CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

05-213/S023

Trade Name: Hycodan

Generic Name: homatropine methylbromide; hydrocodone bitartrate

Sponsor: DuPont

Approval Date: 11/08/1988

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

05-213/S023

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

05-213/S023

APPROVAL LETTER

NOV 8 1988

NDA 5-213/S-023

Dupont Pharmaceuticals
Barley Mill Plaza
Building #26
Wilmington, DE 19898

Attention: Edward B. Adams
Senior Regulatory Affairs Consultant

Gentlemen:

Please refer to your supplemental new drug application dated June 1, 1988 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hycodan (hydrocodone bitartrate and homatropine methylbromide) Tablets and Syrup.

Reference is also made to your correspondence dated October 12, 1988 regarding the information and commitments requested by Mr. Stan Koch, of this Division, in a telephone conversation on October 7, 1988.

The supplemental application provides for (b)(4) as a new alternate supplier of hydrocodone bitartrate.

We have completed our review of the supplemental application and it is approved. We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

11/8/88

Guiragos K. Poochikian, Ph.D.
Acting Supervisory Chemist
Division of Surgical-Dental
Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc: NDA 5-213
HFD-160
HFD-160/Koch/Stone JLewis 11/8/88
HFD-80
R/D: JLewis 11/7/88 (w0145V)
R/D Init by GBoyer 11/7/88 GPoochikian 11/7/88
F/T MJO 11/7/88

APPROVAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

05-213/S023

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW
(If necessary, continue any item on 8" x 10½" paper. Key continuation to item by number.)

1. ORGANIZATION	2. NDA NUMBER
FDA/HFD-160	5213

3. NAME AND ADDRESS OF APPLICANT *(City and State)*

E.I. DuPont de Nemeurs & Co.
Wilmington, Deleware 19898

OCT 2 1 1988

4. AF NUMBER

5. SUPPLEMENT (S)

NUMBER(S)	DATE(S)
S-023	6/1/88

6. NAME OF DRUG	7. NONPROPRIETARY NAME
Hycodan Tablets/Syrup	hydrocodone bitartrate & homatropine methylbromide

8. SUPPLEMENT(S) PROVIDES FOR:

[redacted] (b)(4) as new alternate supplier of hydrocodone bitartrate. The [redacted] (b)(4) plant is located at [redacted] (b)(4) Responsible official at facility: Mr. [redacted] (b)(4)

9. AMENDMENTS AND OTHER *(Reports, etc.)* **DATES**

10/12/88 NC

10. PHARMACOLOGICAL CATEGORY	11. HOW DISPENSED
antitussive	☒ Rx ☐ OTC

12. RELATED IND/NDA/DMF(S)

DMF [redacted] (b)(4)
(8/31/88 update)

13. DOSAGE FORM (S)	14. POTENCY *(Iso)*
tablet, syrup	5 mg/1.5 mg

15. CHEMICAL NAME AND STRUCTURE

16. RECORDS AND REPORTS

CURRENT ☐ YES ☐ NO

REVIEWED ☐ YES ☐ NO

17. COMMENTS

See page 2.

NDA 5213
HFD-160
Doc. Rm. 160
R/D SKoch 10/19/88
R/D init by GPoochikian 10/21/88
F/T LSturdivant 10/21/88
Wang 2200M Disk 0101M
CSO JOCELYN LEWIS

18. CONCLUSIONS AND RECOMMENDATIONS

Chemistry aspects of this supplemental application now satisfactory except for lack of word from HFD-320 regarding CGMP evaluation of [redacted] (b)(4) facility in [redacted] (b)(4) This word of acceptability has now been received from HFD-320 as of 10/11/88.

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Stan Koch	Stan Koch	Oct. 19, 1988

DISTRIBUTION ☐ ORIGINAL JACKET ☐ REVIEWER ☐ DIVISION FILE

FORM FDH 2266 (7/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

17. COMMENTS

The [redacted] DMF [redacted] updated as of 8/31/88. Satisfactory responses to FDA letters within past 2 years are in file. Hydrocodone bitartrate is prepared from [redacted] in a [redacted] step process thoroughly reviewed in DMF. The [redacted] preparation is described in DMF [redacted] in process controls provided for [redacted] The [redacted] controls for this drug substance include [redacted] % max, [redacted] % max, [redacted] max, other impurities [redacted] max (related substances), ordinary impurities [redacted] max. These tests for purity determined by GC, LC, TLC. Stability data at CRT to [redacted] yrs, but impurity tests performed as part of controls for recent lots to [redacted] yr. No review of DMF [redacted] considered necessary - data adequate.

DuPont hydrocodone bitartrate controls, stability monograph, stability protocol - satisfactory. Data on raw material [redacted] to 6 months at 25°/40°C.

Additional data to 3 months at 40°/75%RH, 60°, and 25°/600 foot-candles. The 40° and 60° package is [redacted] bottle; the 25° package [redacted], and the 25°/90% RH in [redacted]. Data is within specifications at all stations for 3 lots.

Stability data with Hycodan tablets, Lot ZE133, to 12 weeks at 40°C, 50°C, and 25°C/70%RH, and 25°C/600 footcandles. Some degradation is noticed at [redacted]C in that [redacted] concentration has increased from the order of [redacted]% or so initially, to [redacted]% after 12 weeks, while at 40°C it has increased to [redacted]% after 12 weeks. Firm says that the product history of this formulation shows homatropine methylbromide to be stable for up to [redacted] years at 25°C. DuPont intends to continue to use a [redacted] year expiration date on this drug product as manufactured with [redacted] material, with a pledge to continue to monitor product stability on a continuing basis, and to recall from the marketplace those lots which fail to meet the approved specifications within the expiration dating period when stored under the recommended CRT conditions.

Stability data with Hycodan Syrup, Lot ZE130A, to 12 weeks at 25°C/50%RH, 40°C, 50°C, and 25°C/600 footcandles. No appreciable degradation noted, with the accumulation of [redacted] from an initial assay value of less than [redacted]% to [redacted]% at 50°C after 12 weeks. Firm intends to continue with the [redacted] year expiration date on the syrup with stability to be monitored on a continuing basis, and to recall product as indicated above for the tablets.

The stability lots described above are production lots. Firm says another production lot of both the tablet and syrup will be placed on stability at a temperature of 30° ± 1°C. Data will be submitted at 6 months, 1 year, and annually thereafter to the expiration date, for both sets of production lot data (both Lots ZE133 and ZE130A, and for the lots at 30°C). See MEMO telecon dated 10/7/88. Firm will submit commitments made in this 10/7/88 conversation in a piece of correspondence to this file.

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE: October 7, 1988

NDA NUMBER: 5213/S-023

IND NUMBER: (6-1-88)

TELECON/MEETING

INITIATED BY: ☐ APPLICANT/SPONSOR ☒ FDA

MADE: ☒ BY TELEPHONE ☐ IN PERSON

PRODUCT NAME: Hycodan tablets + syrup

FIRM NAME: Dupont de Nemours Wilmington, DE

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD: Edward B. Adams Senior Regulatory Affairs Consultant.

TELEPHONE NO. 302-992-5094

The stability data on the raw material hydrocodone bitartrate has been accumulated to 6 months at 25°C/40°C. I inquired about the firm's expiration date on this drug substance, and how long they intend to conduct these studies.
I then asked if the data submitted with drug product (tablet, syrup) manufactured with (b) (4) hydrocodone bitartrate represents production lots, and if in fact the studies are being conducted at 25°C while the labeling permits storage up to 30°C. Assuming this is the situation, I asked for a commitment to submit the 6 month and 1 yr. data, and annually thereafter to the expiration date, on lots now being studied, and to place another production lot* under shelf-life review at a temperature of 30° ± 1°, with data to be submitted at 6 months and annually thereafter (i.e., 6 months, 1 year, 2 years, etc.) to the expiration dating period. I asked for verification that all packages for both dosage forms are represented in these studies.
Ed assured me that the only packages for these drug products are the one's being used in the stability studies. The drug substance carries a (b) (4) yr. expiration date, and the studies are conducted up to (b) (4) years. The Lots ZE133 and ZE130A are production lots of (b) (4) tablets and (b) (4) of syrup; these will be marketed if supplement approval occurs shortly. Dupont will put an addn'l production lot each of the tablet and syrup on stability at 30° ± 1°C, and submit data as accumulated on all 4 lots to this file at 6 months, 1 yr., and annually thereafter to the expiry date. Ed Adams will submit these commitments to this file in the form of a New Correspondence to 5-023.
* One lot each, tablet, and syrup.

NDA 5213/S-023
HFD-160
Doc. Rm. 160
R/D StanKoch 10/7/88
R/D init by Goochikian 10/7/88

GG 10/7/88

SIGNATURE: Stan Koch 10/7

DIVISION

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

U. S. GOVERNMENT PRINTING OFFICE-1984-432-976/7126

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA No. 5-213

Date June 9, 1988

E.I. Du Pont De Nemours & Company
Medical Products Department
Wilmington, Delaware 19898

Attention: Edward B. Adams

Gentlemen:

We acknowledge receipt of your supplemental application(s) for the following:

Name of Drug: Hycodan Tablets/ Syrup

NDA Number: 5-213

Supplement Number: S-023

Date of Supplement: June 1, 1988

Date of Receipt: June 7, 1988

File Date: August 7, 1988

All communications concerning this NDA should be addressed as follows:

Center for Drugs and Biologics, HFN-160
Attention: Document Control Room 18B-03
5600 Fishers Lane
Rockville, MD 20857

Sincerely Yours,

Gary H. Boyer

Gary H. Boyer
Supervisory Consumer Safety Officer
Division of Surgical-Dental Drug Products
Center for Drugs and Biologics

FORM FDA 3217f (3/87)