

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 20-714**

**CHEMISTRY REVIEW(S)**

DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG PRODUCTS/HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20 - 714

REVIEW # 3

DATE REVIEWED:

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	01 -05 - 96	03- 05 - 96	09-05 - 96
AMENDMENT	26 -03 - 97	27 - 03- 97	28-03 - 97
AMENDMENT	26 -03 - 97	28 - 03- 97	31-03 - 97
AMENDMENT	07 -04 - 97	11 - 04- 97	

NAME & ADDRESS OF APPLICANT:

Pharmacia Inc.  
7000 Portage Road  
Kalamazoo, MI 49001-0199

DRUG PRODUCT NAME

Proprietary: Nicotrol Inhaler  
Established: Nicotine  
Code Name/#:  
Chem.Type/Ther.Class: 3S

PHARMACOL. CATEGORY:

Relief of nicotine withdrawal symptoms  
associated with smoking reduction or  
cessation

DOSAGE FORM:

Inhaler

STRENGTHS:

10 mg

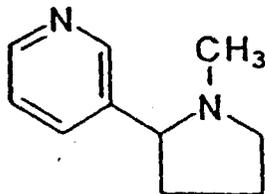
ROUTE OF ADMINISTRATION:

Inhalation

DISPENSED:

Rx  OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND WEIGHT:



S-3(1-methyl-2-pyrrolidiny)pyridine

$C_{10}H_{14}N_2$

Mol.Wt 162.23

SUPPORTING DOCUMENTS:

IND

PHARMACIA, Inc.  
7000 Portage Road  
Kalamazoo, Michigan 49001-0199

Investigational study of the nicotine inhaler

NDA 20-150 -

PHARMACIA, Inc.  
7000 Portage Road  
Kalamazoo, Michigan 49001-0199

Manufactures Nicotrol (Nicotine Transdermal System)

NDA 20-385 -

PHARMACIA, Inc.  
7000 Portage Road  
Kalamazoo, Michigan 49001-0199

Manufactures Nicotine Nasal Spray

1. DMF

Pharmacia AB  
Norrbroplastsen 2  
S-251 Helsingborg, Sweden

Description of facility for manufacturing drug product.

2. DMF

Manufactures drug substance, nicotine.

3. DMF

Manufactures aluminum foil for seal tubes



2. Microbiology information was submitted in amendments dated Jan. 13 & 29, 1997 and Mar. 24, 1997 and were reviewed By our consultant in HFD-160, Dr. Brenda Uratani. Consult sent Feb. 11, 1997. Comments returned Mar. 26, 1997. Conclusion: Information submitted was satisfactory. ( See Attached)
3. The Environmental Assessment Report was reviewed by the chemist and the review was sent to Ms. Nancy Sager, our environmental consultant for final sign-off. Consult was sent: Mar. 6, 1997. Comments returned: Apr. 14, 1997. Conclusion: Environmental Assessment Report is satisfactory.

REMARKS:

Nicotine Inhaler consist of 10 mg of nicotine loaded into a porous plug which is inserted into a transparent plastic tube of acrylonitrile and methylacrylate co-polymer and sealed at both ends with aluminum foil. The tube is lined on the inside with a layer. Six tubes (cartridges) are packed in a plastic tray which is sealed with aluminum foil and placed in an outer carton, together with a white mouth piece of With its top. In order to use the product, the sealed tube(cartridge) is inserted into the mouthpiece causing one end of aluminum seal to break. When the top of the mouth-piece is placed over it, the other end of the seal will break. The patient draws air through the device, which releases gaseous nicotine at a rate equal to or higher than 0.23 mg of nicotine per liter from the porous plug to the air stream and into the mouth, where the main part of nicotine is absorbed through the buccal mucosa.

The Nicotine Inhaler delivers about 15 ug/50 ml puff ( a volume similar to an average puff on a cigarette) at room temperature. The Nicotine Inhaler, as stated above, contains a total of about 10 mg of nicotine of which 4 mg are systematically available and flavoring(menthol). However, in comparing the Nicotine Inhaler with other delivery systems, its rate of absorption is very close to that of cigarettes. While the transdermal route(nicotine patch) is slowest, taking 5-10 hours to produce a peak. The buccal route (nicotine gum) is somewhat faster, requiring each piece of nicotine gum to be chewed for 30 minutes. The nasal route is faster still resulting in peak nicotine in 10 -15 minutes. However, an alternative buccal route is the Nicotine Inhaler. The puffing on the nicotine inhaler produces a nicotine peak maximum in 10-15 minutes after the end of puffing

NDA # Chemistry # 20-714/ Rev. #1  
company/drug Pharmacia/Nicotine Inhaler

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The drug substance, nicotine, is synthesized by \_\_\_\_\_ and the Nicotine Inhaler is manufactured tested, packaged and released by Pharmacia, AB of Helsingborg, Sweden. The amendment dated March 26, 1997 enclosed draft labeling for the patient information leaflet, for the carton, plastic case, cartridge, and the tray. From a chemist viewpoint the labeling is satisfactory.

Currently the methods are being evaluated at the following laboratories:

We have received a satisfactory report from our Compliance Division concerning the sites that were inspected. See attached EER dated April 30, 1997.

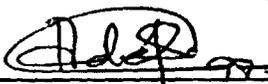
**CONCLUSIONS & RECOMMENDATIONS:**

From a chemist viewpoint, the manufacturing and control information, the draft labeling, the microbiology report, the Environmental Assessment Report, medical device report, and establishment inspection report are all satisfactory; therefore I recommend approval of this application.

NDA # Chemistry # 20-714/ Rev. #1  
company/drug Pharmacia/Nicotine Inhaler

page 6

*Juanita Ross* 4/21/97  
Juanita Ross, M.S. Review Chemist

  
Albinus D'Sa, Ph.D. Team Leader

cc:

Orig. NDA 20-714  
HFD170/Div. File  
HFD-170/JMRoss  
HFD-170/McNeal  
HFD-820/JGibbs  
Init. By:

F/T by: JMRoss/4/18/97

Filename: C:\wpfiles\juanita\n207.14

**DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG PRODUCTS/HFD-170  
Review of Chemistry, Manufacturing, and Controls**

**REVIEW # 2**

**DATE REVIEWED: 2/26/97**

<b>SUBMISSION TYPE</b>	<b>DOCUMENT DATE</b>	<b>CDER DATE</b>	<b>ASSIGNED DATA</b>
SUBMISSION	01 -05 - 96	03- 05 -96	09-05 - 96
AMENDMENT	06-11-96	12-11-96	
AMENDMENT	13-01-97	15-01-97	
AMENDMENT	29-01-97	03-02-97	

**NAME & ADDRESS OF APPLICANT:**

Pharmacia Inc.  
7000 Portage Road  
Kalamazoo, MI 49001-0199

**DRUG PRODUCT NAME :**

Proprietary:	Nicotrol Inhaler
Established:	Nicotine
Code Name/#:	
Chem.Type/Ther.Class:	3S

**PHARMACOL. CATEGORY:**

Relief of nicotine withdrawal symptoms  
associated with smoking reduction or  
cessation

**DOSAGE FORM:**

Inhaler

**STRENGTHS:**

10 mg

**ROUTE OF ADMINISTRATION:**

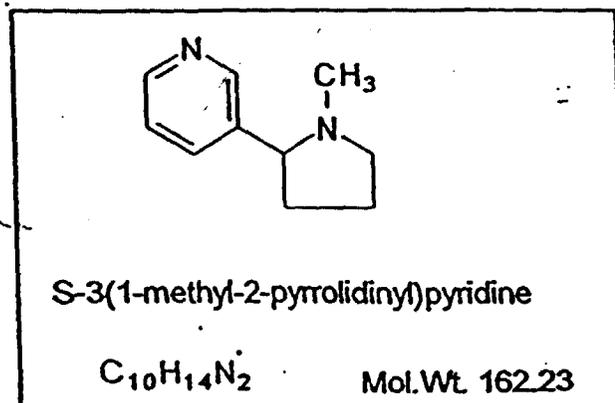
Inhalation

**DISPENSED:**

Rx

OTC

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA AND  
WEIGHT:**



NDA # Chemistry # 20-714/ Rev. #  
company/drug Pharmacia/Nicotine Inhaler

page 2

SUPPORTING DOCUMENTS:

NDA 20-150 - PHARMACIA, Inc.  
7000 Portage Road  
Kalamazoo, Michigan 49001-0199

Manufactures Nicotrol (Nicotine Transdermal System)

NDA 20-385 - PHARMACIA, Inc.  
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Manufactures Nicotine Nasal Spray

1. DMF Pharmacia AB  
Norrbroplastsen 2  
S-251 Helsingborg, Sweden

Description of facility for manufacturing drug product.

2. DMF

Manufactures drug substance, nicotine.

3. DMF

Manufactures aluminum foil for seal tubes



The Establishment Evaluation Request, dated Oct 21, 1996 was sent to our Compliance Division. I received a call on Feb. 24, 1997 from the chemist, Ms. Susan Ting, who plans to inspect Pharmacia around the week of Mar. 7, 1997. She has requested some chemistry, manufacturing and control information and this will be sent to her

Environmental Assessment Information is now under review.

A method validation package has been sent to each of the following laboratories:

#### **CONCLUSIONS & RECOMMENDATIONS:**

The amendments containing responses to our deficiency letter has been reviewed. However, there are still some concerns dealing with the chemistry, manufacturing, and control for the Nicotine Inhaler. They involve a choice of the best analytical methods for assaying, submission of additional specification, submission of drug master files for plastic parts that make up the inhaler and a decision concerning overage in the formulation information is submitted. For more details see, firm's responses to our questions, my comments and the Draft Letter to Applicant. From a chemist viewpoint the application is approvable pending satisfactory responses to the current concerns.

cc:

Orig. NDA 20 - 714  
HFD-170/Division File  
HFD-170/JMROSS  
HFD-170/BmcNeil  
filename: a:\20714a.txt

R/D Init. by: AD'Sa/2-27-97  
F/T by: s1/3-7-97

*Juanita Ross* 2/25/97  
Juanita Ross, Review Chemist

*Albinus D'Sa* 2/27/97  
Albinus D'Sa, Team Leader

DIVISION OF ANESTHETICS, CRITICAL CARE , AND  
ADDICTION DRUG PRODUCTS/HFD-170

Review of Chemistry, Manufacturing, and Controls

NDA #: 20 - 714

REVIEW # 1

DATE REVIEWED:

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
SUBMISSION	01 -05 - 96	03- 05 -96	09-05 - 96
AMENDMENT	24 -06 - 96	03- 07 -96	- -

NAME & ADDRESS OF APPLICANT:

Pharmacia Inc.  
7000 Portage Road  
Kalamazoo, MI 49001-0199 -

DRUG PRODUCT NAME

Proprietary:

Nicotrol Inhaler

Established:

Nicotine

Code Name/#:

Chem. Type/Ther. Class:

3S

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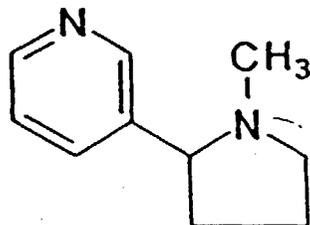
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NDA # Chemistry # 20-714/ Rev. #1  
company/drug Pharmacia/Nicotine Inhaler

page 2

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Norrbroplastsen 2  
S-251 Helsingborg, Sweden

Description of facility for manufacturing drug product.

2. DMF

Manufactures drug substance, nicotine.

3. DMF

Manufactures aluminum foil for seal tubes

4. DMF

Synthesizes the  
tubes.

used to manufacture the plastic

RELATED DOCUMENTS: . None to report

CONSULTS:

The medical officers sent a request to the  
Center for Devices and Radiological Health,  
Investigational Device Exemption Section  
concerning the safety of this nicotine  
Inhaler.

Consult Sent: July 12, 1996

Comments

Returned: Aug. 20, 1996

Conclusion: The Inhaler posed no unusual safety  
concerns. Reviewer: Michael Bazaral M.D., Ph.D.

REMARKS:

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and sealed at both ends with aluminum foil.

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In order to use the product, the sealed tube(cartridge) is inserted into the mouthpiece. The mouth piece is re-assembled at which time the seals on both end of the cartridge is automatically broken. The patient draws air through the device, which releases gaseous nicotine at a rate equal to or higher than 0.23 mg of nicotine per liter from the porous plug to the air stream and into the mouth, where the main part of nicotine is absorbed through the buccal mucosa.

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The drug substance, nicotine is synthesized by  
and the Nicotine Inhaler is manufactured  
tested, packaged and released by Pharmacia, AB of Helsingborg,  
Sweden.

NDA # Chemistry # 20-714/ Rev. #1  
company/drug Pharmacia/Nicotine Inhaler

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This application has been reviewed and the substance of the review can be found in the . The initial deficiencies are found on pages 39-43. These questions were faxed to the applicant. Nov. 22,1996.

The Establishment Evaluation Request, dated Oct 21,1996 has been sent to our Compliance Division. The method validation package has not as yet been sent out. The Environmental Assessment Information is under review.

CONCLUSIONS & RECOMMENDATIONS:

The application has been reviewed and deficiencies have been noted in regard to chemistry, manufacturing and controls which involves updating specifications for related substances in the drug substance, submission of reference numbers to drug master files, submission of microbial data for drug product, and additional stability data to support a 24 months expiration date. From a chemist viewpoint, non-approval is recommended until satisfactory information is submitted. For more details see,

cc:  
Orig. NDA 20 - 714  
HFD-170/Division File  
HFD-170/JMROSS  
HFD-170/BMcNeil  
HFD-820/YYChiu

filename: n2071.4

*Juanita Ross 11/22/96*  
Juanita Ross, Review Chemist

*Albinus D'Sa* 12/9/96  
Albinus D'Sa, Team Leader

## REQUEST FOR TRADEMARK REVIEW

**To:** Labeling and Nomenclature Committee  
**Attention:** Dan Boring, Chair (HFD-530) NLRC

<b>From:</b> Pilot Drug Evaluation Staff	<b>HFD-170</b>
<b>Attention:</b> Bonnie McNeal	<b>Phone:</b> 443-3741
<b>Date:</b> January 22, 1997	
<b>Subject:</b> Request for Assessment of a Trademark for a Proposed New Drug Product	
<b>Proposed Trademark:</b> Nicotrol Inhaler	<b>NDA 20-714</b>
<b>Established name, including dosage form:</b>  Nicotine inhalation system, 10 mg/unit	
<b>Other trademarks by the same firm for companion products:</b>  Nicotrol Nasal Spray; The firm is Pharmacia and Upjohn.	
<b>Indications for Use (may be a summary if proposed statement is lengthy):</b>  To be used as an aid for smoking cessation	
<b>Initial Comments from the submitter (concerns, observations, etc.):</b>  The division has no problems with this name.	

**Note:** Meetings of the Committee are scheduled for the 4<sup>th</sup> Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

Rev. August 95

Consult #751 (HFD-170)

NICOTROL INHALER

nicotine inhalation system

The proprietary name NICOTROL is already in use on marketed products and was not considered by the Committee. The term "inhaler" appears appropriate for the type of product being described.

The Committee has no reason to find the proposed proprietary name unacceptable.

D. U. Boring 3/4/97, Chair  
CDER Labeling and Nomenclature Committee