Capsules, USP 75 mg, ANDA 74-464 has been sent to the Food and Drug Administration, New York District Office, 850 Third Avenue, Brooklyn, New York.

Patricia Kaufold

Patricia Kaufold  
Manager, Regulatory Affairs  
Eon Labs Manufacturing, Inc.

11/20/97

Date



**Eon Labs**  
A Health Care Company

Eon Labs Manufacturing, Inc.  
227-15 N. Conduit Avenue  
Laurelton, NY 11413  
Telephone 718 276-8600  
Fax 718 949-3120

August 20, 1997

Douglas Sporn  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20857

**NDA ORIG AMENDMENT**

*J/JS*

**MINOR AMENDMENT**

**Re: INDOMETHACIN EXTENDED RELEASE CAPSULES, USP, 75 MG**  
**ANDA 74-464**

---

We refer to Dr. Rashmikan M. Patel's letter of July 9, 1997 regarding the above referenced abbreviated new drug application, and to the conference call of July 7, 1997 with the Division of Chemistry I. Herein are the responses to the minor deficiencies.

**Chemistry Deficiencies:**

**A. Chemistry Deficiencies:**

*PAGES 2 - 4*  
*CMC*

**GENERIC DRUGS**

**Comment**

1. **You made a reference to the SUPAC DRAFT guideline for extended release products. Please be advised that the guidance is only in DRAFT form and when finalized, it will only apply to post approval changes.**

**Response**

We acknowledge that the SUPAC MR guidance is only in **DRAFT** form and when finalized, it will only apply to post approval changes. However, the reference was made to demonstrate a key point: that the range variation of ethyl cellulose discussed is minimal compared to the range proposed in the draft guidance of  $\pm 2\%$ , a level 1 change requiring annual reporting only.

**Comment**

2. **In future correspondence, please number the complete amendment sequentially as opposed to numbering each attachment sequentially.**

**Response**

As requested, we have numbered the amendment sequentially.

**Comment**

3. **Please update the tests and specifications for the drug substance and the drug product ( release and stability) to reflect the current changes in the USP.**

**Response**

Current specifications for the drug substance and the drug product, both for release and stability, are included in the Product Monograph, which is constantly updated to the most recent USP requirements. Please refer to **attachment 4** for the Product Monograph.

We are also providing twelve copies (12) of final printed insert labeling to reflect the most recent labeling changes for Indomethacin ER Capsules. A side-by-side comparison to the latest reference insert is included for your review, **attachment 6**.

We hope the responses satisfactorily address the deficiencies noted in your letter. If additional information is required, please contact me at (718) 276-8607, extension 393.

Sincerely,  
Eon Labs Manufacturing, Inc.



Zohra E. Lomri  
Sr. Regulatory Affairs Associate

December 16, 1996

Douglas Sporn  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation  
and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20857

AMENDMENT  
N/A

**Re: ANDA 74-464 - MINOR AMENDMENT  
INDOMETHACIN EXTENDED-RELEASE CAPSULES USP, 75 MG**

We refer to Dr. Rashmikant M. Patel's letter of October 25, 1996 regarding the above referenced abbreviated new drug application, and to the conference call of November 18, 1996 with Mr. Jim Wilson, CSO of the Division of Chemistry I Branch.

Chemistry Deficiencies

PAGES 2-5

CMC

DEC 17 1996

1. **You have made a reference to the SUPAC document as an argument for your changes in the ethyl cellulose amounts. Please be advised that the SUPAC Guidance (dated November 1995) makes reference to immediate release solid oral dosage forms only.**

Response

We acknowledge that the SUPAC Guidance dated November 1995 makes reference to immediate release solid dosage forms. However, we also refer to a draft SUPAC guideline currently in circulation for extended release products.

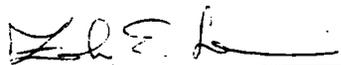
2. **For future correspondence, please commit to following the Policy and Procedure Guide 30-91 with respect to the pagination of the application. You have numbered each volume of the application sequentially as opposed to numbering the complete application sequentially.**

Response

For future correspondence we commit to following the Policy and Procedure Guide 30-91 with respect to the pagination of the application by numbering the complete application sequentially.

If additional information is required, please contact me at (718) 276-8607, extension 343.

Sincerely,



Zohra E. Lomri  
Regulatory Affairs Associate

April 8, 1996

Douglas Sporn  
Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place  
Rockville, Maryland 20855

*[Handwritten signature]*  
MAJOR AMENDMENT  
**RECEIVED**  
APR 15 1996  
GENERIC

**Re: ANDA 74-464 - MAJOR AMENDMENT  
INDOMETHACIN EXTENDED-RELEASE CAPSULES USP, 75 MG**

We refer to Dr. Rashmikant M. Patel's letter of February 5, 1996 commenting on our abbreviated new drug application dated February 2, 1994, and amended June 28, 1995 for Indomethacin Extended-Release Capsules, USP, 75 mg.

We wish to indicate that some company policies have been revised since our June 28, 1995 major amendment particularly with regard to bulk containers and expiration date assignment. Accordingly, our responses are being provided in accordance with these new policies.

Before answering the letter, we feel that a general overview of the manufacturing processes would be helpful to clarify some of the deficiencies with regards to the composition of

PAGES 2-10  
CMC

**B. Labeling Deficiencies**

**CONTAINER: 60's, 100's, 500's, 1000's - Satisfactory.**

**Comments:**

**INSERT:**

**1. DESCRIPTION**

- a. **To be in accord with USP 23, the molecular weight should read 357.80 rather than 375.79.**
- b. **...oral administration contains . . .**

**2. CLINICAL PHARMACOLOGY**

- a. **Please ensure that the “number” and “unit of expression of strength” appear on the same line. Revise throughout the remainder of the text (i.e., . . . 25 mg . . . )**
- b. **Please add the following text to the last paragraph in this section:**  
  
**“Indomethacin has been found to cross the blood-brain barrier and the placenta.”**

**3. WARNINGS**

- a. **General, number 4 - Delete the blank line spaces between “during” and “dosage adjustment.”**
- b. **Gastrointestinal Effects, last paragraph - Replace “. . . the drug . . .” with “indomethacin.”**

4. **PRECAUTIONS**

**General - delete "controlled" from the first paragraph.**

5. **ADVERSE REACTIONS**

- a. **Special Senses, second column - Indent the text following the first line entry.**

**"Deposits..indomethacin"**

- b. **Causal relationship unknown, second paragraph - Correct the spelling of "fasciitis", and the beta symbol " $\beta$ " should replace the "b".**

6. **HOW SUPPLIED**

- a. **We encourage the inclusion of the NDC numbers for each package size.**

- b. **List the 60s as a unit of use of bottle.**

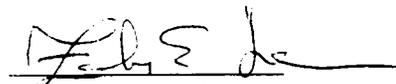
**Please revise your package insert labeling, then prepare and submit final print. Should additional information become available relating to the safety and efficacy of this product to approval you may be ask to further revise your labeling accordingly.**

**Response:**

We have revised our insert according to your comments and 12 final inserts are provided for your review (appendix 7). Please be advised that our insert will be used for all our customers, under which condition the incorporation of an NDC number would be inappropriate.

If additional information is required, please contact me at (718) 276-8600, extension: 343.

Sincerely,



Zohra E. Lomri  
Regulatory Affairs Associate

**E** Eon Labs  
A Health Care Company

Eon Labs Manufacturing, Inc.  
227-15 N. Conduit Avenue  
Laurelton, NY 11413  
Telephone 718 276-8600  
Fax 718 949-3120

NOTE  
11/7/95  
*[Signature]*

October 24, 1995

Dr. Charles Ganley  
Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place, Room 150  
Rockville, Maryland 20855

NEW CORRESP **BIODISAVAILABILITY**

*C 1310*

RE: ANDA 74-464; Amendment  
Indomethacin Extended-Release Capsules USP, 75 mg

**RECEIVED**

OCT 25 1995

Dear Dr. Ganley:

Reference is made to Dr. Keith Chan's letter dated October 12, 1995 regarding bioequivalence studies submitted on February 2, 1994 for Indomethacin Extended-Release Capsules USP, 75 mg. The following are our responses to the deficiencies noted in Dr. Chan's letter, a copy of which immediately follows the Table of Contents.

**GENERIC DRUGS**

A. ANALYTICAL

*[Handwritten signature]*

B. NON-FASTING (STUDY #2)

1. The terminal phase data from the non-fasting study did not show log linear decline which precluded extrapolation of the AUC past 15 hours. In the individual plasma profiles, there was a tendency for the concentrations to increase after the 8 or 10 hour sample, show a secondary peak at 10 or 12 hours, and then decline in the 12 or 15 hour sample. This pattern was evident in 31 of the 54 profiles. This secondary peak did not appear to be related to the dosing conditions (food or fasting) or the formulation. The late peak occurred in 10 of the profiles for Drug 1 (Indocin® SR with food), 11 for Drug 2 (Eon indomethacin fasting), and 10 for Drug 3 (Eon indomethacin with food). The most likely explanation for this secondary peak is enterohepatic recycling, which is known to occur with indomethacin (See Attachment 1: "Clinical Pharmacokinetics of Indomethacin").
2. The ln transformed Cmax and AUC15 are included in Table III.

C. MULTIPLE-DOSE STUDY

1. The data for Subjects 21 and 22 were not included in the final analysis because problems as described on page 683 of the original report (see Attachment 2). The original assay from Subject 21 was rejected because of as well as subject samples, that precluded use of the subject data. Five of the 9 controls and 7 of the 14 standards were outside acceptable limits. Upon repeat of the samples for Subject 21, were again present in the samples, and all of the controls were outside the acceptable range. For the original analytical run with Subject 22, all the control samples were approximately 50% greater than the nominal concentration and the run was rejected. The samples were repeated and all standards and controls were within range, but subject samples exhibited unacceptable
2. Table IV and Table V summarize the analysis of the minimum concentrations from the multiple-dose study. With this study, there were 4 minimum concentrations obtained for each subject treatment: pre-dose on days 2, 3, and 4 and 24 hrs after dose 4. This represents 176 minimum concentrations, of which 81 were below the limit of quantitation, and thus were reported as 0.000 ug/mL in the data base. For both the test and reference formulations, the Newman Keuls a posteriori test indicated that there were no differences ( $p > 0.05$ ) among the four minimum concentrations, demonstrating that steady-state had been reached for both of the products. The complete statistical analysis is included as Attachment 3.

Dr. Charles Ganley  
October 24, 1995  
Page 3 of 3

These aforementioned responses were written with the cooperation and coordination of

D. *In vitro* Dissolution Testing

Comparative dissolution profiles of Eon's Indomethacin Extended-Release Capsules USP, 75 mg vs MSD's Indocin® are contained in Attachment 4. This report contains the relevant experimental, results, and conclusions regarding the specifications of Test 1 and Test 2 of USP 23.

If there are any questions regarding this amendment or if additional information is required, please contact me at (718) 276-8600 ext. 423.

Sincerely,

Eon Labs Manufacturing, Inc.



John Purpura  
Manager  
Regulatory Affairs



Eon Labs  
A Health Care Company

Eon Labs Manufacturing, Inc.  
227-15 N. Conduit Avenue  
Laurelton, NY 11413  
Telephone 718 276-8600  
Fax 718 949-3120

*PPC  
control OK  
N-AC  
PPC  
Label  
4/23/95*

June 28, 1995

Douglas Sporn, HFD-601  
Acting Director  
Office of Generic Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Metro Park North II  
7500 Standish Place  
Rockville, MD 20855

*file*  
**AMENDMENT**

*N-AC*

Re: **ANDA 74-464 - MAJOR AMENDMENT**  
Indomethacin Extended-release Capsules USP, 75 mg

Dear Mr. Sporn:

Reference is made to Dr. R. Patel's January 30, 1995 letter regarding our original abbreviated new drug application submitted February 2, 1994 for Indomethacin Extended-release Capsules USP, 75 mg. The following are our responses to the deficiencies noted in Dr. Patel's letter:

**Comment**

*PAGES 2 - 6*

*CMC*

**GENERIC DRUGS**

*6/28/95  
Patel*

Mr. Sporn  
June 28, 1995  
Page 7

Included in the section addressing labeling deficiencies is a comment that our proposed container of 60 capsules should have a child-resistant closure. In order to comply with the Poison Control Packaging Act and your recommendation, we will package the 60 count

**Comments**

**B. Labeling Deficiencies:**

**Container: 60s, 100s, 500s, 1000s**

- 1. Please increase the prominence of the established name. We suggest bold print, a different color, or some other means of accomplishing this goal.**

2. **Revise the established name to read:**

**Indomethacin Extended-release Capsules, USP**

3. **Revise the Usual Dosage statement as follows:**

**Usual Adult Dosage: See accompanying literature.**

**Response**

Twelve (12) final printed container labels incorporating your comments are included as ATTACHMENT 15. Also included are four (4) copies of the draft label for bulk containers of 30,000 capsules.

**Comment**

4. **The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed container of 60 appears to be in this category. We note that the listed drug is marketed in bottles of 60 which are stated to be of unit-of-use. Therefore, we believe that this package must comply with the Act. Please revise accordingly.**

**Response**

In order to comply with the Poison Control Packaging Act and your recommendation, we will package the 60 count bottle with a plastic overcap called the Saf-Lok Safety Cap. Please refer to the paragraph following the response to comment 3e and preceding your comments on labeling deficiencies.

**Insert:**

1. **GENERAL COMMENT**

**Comments**

- a. **Revise "ER" to read Extended-release.**

- b. **"Nonsteroidal" rather than "non-steroidal" (delete hyphen).  
Revise throughout the insert.**

## **2. DESCRIPTION**

- a. **Divide paragraph 2 into two paragraphs - Relocate the first sentence to appear as a separate paragraph following the molecular weight, then revise as follows:**

**Each extended-release capsule, for oral administration, contains 75 mg of indomethacin. In addition, each capsule contains the following inactive ingredients:...**

- b. **Paragraph 2, Line 6 - Indomethacin is a nonsteroidal, anti-inflammatory, indole... (add comma's).**
- c. **Inactive ingredients**
  - i) **We note that all the inactive ingredients cited in the DESCRIPTION section are not listed in your components/composition statement. Please comment and/or revise accordingly.**
  - ii) **Lactose monohydrate rather than "lactose". In addition, please identify the botanical source of starch.**
  - iii) **We note you have listed printing ink as an inactive ingredient. Inks may contain numerous components. As a minimum you must list the dyes; coloring agents do not have to be included.**

## **3. CLINICAL PHARMACOLOGY**

- a. **Delete the extra blank line/space following paragraph 1.**
- b. **Paragraphs 7 and 8, revise to read:**

**Indomethacin extended-release capsules (75 mg) are designed to release 25 mg of drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours).**

Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin capsules given at 4 to 6 hour intervals. In multiple-dose comparisons, the mean daily steady state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin 25 mg capsules given at 0, 6, and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

- c. Paragraph 10, line 4 - "...regimen of 25 or 50 mg t.i.d., the steady state plasma..." (please note the space before "mg" and deletion of the hyphen).

#### INDICATIONS AND USAGE

4. a. Line 1 - Indomethacin extended-release capsules have been found...
- b. Insert a paragraph break to separate the listed items from the first sentence.
- c. Paragraph 1, last sentence - Revise to read:
- Indomethacin Extended-release capsules are not recommended for the treatment of acute gouty arthritis.
- d. Last paragraph, last sentence - ...(see PRECAUTIONS, Drug Interactions).

#### Comment

#### 5. WARNINGS

- a. General
- i. Insert a paragraph break after paragraph 1, item 1, item 2, and item 3.

- ii. **Delete paragraph 4 under item 3. This is a duplication of the preceding paragraph.**

- b. **Gastrointestinal Effects**

**Revise the last paragraph as follows:**

**...by giving the drug immediately after...**

- c. **Use in Pregnancy and the Neonatal Period**

**Paragraphs 2 and 4 - Delete the period and the terminal zero following the whole numbers (i.e., 4 mg/kg/day).**

**6. PRECAUTIONS**

**General**

- i. **Paragraph 1**

- (1) **Revise line 1 to read - Nonsteroidal, anti-inflammatory drugs, including indomethacin may...of existing infection.**

- (2) **Begin a new paragraph with "Fluid retention..."**

- ii. **Final paragraph, last sentence - Insert a comma after "e.g."**

**ADVERSE REACTIONS**

- 7. a. **The section heading should appear in bold print to be consistent with the other section headings in this insert.**

- b. **Table**

- i. **Differentiate the various categorical headings from the section headings by deleting the bold print.**

ii. **Causal relationship unknown**

**Add the following as the last paragraph:**

**A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A b-hemolytic streptococcus, has been described in persons treated with nonsteroidal ant-inflammatory agents, including indomethacin, sometimes with fatal outcome (see also PRECAUTIONS, General)**

**8. DOSAGE AND ADMINISTRATION**

**Adult Use**

a. **Insert the following after item one:**

**The following information is provided as background only and refers to immediate-release indomethacin capsules (25 mg and 50 mg):**

b. **The information concerning Suggested Dosage should be intended under the newly inserted sentence above.**

c. **Item 2**

i. **Paragraph 1 - "...or tendinitis). Initial dose: 75 mg to 150 mg..."**

ii. **Paragraph 2 - Insert a paragraph break before this paragraph. In addition revise "...7-14 days" to read "...7 to 14 days".**

**Please revise your container labels and package insert labeling, then prepare and submit final print container labels and draft insert labeling. We will not request final print insert labeling until we have reviewed your bioequivalence data.**

**Response**

ATTACHMENT 16 contains four (4) copies of the draft package insert labeling which has been revised in accordance with your comments.

- C. In addition to responding to these deficiencies, please note and acknowledge the following in your response:**

**Comments**

- 1. The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with current CGMPs at the time of approval. We will request an evaluation from the Division of Manufacturing and Product Quality at the appropriate time.**
- 2. Please be advised that all Drug Master Files (DMFs) referenced in this application have to be found satisfactory at the time of approval. Some of the DMF holders may have to be inspected by our Division of Manufacturing and Product Quality. Any unsatisfactory review or evaluation will delay approval of the application. Thus, you are advised to withdraw any DMF references which are not necessary to support the application.**

**Response**

We acknowledge that all firms referenced in ANDA 74-464 must be in compliance with cGMPs at the time the application is approved.

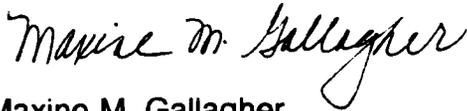
We understand that all DMFs referenced in ANDA 74-464 must be found satisfactory and that some DMF holders may have to be inspected. We do not wish to withdraw any DMF references filed in support of this application.

We also wish to include as ATTACHMENT 17 the 24 month controlled room temperature stability data for the 60 capsule and 1000 capsule bottles of this product.

Mr. Sporn  
June 28, 1995  
Page 14

If there are any questions regarding this amendment or if additional information is required, please contact me at (718) 276-8600, extension 424.

Sincerely,  
Eon Labs Manufacturing, Inc.  
A Health Care Company

A handwritten signature in cursive script that reads "Maxine M. Gallagher". The signature is written in black ink and is positioned above the printed name and title.

Maxine M. Gallagher  
Vice President  
Regulatory Affairs and Compliance

*Attache to  
505(j)(2)(A)  
2-15-94 2/16/94*

COPY 1 ✓  
COPY 2

February 2, 1994

Douglas L. Sporn  
Acting Director  
Office of Generic Drugs, HFD-600  
Center for Drug Evaluation & Research  
Food and Drug Administration  
Document Control Room  
Metro Park North II  
7500 Standish Place  
Room 150  
Rockville, MD 20855-2773

**Re: New ANDA  
Indomethacin ER Capsules, USP, 75 mg**

Dear Mr. Sporn:

Attached is an original Abbreviated New Drug Application for indomethacin ER capsules, USP, 75 mg. An ANDA for this dosage form was originally submitted by the previous owners of this company on September 16, 1986. The application, ANDA 71-531, was approved July 21, 1987. Subsequently, at the request of the company's new owner, Eon Labs Manufacturing Inc., approval of ANDA 71-531 was withdrawn. Copies of the relevant correspondence and Federal Register notices are included in Section XXI of this application.

The present ANDA consists of the following 9 volumes:

- |             |   |
|-------------|---|
| Volumes 1-3 | Section 505(j)(2)(A) information, labelling, manufacturing and controls data, |
| Volumes 4-9 | Bioequivalency data.  |

**[ RECEIVED ]**

FEB 0 4 1994

**GENERIC DRUGS**

Indomethacin ER Capsules, USP, 75 mg  
Page 2

In addition to the archival and review copies, we are submitting a copy of the manufacturing and controls data to the District Field Office at Brooklyn, New York. Subsequent amendments or supplements containing manufacturing and controls data will similarly be submitted to the District Field Office.

If there are any questions or comments regarding this application, please contact the undersigned at (718) 276-8600.

Very truly yours,

EON LABS MANUFACTURING, INC.

A handwritten signature in cursive script, appearing to read "Yau Kit Lam".

Yau Kit Lam  
Regulatory Affairs Specialist

YL:lr

ANDA 74-464

Eon Labs Manufacturing, Inc.  
Attention: Yau-Kit Lam  
227-15 North Conduit Avenue  
Laurelton, NY 11413

JAN 30 1995

Dear Sir:

This is in reference to your abbreviated new drug application dated February 2, 1994, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Indomethacin Extended-release Capsules USP, 75 mg.

Reference is also made to your amendment, dated March 15, 1994.

The application is deficient and, therefore, not approvable under Section 505 of the Act for the following reasons:

A. Chemistry Deficiencies:

PAGE 2  
CMC

**B. Labeling Deficiencies:**

**Container: 60s, 100s, 500s, 1000s**

1. Please increase the prominence of the established name. We suggest bold print, a different color, or some other means of accomplishing this goal.
2. Revise the established name to read:  

Indomethacin Extended-release Capsules, USP
3. Revise the Usual Dosage statement as follows:  

Usual Adult Dosage: See accompanying literature.
4. The Poison Prevention Packaging Act notes that special packaging (child-resistant closures) should be the responsibility of the manufacturer when the container is clearly intended to be utilized in dispensing (unit-of-use packaging). Your proposed packaging appears to be in this category. We note that the listed drug is marketed in bottles of 60 which are stated to be of unit-of-use. Therefore, we believe that this package must comply with the Act. Please revise accordingly.

Insert:

1. GENERAL COMMENT
  - a. Revise "ER" to read Extended-release.
  - b. "Nonsteroidal" rather than "non-steroidal" (delete hyphen). Revise throughout the insert.
2. DESCRIPTION
  - a. Divide paragraph 2 into two paragraphs - Relocate the first sentence to appear as a separate paragraph following the molecular weight, then revise as follows:  

Each extended-release capsule, for oral administration, contains 75 mg of indomethacin. In addition, each capsule contains the following inactive ingredients:...
  - b. Paragraph 2, Line 6 - Indomethacin is a nonsteroidal, anti-inflammatory, indole... (add comma's).

**c. Inactive ingredients**

- i) We note that all the inactive ingredients cited in the DESCRIPTION section are not listed in your components/composition statement. Please comment and/or revise accordingly.
- ii) Lactose monohydrate rather than "lactose". In addition, please identify the botanical source of starch.
- iii) We note you have listed printing ink as an inactive ingredient. Inks may contain numerous components. As a minimum you must list the dyes; coloring agents do not have to be included.

**3. CLINICAL PHARMACOLOGY**

~~Delete the extra blank line in the following paragraph 1.~~

- b. Paragraphs 7 and 8, revise to read:

Indomethacin extended-release capsules (75 mg) are designed to release 25 mg of drug initially and the remaining 50 mg over approximately 12 hours (90% of dose absorbed by 12 hours). Plasma concentrations of indomethacin fluctuate less and are more sustained following administration of indomethacin extended-release capsules than following administration of 25 mg indomethacin capsules given at 4 to 6 hour intervals. In multiple-dose comparisons, the mean daily steady state plasma level of indomethacin attained with daily administration of indomethacin extended-release capsules 75 mg was indistinguishable from that following indomethacin 25 mg capsules given at 0, 6, and 12 hours daily. However, there was a significant difference in indomethacin plasma levels between the two dosage regimens especially after 12 hours.

- c. Paragraph 10, line 4 - "...regimen of 25 or 50 mg t.i.d, the steady state plasma..." ( please note the space before "mg" and deletion of the hyphen).

**4. INDICATIONS AND USAGE**

- a. Line 1 - Indomethacin extended-release capsules have been found...

b. Insert a paragraph break to separate the listed items from the first sentence.

c. Paragraph 1, last sentence - Revise to read:

Indomethacin Extended-release capsules are not recommended for the treatment of acute gouty arthritis.

d. Last paragraph, last sentence - ...(see PRECAUTIONS, Drug Interactions).

## 5. WARNINGS

a. General

i. Insert a paragraph break after paragraph 1, item 1, item 2, and item 3.

ii. Delete paragraph 4 under item 3. This is a duplication of the

b. Gastrointestinal Effects

Revise the last paragraph as follows:

...by giving the drug immediately after...

c. Use in Pregnancy and the Neonatal Period

Paragraphs 2 and 4 - Delete the period and the terminal zero following the whole numbers (i.e., 4 mg/kg/day).

## 6. PRECAUTIONS

General

i. Paragraph 1

(1) Revise line 1 to read - Nonsteroidal, anti-inflammatory drugs, including indomethacin may...of existing infection.

(2) Begin a new paragraph with "Fluid retention...".

ii. Final paragraph, last sentence - Insert a comma after "e.g.".

7. **ADVERSE REACTIONS**

a. The section heading should appear in bold print to be consistent with the other section headings in this insert.

b. Table

i. Differentiate the various categorical headings from the section headings by deleting the bold print.

ii. Causal relationship unknown

Add the following as the last paragraph:

A rare occurrence of fulminant necrotizing fasciitis, particularly in association with Group A  $\beta$ -hemolytic streptococcus, has been described in patients receiving nonsteroidal anti-inflammatory agents, including indomethacin, sometimes with fatal outcome (see also PRECAUTIONS, General)

8. **DOSAGE AND ADMINISTRATION**

Adult Use

a. Insert the following after item one:

The following information is provided as background only and refers to immediate-release indomethacin capsules (25 mg and 50 mg):

b. The information concerning Suggested Dosage should be indented under the newly inserted sentence above.

c. Item 2

i. Paragraph 1 - "...or tendinitis). Initial dose: 75 mg to 150 mg..."

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Please revise your container labels and package insert labeling, then prepare and submit final print container labels and draft insert labeling. We will not request final print insert labeling until we have reviewed your bioequivalence data.

C. In addition to responding to these deficiencies, please note and acknowledge the following in your response:

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The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all the deficiencies listed. A partial reply 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 a MAJOR amendment and should be so designated in your cover letter. You will be notified in a separate letter of any deficiencies identified in the bioequivalence portion of your application. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

*JL 1/27/95*  
Rashmikant M. Patel, Ph.D.  
Director  
Division of Chemistry I  
Office of Generic Drugs  
Center for Drug Evaluation and Research