CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

40-140

Generic Name: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL

Sponsor: Abbott Laboratories

Approval Date: November 20, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
40-140

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

APPROVAL LETTER

ANDA 40-140

Abbott Laboratories
Hospital Products Division
Attention: Leslie Koehler
200 Abbott Park Road, D-389, AP30
Abbott Park, IL 60064-3537

Dear Madam:

This is in reference to your abbreviated new drug application dated April 7, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Diphenhydramine Hydrochloride Injection USP, (Preservative-Free), 50 mg/mL, (Syringe).

Reference is also made to your amendments dated February 27, March 27, April 17, May 29, June 10, July 17 and September 23, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Diphenhydramine Hydrochloride Injection USP, (Preservative-Free) 50 mg/mL, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Benadryl® Injection, (Preservative-Free), 50 mg/mL, of Parke Davis).

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

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

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253

(Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/ 11/23/98

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

Final Printed Labeling

particulate matter and discoloration prior to administration, whenever solution and container permit.

DOSAGE SHOULD BE INDIVIDUALIZED ACCORDING TO THE NEEDS AND THE RESPONSE OF THE PATIENT.

Pediatric Patients, other than premature infants and neonates: 5 mg/kg/24 hr or 150 mg/m²/24 hr. Maximum daily dosage is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly.

Adults: 10 mg to 50 mg intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly, 100 mg if required; maximum daily dosage is 400 mg.

HOW SUPPLIED

Diphenhydramine Hydrochloride Injection, USP is available as:

50 mg/mL (1 mL fill in 2 mL cartridge) **CARPUJECT®** Sterile Cartridge Unit (22-Gauge, 1¼" needle), box of 10, List 2290.

Store at controlled room temperature 15°C to 30°C (59°F to 86°F).

Protect from light and freezing. Retain in carton until time of use.

℞ only

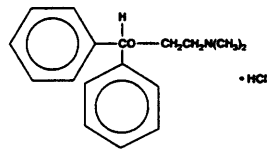
APPEARS THIS WAY
ON ORIGINAL

58-0425-R1-Rev. June, 1998 Printed in USA
ABBOTT LABORATORIES, NORTH CHICAGO, IL 60064, USA

Diphenhydramine Hydrochloride Injection, USP

DESCRIPTION

Diphenhydramine hydrochloride is an antihistamine drug having the chemical name 2-(Diphenylmethoxy)-N,N-dimethylethylamine hydrochloride. It occurs as a white, crystalline powder, is freely soluble in water and alcohol and has a molecular weight of 291.82. The molecular formula is $C_{17}H_{21}NO \cdot HCl$ and the structural formula is:



Diphenhydramine hydrochloride in the parenteral form is a sterile, pyrogen-free solution available in a concentration of 50 mg of diphenhydramine hydrochloride per mL for intramuscular or intravenous use. The solution for parenteral use has been adjusted to a pH between 4 and 6.5 with either sodium hydroxide or hydrochloric acid.

CLINICAL PHARMACOLOGY

Diphenhydramine hydrochloride is an antihistamine with anticholinergic (drying) and sedative side effects. Antihistamines appear to compete with histamine for cell receptor sites on effector cells.

Diphenhydramine hydrochloride in the injectable form has a rapid onset of action. Diphenhydramine hydrochloride is widely distributed throughout the body, including the CNS. A portion of the drug is excreted unchanged in the urine, while the rest is metabolized via the liver. Detailed information on the pharmacokinetics of Diphenhydramine Hydrochloride Injection is not available.

INDICATIONS AND USAGE

Diphenhydramine hydrochloride in the injectable form is effective for the following conditions when diphenhydramine hydrochloride in the oral form is impractical.

Antihistaminic: For amelioration of allergic reactions to blood or plasma, in anaphylaxis as an adjunct to epinephrine and other standard measures after the acute symptoms have been controlled, and for other uncomplicated allergic conditions of the immediate type when oral therapy is impossible or contraindicated.

Motion sickness: For active treatment of motion sickness.

Antiparkinsonism: For use in parkinsonism, when oral therapy is impossible or contraindicated, as follows: parkinsonism in the elderly who are unable to tolerate more potent agents; mild cases of parkinsonism in other age groups, and in other cases of parkinsonism in combination with centrally acting anticholinergic agents.

CONTRAINDICATIONS

Use in Neonates or Premature Infants: This drug should *not* be used in neonates or premature infants.

Nursing Mothers: Because of the higher risk of antihistamines for infants generally, and for neonates and prematures in particular, antihistamine therapy is contraindicated in nursing mothers.

Use as a Local Anesthetic: Because of the risk of local necrosis, this drug should not be used as a local anesthetic.

Antihistamines are also contraindicated in the following conditions: Hypersensitivity to diphenhydramine hydrochloride and other antihistamines of similar chemical structure.

WARNINGS

Antihistamines should be used with considerable caution in patients with narrow-angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, or bladder-neck obstruction.

Local necrosis has been associated with the use of subcutaneous or intradermal use of intravenous diphenhydramine.

Use in Pediatric Patients: In pediatric patients, especially, antihistamines in *overdosage* may cause hallucinations, convulsions, or death.

As in adults, antihistamines may diminish mental alertness in pediatric patients. In the young child, particularly, they may produce excitation.

Use in the Elderly (approximately 60 years or older): Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

PRECAUTIONS

General: Diphenhydramine hydrochloride has an atropine-like action and, therefore, should be used with caution in patients with a history of bronchial asthma, increased intraocular pressure, hyperthyroidism, cardiovascular disease or hypertension. Use with caution in patients with lower respiratory disease including asthma.

Information for Patients: Patients taking diphenhydramine hydrochloride should be advised that this drug may cause drowsiness and has an additive effect with alcohol.

Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc.

Drug Interactions: Diphenhydramine hydrochloride has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc).

MAO inhibitors prolong and intensify the anticholinergic (drying) effects of antihistamines.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Long-term studies in animals to determine mutagenic and carcinogenic potential have not been performed.

Pregnancy: Pregnancy Category B. Reproduction studies have been performed in rats and rabbits at doses up to 5 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to diphenhydramine hydrochloride. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Pediatric Use: Diphenhydramine should not be used in neonates and premature infants (see CONTRAINDICATIONS).

Diphenhydramine may diminish mental alertness, or in the young pediatric patient, cause excitation. Overdosage may cause hallucinations, convulsions, or death (see WARNINGS and OVERDOSAGE).

See also DOSAGE AND ADMINISTRATION section.

ADVERSE REACTIONS

The most frequent adverse reactions are underscored:

1. General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, chills, dryness of mouth, nose, and throat.

2. Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

3. Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

4. Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, confusion, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paresthesia, blurred vision, diplopia, vertigo, tinnitus, acute labyrinthitis, neuritis, convulsions.

5. GI System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

6. GU System: Urinary frequency, difficult urination, urinary retention, early menses.

7. Respiratory System: Thickening of bronchial secretions, tightness of chest and wheezing, nasal stuffiness.

OVERDOSAGE

Antihistamine overdosage reactions may vary from central nervous system depression to stimulation. Stimulation is particularly likely in children. Atropine-like signs and symptoms; dry mouth; fixed, dilated pupils; flushing; and gastrointestinal symptoms may also occur.

Stimulants should not be used.

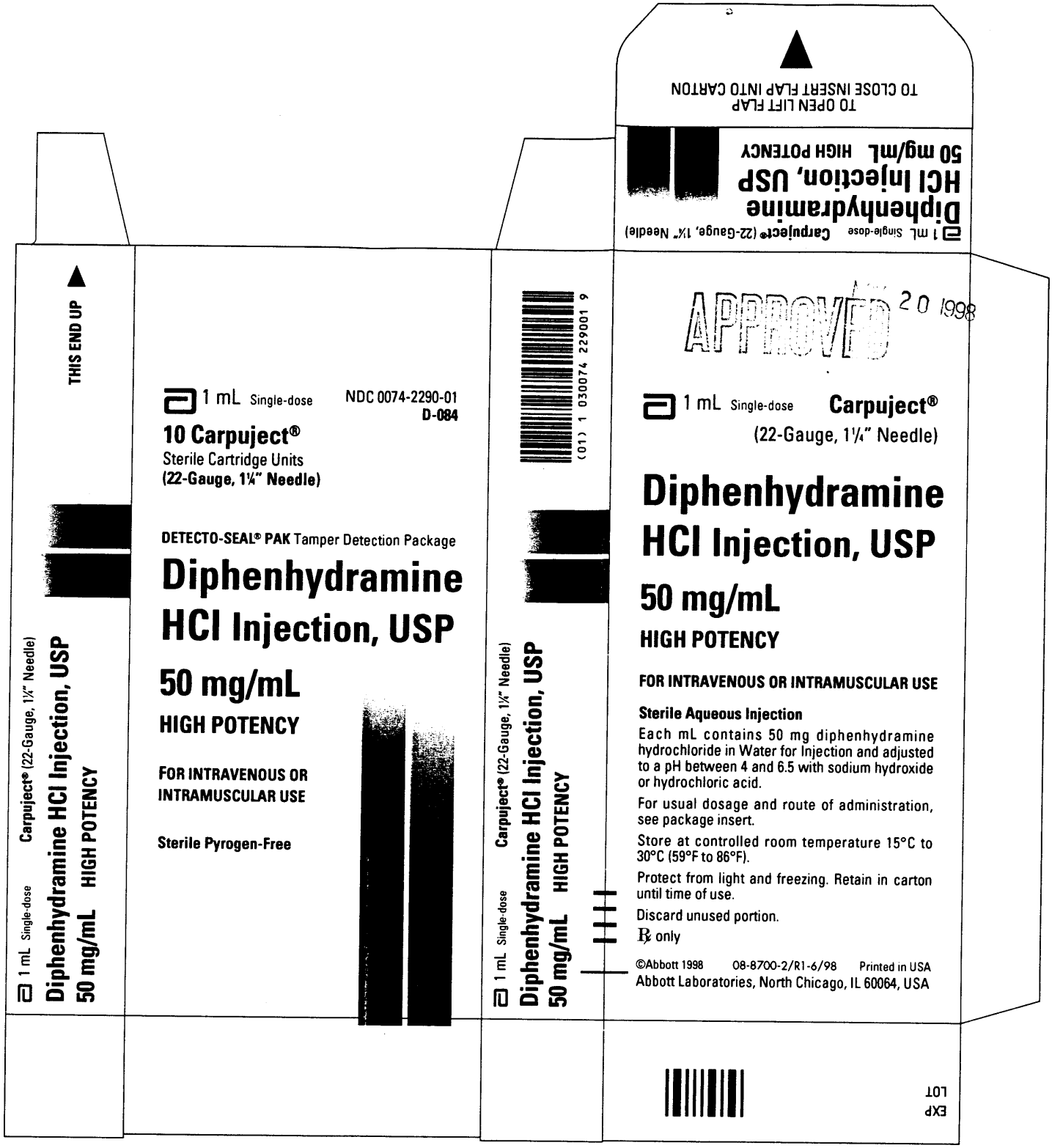
Vasopressors may be used to treat hypotension.

DOSAGE AND ADMINISTRATION

THIS PRODUCT IS FOR INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION ONLY.

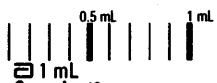
Diphenhydramine hydrochloride in the injectable form is indicated when the oral form is impractical.

Parenteral drug products should be inspected visually for


THIS END UP
1 mL Single-dose Carpuject® (22-Gauge, 1¼" Needle)
Diphenhydramine HCl Injection, USP
50 mg/mL HIGH POTENCY
1 mL Single-dose NDC 0074-2290-01
D-084
10 Carpuject®
Sterile Cartridge Units
(22-Gauge, 1¼" Needle)
DETECTO-SEAL® PAK Tamper Detection Package
Diphenhydramine HCl Injection, USP
50 mg/mL
HIGH POTENCY
FOR INTRAVENOUS OR INTRAMUSCULAR USE
Sterile Pyrogen-Free
(01) 1 030074 229001 9
1 mL Single-dose Carpuject® (22-Gauge, 1¼" Needle)
Diphenhydramine HCl Injection, USP
50 mg/mL HIGH POTENCY
APPROVED 2 0 1998
1 mL Single-dose Carpuject® (22-Gauge, 1¼" Needle)
Diphenhydramine HCl Injection, USP
50 mg/mL
HIGH POTENCY
FOR INTRAVENOUS OR INTRAMUSCULAR USE
Sterile Aqueous Injection
Each mL contains 50 mg diphenhydramine hydrochloride in Water for Injection and adjusted to a pH between 4 and 6.5 with sodium hydroxide or hydrochloric acid.
For usual dosage and route of administration, see package insert.
Store at controlled room temperature 15°C to 30°C (59°F to 86°F).
Protect from light and freezing. Retain in carton until time of use.
Discard unused portion.
℞ only
©Abbott 1998 08-8700-2/R1-6/98 Printed in USA
Abbott Laboratories, North Chicago, IL 60064, USA
EXP
LOT
TO CLOSE INSERT FLAP INTO CARTON
TO OPEN LIFT FLAP
1 mL Single-dose Carpuject® (22-Gauge, 1¼" Needle)
Diphenhydramine HCl Injection, USP
50 mg/mL HIGH POTENCY

NOV 20 1998

APPROVED



NDC 0074-2290-01

1 mL

Abbott Labs., N. Chgo., IL 60064, USA

Carpuject® Sterile Cartridge Unit **(22-Gauge, 1¼")** 58-1171-2/R1-6/98

Diphenhydramine HCl Injection, USP

50 mg/mL ℞ only

FOR IV OR IM USE **HIGH POTENCY**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

CHEMISTRY REVIEW(S)

1. CHEMIST'S REVIEW NO. 1

2. ANDA # 40-140

3. NAME AND ADDRESS OF APPLICANT

[redacted]

4. LEGAL BASIS FOR ANDA SUBMISSION:

Patent is expired and there is no patent exclusivity.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Diphenhydramine Hydrochloride, Injection

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

April 7, 1995: Date of submission of ANDA
May 8, 1995: Additional information
May 12, 1995: Micro information

10. PHARMACOLOGICAL CATEGORY

Antihistamine

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)
See Checklist

13. DOSAGE FORM
Injection 1 ml fill in 2 mil carpuject

14. POTENCY
50 mg/ml

15. CHEMICAL NAME AND STRUCTURE
2-(Diphenylmethoxy)-N,N-dimethylamine Hydrochloride
$C_{17}H_{21}NO.HCl$ 291.82
CAS # 47-24-0

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable

19. REVIEWER:
Dave Gill

DATE COMPLETED:
September 29, 1995

/S/

/S/
10-13-95

cc: ANDA
Division File
DUP File
Field Copy

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pages of trade secret and/or confidential commercial information

1. CHEMIST'S REVIEW NO. 2

2. ANDA # 40-140

3. NAME AND ADDRESS OF APPLICANT

[redacted]

4. LEGAL BASIS FOR ANDA SUBMISSION:

Patent is expired and there is no patent exclusivity.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Diphenhydramine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

April 7, 1995: Date of submission of ANDA
December 19, 1996 : Amendment (subject of this review)
January 14, 1997: New correspondence for change in name

10. PHARMACOLOGICAL CATEGORY

Antihistamine

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)
See Checklist

13. DOSAGE FORM
Injection 1 ml fill in 2 mil carpuject

14. POTENCY
50 mg/ml

15. CHEMICAL NAME AND STRUCTURE
2-(Diphenylmethoxy)-N,N-dimethylamine Hydrochloride
$C_{17}H_{21}NO.HCl$ 291.82
CAS # 47-24-0

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable

19. REVIEWER:
Dave Gill

DATE COMPLETED:
May 30, 1997

/S/
6-3-97

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1. CHEMIST'S REVIEW NO.3

2. ANDA # 40-140

3. NAME AND ADDRESS OF APPLICANT
Abbott Hospital Products Division
Attention: Leslie Koehler
D-389, Bldg. AP 30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

4. LEGAL BASIS FOR ANDA SUBMISSION:

Patent is expired and there is no patent exclusivity.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Diphenhydramine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

April 7, 1995: Date of submission of ANDA
Setember 4, 1997: Amendment

10. PHARMACOLOGICAL CATEGORY

Antihistamine

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)
See Checklist

13. DOSAGE FORM
Injection 1 ml fill in 2 ml carpuject

14. POTENCY
50 mg/ml

15. CHEMICAL NAME AND STRUCTURE
2-(Diphenylmethoxy)-N,N-dimethylamine Hydrochloride
$C_{17}H_{21}NO.HCl$ 291.82
CAS # 47-24-0

16. RECORDS AND REPORTS: None

18. CONCLUSIONS AND RECOMMENDATIONS: Not Approvable

19. REVIEWER:
Dave Gill

DATE COMPLETED:
November 22, 1997

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pages of trade secret and/or confidential commercial information

1. CHEMIST'S REVIEW NO.4

2. ANDA # 40-140

3. NAME AND ADDRESS OF APPLICANT
Abbott Hospital Products Division
Attention: Leslie Koehler
D-389, Bldg. AP 30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

4. LEGAL BASIS FOR ANDA SUBMISSION:

Patent is expired and there is no patent exclusivity.

5. SUPPLEMENT(S): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME

Diphenhydramine Hydrochloride

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:

April 7, 1995: Date of submission of ANDA
February 27, 1998: Amendment
March 27, 1998: Amendment
June 10, 1998: Amendment

10. PHARMACOLOGICAL CATEGORY

Antihistamine

11. Rx or OTC

Rx

12. RELATED IND/NDA/DMF(s)
See Checklist

13. DOSAGE FORM
Injection 1 ml fill in 2 mil carpuject

14. POTENCY
50 mg/ml

15. CHEMICAL NAME AND STRUCTURE
2-(Diphenylmethoxy)-N,N-dimethylamine Hydrochloride
$C_{17}H_{21}NO.HCl$ 291.82
CAS # 47-24-0

16. RECORDS AND REPORTS: None
17. COMMENTS : None
18. CONCLUSIONS AND RECOMMENDATIONS: Approvable

19. REVIEWER:
Dave Gill

DATE COMPLETED:
June 15, 1998

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

MICROBIOLOGY REVIEW

FACSIMILE AMENDMENT

ANDA 40-140

Sep 9, 1998

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Abbott Hospital Products Division PHONE: (847) 938-7873

ATTN: Leslie Koehler FAX: (847) 938-7867

FROM: Denise Huie PROJECT MANAGER (301) 827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated April 7, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Diphenhydramine Hydrochloride Injection USP, 50 mg/ mL.

Reference is also made to your amendment(s) dated February 27, March 27, April 17, and June 10, 1998.

Attached are (2) pages of micrbiology deficiencies and/or comments that should be responded to within 30 calendar days from the date of this document. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your complete response should be (1) faxed directly to our document control room at 301- 827-4337, (2) mailed directly to the above address, and (3) the cover sheet should be clearly marked a FACSIMILE AMENDMENT.

Please note that if you are unable to provide a complete response within 30 calendar days, the file on this application will be closed as a MINOR AMENDMENT and you will be required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Accordingly, a response of greater than 30 days should be clearly marked MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Facsimiles or incomplete responses received after 30 calendar days will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data.

SPECIAL INSTRUCTIONS:

Microbiology comments are provided.

X:\new\ogdadmin\macros\faxfax.frm

Microbiology Comments to be Provided to the Applicant

ANDA: 40-140 APPLICANT: Abbott Laboratories

DRUG PRODUCT: Diphenhydramine Hydrochloride

A. Microbiology Deficiencies:

1. Please refer to page 1-228 of the original application. Please provide [redacted] and justification. Please describe the [redacted] and limits used for this drug product. Bioburden levels based on history of the product or similar product bioburdens will be more usefull in detecting adverse changes in the materials, equipment or process.

2. The environmental monitoring limits described are high. Are they based on current incidences of environmental contamination? What levels do you normally see? Please set the limits based on trend analysis of current data such that unusual events would be detected.

3. Please provide a validation summary for the [redacted] in [redacted]

4. Please provide validation data summaries for the [redacted] not provided in the application (See page 2-38).

5. [redacted]

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in the cover page/letter.

Sincerely yours,

/S/

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

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
Microbiologists Review #1
August 27, 1998

A. 1. ANDA: **40-140**

APPLICANT: Abbott Laboratories
Attention: David T. Guzek
D-389, Bldg AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

2. PRODUCT NAME: **Diphenhydramine HCl Injection, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg/mL, 1 mL fill in a 2 mL Carpuject® for IV or IM injection.

4. METHOD(S) OF STERILIZATION: [redacted]

5. PHARMACOLOGICAL CATEGORY: Antihistamine

B. 1. DATE OF INITIAL SUBMISSION: Recieved 4/10/97, RTF 4/28/97. Filed Letter dated 6/2/97.

2. DATE OF AMENDMENT: 5/8/97 - response to RTF.
5/29/98 - Chemistry.
6/10/98 - Chemistry.
2/27/98 - Chemisrty.
9/4/97 - Chemisrty.

3. RELATED DOCUMENTS: Correspondence dated 6/18/97 - [redacted] to Abbott Laboratories.

4. ASSIGNED FOR REVIEW: August 21, 1998.

C. [redacted]

D. CONCLUSIONS: The submission is not recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to Applicant".

/S/ 8/27/98
James L. McVey

initialed by F. Fang or F. Holcombe /S/ 8/27/98

cc:

Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

APPEARS THIS WAY
ON ORIGINAL

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pages of trade secret and/or confidential commercial information

OFFICE OF GENERIC DRUGS
Microbiologists Review #2
October 15, 1998

A. 1. ANDA: **40-140**
APPLICANT: Abbott Laboratories
Attention: David T. Guzek
D-389, Bldg AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

2. PRODUCT NAME: **Diphenhydramine HCl Injection, USP**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: 50 mg/mL, 1 mL fill in a 2 mL Carpuject® for IV or IM injection.

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antihistamine

B. 1. DATE OF INITIAL SUBMISSION: Received 4/10/97, RTF 4/28/97. Filed Letter dated 6/2/97.

2. DATE OF AMENDMENT: 5/8/97 - response to RTF.
5/29/98 - Chemistry.
6/10/98 - Chemistry.
2/27/98 - Chemistry.
9/4/97 - Chemistry.
9/23/98 - Subject of this Review.

3. RELATED DOCUMENTS: Correspondence dated 6/18/97 - to Abbott Laboratories.

4. ASSIGNED FOR REVIEW: October 8, 1998.

C. REMARKS:

conditions according to the applicant.

D. CONCLUSIONS: The submission is ~~not~~ recommended for approval on the basis of sterility assurance. Specific comments are provided in "E. Review Notes" and "Microbiologist's Draft of Letter to Applicant".

/S/ 10/15/98
James L. McVey

Initialed by: F. Fang, F. Holcombe, R. Patel or M. Fanning /S/ 10/19/98

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey

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pages of trade secret and/or confidential commercial information

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pages of trade secret and/or confidential commercial information

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

BIOEQUIVALENCE REVIEW

OCT 4 1995

Diphenhydramine Hydrochloride
Injection
50 mg/mL, 1 mL fill in 2 mL Carpuject®
ANDA #40-140
Reviewer: Kuldeep R. Dhariwal
File Name: 40140W.495

REVIEW OF A WAIVER REQUEST

The firm requests a waiver of *in vivo* bioavailability requirements for Diphenhydramine Hydrochloride Injection 50 mg/mL, 1 mL fill in 2 mL Carpuject® (sterile, pyrogen-free solution) under 21 CFR 320.22(b)(1)(ii). The agency issued a "Refusal to File" and asked for additional information. The information was submitted as amendment. The reference listed drug is Benadryl injection (Parke Davis) and is available as follows:

Benadryl Steri-Vials® : Sterile, pyrogen-free solution; 10 mg/mL and 50 mg/mL; both strengths are available in 10 mL Steri-Vials
Benadryl Steri-Dose® : Sterile, pyrogen-free solution; 50 mg/mL in a 1 mL disposable syringe
Benadryl Ampoule: Sterile, pyrogen-free solution; 50 mg/mL in a 1 mL ampoule

FORMULATIONS: **Not to be released under FOI**

Ingredients	Amount (mg/mL) Test	Reference* (Parke Davis)
Diphenhydramine HCl	50	50
Water for injection	q.s.	q.s.
Sodium Hydroxide	adjust pH	adjust pH
Hydrochloric acid	adjust pH	adjust pH
	pH 4.0-6.5**	pH 5.0-6.0

* Obtained from FDA Comis Data Base for Benadryl NDA #009486
** pH of the finished product was 5.2 (USP specifications are 4.0 to 6.5)

COMMENTS:

1. The drug product is for intravenous or intramuscular use.

2. The conditions of use, route of administration, and dosage form are identical to innovator product. Both products are

supplied as sterile, pyrogen-free solutions. Active and inactive ingredients are also same in test and reference listed drug.

3. The firm states that the drug product is manufactured at the [redacted] which is registered under the name [redacted]. However, the product, when approved, will be marketed by [redacted] which is an affiliate of [redacted]. The labeling included in the application reflects the name [redacted] Division of labeling may make a note of this.

RECOMMENDATION :

The Division of Bioequivalence agrees that the information submitted by [redacted] demonstrates that Diphenhydramine Hydrochloride Injection 50 mg/mL, 1 mL fill in 2 mL Carpuject^{R} falls under 21 CFR 320.22(b)(1)(ii) of the Bioavailability/Bioequivalence Regulations. The waiver of the *in vivo* bioequivalence study requirements for the 50 mg/mL, 1 mL fill in 2 mL Carpuject^{R}, injection of the test product is granted. From the bioequivalence point of view, the Division of Bioequivalence deems the test injectable formulation to be bioequivalent to Benadryl 1 mL containing 50 mg of diphenhydramine hydrochloride by Parke Davis.

/S/ 9/13/95
Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED R. PATNAIK
FT INITIALED R. PATNAIK /S/ Date 9/21/95

Concur: /S/ Date 10/4/95
Keith K. Chan, Ph.D.
Director, Division of Bioequivalence

cc: ANDA #40-140 (original, duplicate), HFD-600 (Hare), HFD-630, HFD-655 (Patnaik, Dhariwal), Drug File, Division File

KRD/Draft:090895/Final:091395

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #40-140 SPONSOR: [redacted] → Abbott labs
DRUG: Diphenhydramine Hydrochloride
DOSAGE FORM: Injection
STRENGTHS/(s): 50 mg/mL, 1 mL fill in 2 mL Carpuject®
TYPE OF STUDY: Waiver request
STUDY SITE: Not applicable

STUDY SUMMARY: The test and reference products are supplied as sterile, pyrogen-free solutions for intravenous or intramuscular use. Active and inactive ingredients are same in test and reference products. The waiver is granted.

DISSOLUTION: Not applicable.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: /S/ DATE 8/7/98

BRANCH CHIEF: Shriniwas Nerurkar, Ph.D., BRANCH: II

INITIAL: /S/ DATE 8/7/1998

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Dale P. Conner, Pharm. D.

INITIAL: /S/ DATE 8/7/98

DIRECTOR
OFFICE OF GENERIC DRUGS:

INITIAL: _____ DATE _____

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 9, 1995

FROM: William Russell, CSO, Regulatory Support Branch

SUBJ: ANDA Amendment via Fax

TO: ANDA 40-140

[redacted] faxed their response to our Refuse to File letter dated April 28, 1995. I called her to explain we do not accept faxed responses to Refuse to File nor do we review them submitted in that manner. She said she sent other faxes and I explained that sometimes we do call and request the information to be faxed but not on Refuse to File issues since that might give an unfair advantage in some cases and we try to maintain equitability.

APPEARS THIS WAY
ON ORIGINAL

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 19, 1995

FROM: Bill Russell, CSO

SUBJ: Binder covers

TO: ANDA 40-140

When this application was received, the tab on the back cover was facing the wrong direction for bar-coding. I corrected the Archival copies and spoke to [redacted] regarding the proper positioning of the tab for bar coding. She said she would be aware of this in future submissions.

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING

DATE
5/4/95

NDA NUMBER
40-140

IND NUMBER

TELECON/MEETING

INITIATED BY
☐ APPLICANT/ SPONSOR
☐ FDA

MADE
☐ BY TELEPHONE
☐ IN PERSON

PRODUCT NAME
Diphenhydramine HCl

FIRM NAME
[redacted]

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
[redacted]

TELEPHONE NO.

[redacted] called questioning our Refuse to file letter re q+q comparison She stated the q+q comparison was on pg 17. I informed her it was not adequate. The comparison states sterile pyrogen free solution, but does not state what kind of solution. How can they determine what is in the innovator product when it is not listed on the labeling? re: Analytical methods A side by side comparison of the formulation is necessary to show the product is q+q the same

SIG: [redacted]

DIVISION
HFD615

FORM FD 2587 (11/77)

ORIGINAL IND/NDA

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

Redacted 3

pages of trade secret and/or confidential commercial information

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
FOOD AND DRUG ADMINISTRATION

ESTABLISHMENT EVALUATION REQUEST

REQUEST TYPE *(Check One)* ☒ Original ☐ FollowUp ☐ FUR	DATE ~~May~~ 9.29.95 ~~April 18, 1995~~	PHONE NO. (301)594-0310	EER ID #
REQUESTORS NAME: D. GILL	DIVISION: Office of Generic Drugs		MAIL CODE: **HFD-623**
APPLICATION AND SUPPLEMENT NUMBER: ANDA 40-140			
BRAND NAME:	ESTABLISHED NAME: Diphenhydramine Hydrochloride Injection		
DOSAGE STRENGTH: 50 mg/mL, 1 mL Carpuject			STERILE ☒ Yes ☐ No
PROFILE CLASS:: SVS	PRIORITY CLASSIFICATION *(See SMG CDER-4820.3)*		
APPLICANT'S NAME: [redacted]			
APPLICANT'S ADDRESS: [redacted]			
COMMENTS :			

FACILITIES TO BE EVALUATED

(Name and Complete Address)

	RESPONSIBILITY	DMF NUMBER/ PROFILE CODE	FKEY CIRTS ID	HFD-324 USE ONLY~	
1. [redacted]		SVS			
2. [redacted] 9610215		CCS			
3.					
4.					
5.					

FOR HFD-324 USE ONLY:	CSO	DATE RECEIVED
	CGMP COMPLIANCE STATUS	DATE

FORM FDA 3274 (8/92) Distribution: Original and Yellow Copy: HFD-324.

cc: ANDA 40-140 HFD-623/Div File, HFD-617/JWilson, HFD-617/TAmes, HFD-623/JSimmons HFD-623/GJSmith

x:\wpfile\eerforms\40140

Redacted 3

pages of trade secret and/or confidential commercial information

REVIEW OF PROFESSIONAL LABELING #1

ORIGINAL

DRAFT

DATE OF REVIEW: November 15, 1995

ANDA #: 40-140

NAME OF FIRM: [redacted]

NAME OF DRUG: Diphenhydramine Hydrochloride Injection USP, 50mg/mL

DATE OF SUBMISSION: April 7, 1995

COMMENTS:

Container: (1 mL Carpuject®)

[redacted]

Carton: (Box of 10s)

Add the following statement to appear in conjunction with the "Protect from light" statement: "Retain in carton until time of use".

Insert:

1. GENERAL
2. CONTRAINDICATIONS

[redacted]

~~~~ rather than "**Nursing Mothers**."

3. DOSAGE AND ADMINISTRATION

In line 9, **"Adults"** is to appear in bold to be consistent with ~~~~

RECOMMENDATIONS:

1. Inform the firm of the above comments.

2. Request the firm revise their container labels, carton labeling, and package insert labeling, then prepare and submit final printed labels and labeling.

NOTE TO CHEMIST:

[ ]

FOR THE RECORD:

1. Review based on the labeling of Benadryl® Injection (Parke-Davis), revised July 1993; approved November 29, 1993.

2. Patent/ Exclusivities: None

3. Storage Conditions:

PD — Store at CRT, 15° - 30°C (59° - 86°F). Protect from freezing and light.

~~~~ — Store at CRT, 15° - 30°C (59° - 86°F). Protect from light and freezing.

USP — Preferably use containers of Type I glass protected from light.

Note: We have asked ~~~~ add the following statement to appear in conjunction with the "Protect from light" statement: "Retain in carton until time of use".

4. Product Line:

The innovator markets their product as:

- o Steri-Vials - 10 mg diphenhydramine HCl in each mL of solution with 0.1 mg/mL Benzethonium chloride, 10 mL
- o Steri-Dose - 50 mg diphenhydramine HCl in a 1 mL disposable syringe, packages of 10 individually cartoned syringes; packages of 2 trays of 5 syringes
- o Ampoule - 50 mg diphenhydramine HCl in a 1 mL ampoule, packages of ten

The applicant proposes to market their product as:

- o Carpuject® - 50 mg/mL (1 mL fill in 2 mL cartridge), box of ten

We have concerns about this proposed packaging regarding the [redacted]. The firm has been asked to revise/comment.

5. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 123 (Volume 1.1).

6. The visual inspection of particulate matter as been included in the DOSAGE AND ADMINISTRATION section as required by 21 CFR 201.57 (j).

7. It was brought to the chemist's attention that [redacted] product uses USP's pH rather than that of the innovator. He stated that is was OK and that USP has the legal authority.

/S/

Lillie D. Golson

CDER Establishment Evaluation Report
for May 07, 1997

Application: **ANDA 40140/000**
Stamp: **10-APR-1995** Regulatory Due:
Applicant: [redacted]

Priority:
Org Code: **600**
Action Goal:
District Goal: **10-JUN-1996**
Brand Name:
Established Name: **DIPHENHYDRAMINE HYDROCHL**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **50 MG/ML CARPUJECT**

FDA Contacts:			
	J. WILSON III	**(HFD-617)**	**301-594-0310 , Project Manager**
	D. GILL	**(HFD-623)**	**301-594-0310 , Review Chemist**
	V. SAYEED	**(HFD-629)**	**301-594-1841 , Team Leader**

Overall Recommendation:

Establishment: [redacted]
DMF No: [redacted]

Profile: **CSN** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC** **07-MAY-1997**

Responsibilities: [redacted]

Establishment: [redacted]
DMF No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **SUBMITTED TO OC** **07-MAY-1997**

Responsibilities: [redacted]

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

ANDA Number: 40-140 Date of Submission: December 19, 1996

Applicant's Name: [redacted]

Established Name: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (Carpuject®)

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

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 1 mL Carpuject®

Satisfactory in FPL as of 12/19/96 submission

Carton Labeling: 10's

Satisfactory in FPL as of 12/19/96 submission

Professional Package Insert Labeling:

Satisfactory in FPL as of 12/19/96 submission

Revisions needed post-approval:

1. CARTON

   Encourage the inclusion of directions for proper use of Carpuject®

2. INSERT

   a. CONTRAINDICATIONS

      Revise the subsection heading to read " [redacted] rather than **"Nursing Mothers."**

   b. DOSAGE AND ADMINISTRATION - Adults

      i. **"Adults"** should appear in bold to be consistent with " [redacted]

      ii. See comment under CARTON.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Benadryl® (Steri-Dose Syringes and Ampules)

NDA Number: 09-486

NDA Drug Name: Benadryl®

NDA Firm: Parks-Davis

Date of Approval of NDA Insert and supplement #: May 13, 1996/S-019
Has this been verified by the MIS system for the NDA?
Yes

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Benadryl® (Steri-Dose Syringes and Ampules)

Basis of Approval for the Carton Labeling: Benadryl® (Steri-Dose Syringes and Ampules)

Other Comments:

The firm does not use [redacted] n the manufacturing of this drug product.

REVIEW OF PROFESSIONAL LABELING CHECK LIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 23	x		
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		x	

Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		x	
Does the package proposed have any safety and/or regulatory concerns?		x	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?		x	
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		x	
Is the strength and/or concentration of the product unsupported by the insert labeling?		x	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		x	
Are there any other safety concerns?		x	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		x	
Has applicant failed to clearly differentiate multiple product strengths?			x
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		x	
Labeling (continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		x	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		x	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?			x
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?			x
Has the firm failed to describe the scoring in the HOW SUPPLIED section?			x
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		x	
Do any of the inactives differ in concentration for this route of administration?		x	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		x	o
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		x	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?			x

Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			x
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)			x
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?		x	
Does USP have labeling recommendations? If any, does ANDA meet them?		x	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		x	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		x	
Bioequivalence Issues: (Compare bioeqivalency values: insert to study. List Cmax, Tmax, T ½ and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?			x
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		x	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD: (From a previous review with a modification)

1. Review based on the labeling of Benadryl® Injection (Parks-Davis), April, 1994; approved May 13, 1996.

2. Patent/ Exclusivities: None

3. Storage Conditions:

   NDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from freezing and light.

   ANDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from light and freezing.

   USP Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

4. Product Line:

   The innovator markets their product as:

   - Steri-Vials - 10 mg diphenhydramine HCl in each mL of solution with 0.1 mg/mL Benzethonium chloride, 10 mL
   - Steri-Dose - 50 mg diphenhydramine HCl in a 1 mL disposable syringe, packages of 10 individually cartoned syringes; packages of 2 trays of 5 syringes
   - Ampule - 50 mg diphenhydramine HCl in a 1 mL ampule, packages of ten

The applicant proposes to market their product as:

- o Carpuject® - 50 mg/mL (1 mL fill in 2 mL cartridge), box of ten

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 123 (Volume 1.1).

6. The visual inspection of particulate matter as been included in the DOSAGE AND ADMINISTRATION section as required by 21 CFR 201.57 (j).

7. **It was brought to the chemist's attention that [redacted] product uses USP's pH rather than that of the innovator. He stated that is was OK and that USP has the legal authority.**

8. The firm does not use [redacted], in the manufacturing of this drug product. (See the firm's letter dated 12/19/96). Therefore, the labels and labeling of the applicant [redacted]

9. CONTAINER

   Glass cartridge: 2 mL USP Type I glass cartridge (vol.1.1, p.365)

Review cycle:

Primary Reviewer: Chan Park /S/ **Date:** 3/21/97

Secondary Reviewer: Charlie Hoppes /S/ **Date:** 3/24/97

Team Leader: John Grace /S/ **Date:** 3/24/97

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cc: /S/ 3/24/97

ANDA 40-140
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
njg/3/21/97/x:\new\firms\\ltrs&rev\
Review

40-140

RECORD OF TELEPHONE CONVERSATION

Mark Anderson and I called to speak with David Guzek of the firm this morning regarding this application and other applications recently

[redacted] Mr. Guzek was not available and we spoke with Ms. Conaway instead. Ms. Conaway informed us that the firm intends to market the transferred products under the Abbott name and labeling. We informed her that we could see the revised labeling in annual reports for the approved applications but that for the pending applications we would need to review all labeling revised to include Abbott prior to approval. We let Ms. Conaway know that 12 FPL copies of labeling for this application should be submitted as a telephone amendment.

DATE 8/5/97

ANDA NUMBER 74-160

IND NUMBER

TELECON

INITIATED BY _ APPLICANT/ SPONSOR X FDA

MADE X BY TELE. _ IN PERSON

FPRODUCT NAME Bumetanide Injection

FIRM NAME Abbott

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Jean Conaway
Reg. Affair

TELEPHONE NUMBER
847-937-3216
(Guzek's #)

SIGNATURE /S/

/S/

(Supersedes the Approval Summary dated 3/21/97, under Sanofi)

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

ANDA Number: 40-140 Date of Submission: February 27, 1998

Applicant's Name: Abbott laboratories

Established Name: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (Carpuject®)

Labeling Deficiencies:

1. CONTAINER - 1 mL Carpuject®

   Satisfactory

2. CARTON - 10's

   a. Revise the net quantity statement to read "1 mL single-dose".

   b. Add the statement "Discard unused portion.".

3. INSERT

   a. GENERAL COMMENTS:

      Due to changes in the approved labeling of the listed drug (Benadryl® - Park-Davis Company; revised April, 1997 and approved November 18, 1997), we ask that you revise your insert labeling as follows. In addition, other editorial changes are also indicated.

   b. WARNINGS

      i. Include the following as the second paragraph:

         Local necrosis has been associated with the use of subcutaneous or intradermal use of

intravenous diphenhydramine.

ii. Use in ———————

A) Replace '——————— or ——————— ——————' with "pediatric patients" in four places including the subsection heading.

B) Relocate the second sentence to begin as a new paragraph.

c. PRECAUTIONS - Include the following as the last subsection:

Pediatric Use

Diphenhydramine should not be used in neonates and premature infants (see CONTRAINDICATIONS).

Diphenhydramine may diminish mental alertness, or in the young pediatric patient, cause excitation. Overdosage may cause hallucinations, convulsions, or death (see WARNINGS and OVERDOSAGE).

See also DOSAGE AND ADMINISTRATION section.

d. DOSAGE AND ADMINISTRATION

i. Include the following statement to immediately follow the section heading.

THIS PRODUCT IS FOR INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION ONLY.

ii. ———————

A) Replace the subsection '——————' with **"Pediatric Patients, other than premature infants and neonates:".**

B) Revise to read as follows:

... is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly.

iii. Adults

A) **"Adults"** should appear in bold to be consistent with

B) Revise to read as follows:

... intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly, 100 mg if required; maximum daily dosage is 400 mg.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD: (From a previous review with a modification)

1. Review based on the labeling of Benadryl® Injection (NDA 09-486/S-022; Parks-Davis), approved November 18, 1997.

2. According to the PM for Benadryl Inj. (Beverly Gellauresi), this insert labeling was revised April, 1998. (Telephone conversation).

3. Patent/ Exclusivities: None

4. Storage Conditions:

   NDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from freezing and light.

   ANDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from light and freezing.

   USP Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

5. Product Line:

   The innovator markets their product as:

   - Steri-Vials - 10 mg diphenhydramine HCl in each mL of solution with 0.1 mg/mL Benzethonium chloride, 10 mL
   - Steri-Dose - 50 mg diphenhydramine HCl in a 1 mL disposable syringe, packages of 10 individually cartoned syringes; packages of 2 trays of 5 syringes
   - Ampule - 50 mg diphenhydramine HCl in a 1 mL ampule, packages of ten

   The applicant proposes to market their product as:

   - Carpuject® - 50 mg/mL (1 mL fill in 2 mL cartridge), box of ten

6. [redacted] Abbott [redacted]

7. Inactive Ingredients:

The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 123 (Volume 1.1).

8. The visual inspection of particulate matter as been included in the DOSAGE AND ADMINISTRATION section as required by 21 CFR 201.57 (j).

9. **It was brought to the chemist's attention that [redacted] product uses USP's pH rather than that of the innovator. He stated that is OK and that USP has the legal authority.**

10. The firm does not use [redacted] in the manufacturing of this drug product. (See the firm's letter dated 12/19/96). Therefore, the labels and labeling of the applicant [redacted]

11. CONTAINER

Glass cartridge: 2 mL USP Type I glass cartridge (vol.1.1, p.365)

Review cycle: #2

Primary Reviewer: Chan Park 3/20/98 /S/ **Date: March 20, 1998**

Team Leader: John Grace /S/ **Date:** 3/23/98

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cc:

ANDA 40-140
DUP/DIVISION FILE
HFD-613/CPark/CHoppes/JGrace (no cc)
X:\NEW\FIRMSAM\ABBOTT\LTRS&REV\40140NA2.L
Review

RECORD OF TELEPHONE CONVERSATION

Reference is made to the t-amendment dated May 29, 1998.

After consulting with Dr. Vilayat Sayeed, the firm was asked to reduce total impurity limits to [redacted] and reduce expiry accordingly (perhaps to as low as 9 months).

This limit is requested because the RLD has a similar limit. By law, OGD can only approve generic products that are at least as good as the innovator. OGD will not approve generic products with significantly highly impurity profiles.

Abbott will consult with the manufacturing staff to inquire about their capability of manufacturing a product with such tight specifications. They will respond in one week.

I said that I will withhold further action for one week. After that, a NA-fax will be drafted.

cc:
T-con binder
ANDA
Division File

X:\new\firmsam\abbott\telecons\40140.002

DATE
6/9/98

APPLICATION NUMBER
40-140

TELECON

INITIATED BY FDA

PRODUCT NAME
Diphenhydramine HCl Inj. 50 mg/mL

FIRM NAME
Abbott Labs

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Leslie Koehler

TELEPHONE NUMBER
847-938-7873

SIGNATURE
/S/ 6/9/98
Joseph Buccine

RECORD OF TELEPHONE CONVERSATION

Reference is made to the submission dated April 17, 1998.

With Dr. Vilayat Sayeed participating, the firm was asked to reduce impurity limits to observed data at 12 months. The firm was previously asked to reduce expiry to 12 months and reduce the impurity limits accordingly. The firm reduced the expiry but did not reduce the limits. This t-con was intended to correct this mistake.

Ms. Koehler indicated that Abbott would submit a t-amendment within the week to resolve the issue.

Cc:
T-con binder
ANDA
Division File

X:\new\firmsam\abbott\telecons\62212.001

DATE
5/26/98

APPLICATION NUMBER
40-140

TELECON

INITIATED BY FDA

PRODUCT NAME
Diphenhydramine HCl Inj 50 mg/mL

FIRM NAME
Abbott Labs

NAME AND TITLE OF PERSON WITH WHOM CONVERSATION WAS HELD
Leslie Koehler

TELEPHONE NUMBER
847-938-7873

SIGNATURE
/S/ 5/26/98

E L E C T R O N I C M A I L M E S S A G E

Sensitivity: COMPANY CONFIDENTIAL

Date: 25-Mar-1998 01:43pm EDT
From: Craig Bertha
BERTHAC
Dept: HFD-570 PKLN 10B45
Tel No: 301-827-1095 FAX 301-827-1271

TO: Devinder Gill (GILLD)

CC: Guiragos Poochikian (POOCHIKIAN)

Subject: Re: NDA # 0009846

Dave,

I was able to dig up the following on N 9486. The current specifications for impurities in the drug substance, diphenhydramine hydrochloride, are:

Impurity	Specification
[redacted]	NMT [redacted] (w/w)
[redacted]	NMT [redacted] (w/w)
[redacted]r impurities	NMT [redacted] each (area %)
Total impurities	NMT [redacted] (sum of [redacted] and other impurities)

The applicant notes that the initial decomposition product of diphenhydramine hydrochloride is [redacted] which [redacted] to [redacted]. The following are the stability specifications for the drug product:

Impurity	Specification
[redacted]	NMT [redacted] (w/w)
[redacted]	NMT [redacted] (w/w)
Total Impurities	NMT [redacted] (sum of [redacted]

The analytical method is based on the current USP assay method and responses are calculated against known standards for the specified impurities.

I hope this is helpful to you.

Craig

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

OFFICE OF GENERIC DRUGS
HFD-600, 7500 Standish Place, Rockville, MD 20855

TO: Leslie Koehler		**FROM:** Joseph Buccine
		Project Manager
PHONE:		**PHONE:** (301) 827-5848
FAX: 847 938 7867		**FAX:** (301) 594-0180

Total number of pages, excluding this cover sheet: 3 **Date:** 6/18/98

COMMENTS:

Please provide FPL as a Telephone Amendment within 30 days.

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

ANDA Number: 40-140 Date of Submission: February 27, 1998

Applicant's Name: Abbott laboratories

Established Name: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (Carpuject®)

Labeling Deficiencies:

1. CONTAINER - 1 mL Carpuject®

   Satisfactory

2. CARTON - 10's

   a. Revise the net quantity statement to read "1 mL single-dose".

   b. Add the statement "Discard unused portion.".

3. INSERT

   a. GENERAL COMMENTS:

      Due to changes in the approved labeling of the listed drug (Benadryl® - Park-Davis Company; revised April, 1997 and approved November 18, 1997), we ask that you revise your insert labeling as follows. In addition, other editorial changes are also indicated.

   b. WARNINGS

      i. Include the following as the second paragraph:

         Local necrosis has been associated with the use of subcutaneous or intradermal use of intravenous diphenhydramine.

ii. Use in [redacted]

A) Replace " [redacted] or " [redacted] with "pediatric patients" in four places including the subsection heading.

B) Relocate the second sentence to begin as a new paragraph.

c. PRECAUTIONS - Include the following as the last subsection:

Pediatric Use

Diphenhydramine should not be used in neonates and premature infants (see CONTRAINDICATIONS).

Diphenhydramine may diminish mental alertness, or in the young pediatric patient, cause excitation. Overdosage may cause hallucinations, convulsions, or death (see WARNINGS and OVERDOSAGE).

See also DOSAGE AND ADMINISTRATION section.

d. DOSAGE AND ADMINISTRATION

i. Include the following statement to immediately follow the section heading.

THIS PRODUCT IS FOR INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION ONLY.

ii. [redacted]

A) Replace the subsection "[redacted] " with **"Pediatric Patients, other than premature infants and neonates:".**

B) Revise to read as follows:

... is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly.

iii. Adults

A) **"Adults"** should appear in bold to be consistent with [redacted]

B) Revise to read as follows:

... intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly, 100 mg if required; maximum daily dosage is 400 mg.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

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

/S/ 5/2/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

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

ANDA Number: 40-140 Date of Submission: July 17, 1998

Applicant's Name: ~~[redacted]~~ transferred ownership to Abbott Labs /S/ 8/18/98

Established Name: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (Carpuject®)

APPROVAL SUMMARY:

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels: 1 mL Carpuject®

Satisfactory in FPL as of 7/17/98 submission

Carton Labeling: 10's

Satisfactory in FPL as of 7/17/98 submission

Professional Package Insert Labeling:

Satisfactory in FPL as of 7/17/98 submission

Revisions needed **post-approval:**

1. CARTON

   Encourage the inclusion of directions for proper use of Carpuject®

2. INSERT

   a. CONTRAINDICATIONS

      Revise the subsection heading to read ~~[redacted]~~ ' rather than **"Nursing Mothers."**

   b. DOSAGE AND ADMINISTRATION

      See comment under CARTON.

BASIS OF APPROVAL:

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Benadryl® (Steri-Dose Syringes and Ampules)

NDA Number: 09-486

NDA Drug Name: Benadryl®

NDA Firm: Parks-Davis

Date of Approval of NDA Insert and supplement #: November 18, 1997/S-022

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

Was this approval based upon an OGD labeling guidance? No

Basis of Approval for the Container Labels: Benadryl® (Steri-Dose Syringes and Ampules)

Basis of Approval for the Carton Labeling: Benadryl® (Steri-Dose Syringes and Ampules)

Other Comments:

The firm does not use [redacted] in the manufacturing of this drug product.

APPEARS THIS WAY
ON ORIGINAL

FOR THE RECORD: (From a previous review with a modification)

1. Review based on the labeling of Benadryl® Injection, NDA# 09-486/S-022 (Parks-Davis), March 5, 1997; approved November 18, 1997.

2. Patent/ Exclusivities: None

3. Storage Conditions:

   NDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from freezing and light.

   ANDA: Store at CRT, 15° - 30°C (59° - 86°F). Protect from light and freezing.

   USP Preserve in single-dose or in multiple-dose containers, preferably of Type I glass, protected from light.

4. Product Line:

   The innovator markets their product as:

   - Steri-Vials - 10 mg diphenhydramine HCl in each mL of solution with 0.1 mg/mL Benzethonium chloride, 10 mL
   - Steri-Dose - 50 mg diphenhydramine HCl in a 1 mL disposable syringe, packages of 10 individually cartoned syringes; packages of 2 trays of 5 syringes
   - Ampule - 50 mg diphenhydramine HCl in a 1 mL ampule, packages of ten

   The applicant proposes to market their product as:

   - Carpuject® - 50 mg/mL (1 mL fill in 2 mL cartridge), box of ten

5. Inactive Ingredients:

   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 123 (Volume B,1.1).

6. The visual inspection of particulate matter as been included in the DOSAGE AND ADMINISTRATION section as required by 21 CFR 201.57 (j).

7. It was brought to the chemist's attention that [redacted] product uses USP's pH rather than that of the innovator. He stated that is was OK and that USP has the legal authority.

8. The firm does not use [redacted] in the manufacturing of this drug product. (See the firm's letter dated 12/19/96). Therefore, the labels and labeling of the applicant [redacted]

9. CONTAINER

Glass cartridge: 2 mL USP Type I glass cartridge (vol B.1.1, p.365)

Primary Reviewer: Jim Barlow JB **Date: July 27, 1998.**

Team Leader: John Grace 1st. **Date:** 7/29/98

---

cc:

ANDA 40-140
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
X:\NEW\FIRMSNZ\SANOFI\LTRS&REV\40140APS.2
Review

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 40140/000**
Stamp: **10-APR-1995** Regulatory Due:
Applicant: **ABBOTT LABS**
200 ABBOTT PARK RD D389 AP30
ABBOTT PARK, IL 600643537

Priority:
Org Code: **600**
Action Goal:
District Goal: **10-JUN-1996**
Brand Name:
Established Name: **DIPHENHYDRAMINE HYDROCHLORIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **50 MG/ML CARPUJECT**

FDA Contacts:

J. BUCCINE	**(HFD-617)**	**301-827-5848**	**, Project Manager**
D. GILL	**(HFD-623)**	**301-827-5848**	**, Review Chemist**
V. SAYEED	**(HFD-629)**	**301-827-5848**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 27-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 22-JUN-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 12-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1925262**
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment:

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **27-OCT-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities:

Establishment:

DMF No:
AADA No:

Profile: **CSN** OAI Status: **NONE**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Responsibilities:

Last Milestone: **OC RECOMMENDATION**
Milestone Date: **19-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **ANDA 40140/000**
Stamp: **10-APR-1995** Regulatory Due:
Applicant: **ABBOTT LABS**
200 ABBOTT PARK RD D389 AP30
ABBOTT PARK, IL 600643537

Priority:
Org Code: **600**
Action Goal:
District Goal: **10-JUN-1996**
Brand Name:
Established Name: **DIPHENHYDRAMINE HYDROCHLORIDE**
Generic Name:
Dosage Form: **INJ (INJECTION)**
Strength: **50 MG/ML CARPUJECT**

FDA Contacts:			
	J. BUCCINE	**(HFD-617)**	**301-827-5848 , Project Manager**
	D. GILL	**(HFD-623)**	**301-827-5848 , Review Chemist**
	V. SAYEED	**(HFD-629)**	**301-827-5848 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 27-OCT-1998 by J. D AMBROGIO (HFD-324) 301-827-0062
ACCEPTABLE on 22-JUN-1998 by M. EGAS (HFD-322) 301-594-0095
ACCEPTABLE on 12-MAY-1997 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1925262**
ABBOTT LABORATORIES
1776 NORTH CENTENNIAL DR
MCPHERSON, KS 67460

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: [redacted]

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **27-OCT-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: [redacted]

Establishment: [redacted]

DMF No: [redacted]
AADA No:

Profile: **CSN** OAI Status: **NONE**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Responsibilities: _____

Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-JUN-1998**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

APPROVAL PACKAGE SUMMARY

ANDA #: 40-140

FIRM: Abbott Labs **DRUG:** Diphenhydramine Hydrochloride
\GE: Injection **STRENGTH:** 50 mg/mL.

cGMP STATEMENT/EIR UPDATE STATUS:
cGMP: Satisfactory (page 150)
EER: Acceptable June 22, 1998
BIO STUDY(ies)/BIOEQUIVALENCE STATUS:
Satisfactory dated August 7, 1998.
METHODS VALIDATION(Including dosage form description):
Not required; USP articles.
STABILITY(Conditions, Containers, methods):
Bio batch?

Stability specifications:

Test	Limits
Description	clear, colorless solution
Clarity of solution	clear
Sterility	meets USP requirements
pH	4.0-6.5
Degradation Products	——— nmt ——— ——— .nmt ——— Total impurities: nmt ———
Assay	USP
clarity of solution	clear
sterility	meets USP
Bacterial endotoxins[2]	nmt ——— of DS

Stability batches are the same as the test batches and containers correspond to container section.

LABELING REVIEW STATUS:

Satisfactory dated December 19, 1996. also endorsed 8/18/98
STERILIZATION VALIDATION(If Applicable): Micro acceptable 10/19/98

BATCH SIZES:

BIO BATCH(identity #, DS source):
Batch #: PD4-712
Size: ———
NDS source: ——— Batch size:

PROPOSED PRODUCTION BATCH(same manuf. process, #s, quant.)

——— Process and equipment is the same as the bio batch.

.MENTS: Approvable

DSGN
10-28-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40-140

CORRESPONDENCE

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

NDA ORIG AMENDMENT

N/A S

September 23, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
FACSIMILE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's faxed letter received September 9, 1998 covering microbiology deficiencies. Our response follows in Comment / Response format.

A. Microbiology Deficiencies:

COMMENT: "1. **Please refer to page 1-228 of the original application. Please provide extension of ——— data and justification.**

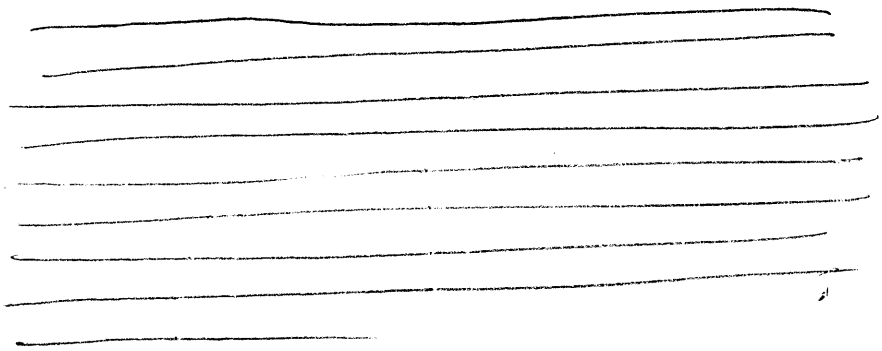
RESPONSE:

SEP 24 1998

GENERIC DRUG

Redacted 2

pages of trade secret and/or confidential commercial information



We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Leslie R. Koehler
Manager, Regulatory Affairs
Hospital Products division
Phone: (847) 938-7873
Fax: (847) 938-7867
email: Leslie.Koehler@abbott.com

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ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

July 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

NDA ORIG AMENDMENT
AF

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's faxed letter dated June 18, 1998 covering labeling deficiencies. Our response follows in Comment / Response format.

RECEIVED
JUL 21 1998
GENERIC DRUGS

COMMENT:

"Labeling Deficiencies:

1. **CONTAINER - 1 mL Carpuject - satisfactory**
2. **CARTON - 10's**
   a. **Revise the net quantity statement to read "1 mL single-dose".**
   b. **Add the statement "Discard unused portion.".**

3. **INSERT**
   a. **GENERAL COMMENTS:**
   Due to changes in the approved labeling of the listed drug (Benadryl-Park-Davis Company; revised April, 1997 and approved November 18, 1997), we ask that you revise your insert labeling as follows. In addition, other editorial changes are also indicated.
   b. **WARNINGS**
      i. **Include the following as the second paragraph:**
      Local necrosis has been associated with the use of subcutaneous or intradermal use of intravenous diphenhydramine.
      ii. **Use in**
         A) **Replace "** **with "pediatric patients" in four places including the subsection heading.**

B) Relocate the second sentence to begin as a new paragraph.

c. PRECAUTIONS - Include the following as the last subsection:
Pediatric Use
Diphenhydramine should not be used in neonates and premature infants (see CONTRAINDICATIONS).
Diphenhydramine may diminish mental alertness, or in the young pediatric patient, cause excitation. Overdosage may cause hallucinations, convulsions, or death (see WARNINGS and OVERDOSAGE).
See also DOSAGE AND ADMINISTRATION section.

d. DOSAGE AND ADMINISTRATION

i. Include the following statentent to immediately follow the section heading.
THIS PRODUCT IS FOR INTRAVENOUS OR INTRAMUSCULAR ADMINISTRATION ONLY.

ii.

A) Replace the subsection " with "Pediatric Patients, other than premature infants and neonates:".

B) Revise to read as follows:
...is 300 mg. Divide into four doses, administered intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly.

iii. Adults

A) "Adults" should appear in bold to be consistent with

B) Revise to read as follows.
...intravenously at a rate generally not exceeding 25 mg/min, or deep intramuscularly, 100 mg if required; maximum daily dosage is 400 mg.

Please revise your labels and labeling, as instructed above, and submit in final print.

Please note that we reserve the right to request further changes in your labels and/or labeling based upon changes in the approved labeling of the listed drug or upon further review of the application prior to approval.

APPEARS THIS WAY
ON ORIGINAL

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

RESPONSE: For the convenience of the Agency, we provide annotated labeling noting the changes that were made in response to the Agency request of June 18, 1998, in Exhibit I, and 12 copies final printed container, carton and insert labeling in Exhibits II, III, and IV, respectively.

We trust that this information is complete and that the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

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attachment

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APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

June 10, 1998

ORIG AMENDMENT

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

via FAX: (301)594-0180
(paper copy by mail)

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's request per a telephone conversation of June 9, 1998, between Mr. Joe Buccine, FDA, and Ms. Leslie Koehler.

We have tightened the finished product and stability specifications for the impurities as follows: ——— NMT —, ——————— NMT —, other individual NMT —— and total impurities NMT —— Sections XV, XVI.3.c and XVII.1 of the submission are amended and attached in Exhibit I.

We trust that this information is complete and that the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

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ABBOTT

NDA ORIG AMENDMENT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

May 29, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

via FAX: (301)594-0180
(paper copy by mail)

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's request per a telephone conversation of May 26, 1998, between Dr. Sayeed and Mr. Joe Buccine, FDA, and Ms. Leslie Koehler.

We have tightened the finished product and stability specifications for the impurities to more closely reflect levels seen at 12 months room temperature. The revised limits are: [redacted] NMT [redacted] NMT [redacted], other individual NMT [redacted] and total impurities NMT [redacted] Sections XV, XVI.3.c and XVII.1 of the submission are amended and attached in Exhibit I.

We trust that this information is complete and that the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

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RECEIVED
JUN 19 1998
GENERIC DRUGS

ORIG AMEN
N/AM

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

April 17, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

via FAX: (301)594-0180
(paper copy by mail)

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's request per a telephone conversation of April 15, 1998, between Dr. Sayeed, Dr. Gill, Mr. Jim Wilson, FDA, and Mr. Chris Markos. Abbott Laboratories agrees to accept 12-month expiration dating for the subject drug, until such time as a supplement to the application may be approved to extend the expiration.

Abbott Laboratories further commits to the impurities limits submitted in our correspondence of March 27, 1998, that is, [redacted] NMT [redacted] NMT [redacted] and total impurities NMT [redacted]

We trust that this information is complete and that the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

RECEIVED
APR 21 1998
GENERIC DRUGS

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LK:lk

ABBOTT

ORIG AMENDMENT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

March 27, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

via FAX: (301)594-0180
and paper copy by mail

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
TELEPHONE AMENDMENT

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's request per our telephone conversation of March 26, 1998, between Dr. Sayeed, Dr. Gill, Mr. Jim Wilson, FDA, and Dr. T. Willer and Ms. L.. Koehler, related to previously submitted impurities limits. The responses follow below in comment/response format.

COMMENT: **Please provide data on the levels of ——— and ——— for the reference listed drug.**

RESPONSE: A chromatogram is attached in Exhibit I showing no detectable amounts of the degradants at approximately 10 months prior to expiry. No inferences can be made about the levels of ——— and ——— , at expiry.

COMMENT: **Please revise your finished product and stability specifications for ——— and ——— The current limits are too high.**

RESPONSE: We have reviewed product stability information for impurities data. At the request of the Agnecy and based on this latest review, we have tightened the finished product and stability specifications for ——— and total impurities. Sections XV, XVI.3.c and XVII.1 of the submission are amended and attached in Exhibit II.

COMMENT: **We encourage you to use commercially available impurities standards for the degradants.**

RECEIVED
MAR 30 1998
GENERIC DRUGS

RESPONSE: We confirm that commercially available standard is used for [redacted] which is [redacted] However, since there is no commercial standard available for [redacted] at the time of method development, quantitation of [redacted] is performed based upon area percent relative to diphenhydramine. Use of a commercial standard will be considered.

We trust that this information is complete and the application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

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attachment

LK:lk

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

ORIG AMENDMENT

w/am

February 27, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn
Director

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL
Minor Amendment

Abbott Laboratories hereby amends the above-referenced Abbreviated New Drug Application for the subject drug. We are responding to the Agency's faxed letter dated January 8, 1998, covering chemistry and labeling deficiencies. Our responses follow below in Comment/Response format.

COMMENT: "1. **The DMF [redacted] for the drug substance, Diphenhydramine Hydrochloride, is deficient. The DMF holder is being notified about the deficiencies. Please note that a successful resolution of the deficiencies is essential prior to the approval of your application."**

RESPONSE: The DMF holder, [redacted], has responded to the deficiencies in the DMF on December 22, 1997.

COMMENT: "2. **Since [redacted] and [redacted] are formed [redacted] the drug substance in a 1:1 ratio, please explain shy the limit for [redacted] should be twice as much as that for [redacted] Please provide a description and validation data for the analytical method used for analyzing the degradation products."**

RESPONSE: [redacted]

/S/ 3-3-98

(NMT — should be twice as much as that for —— (NMT ——

Test methods and validation data used for the analysis of degradation products were provided in our amendment dated December 16, 1996, Attachment 6, pages 24-45. For your convenience, we have included a copy of pages 24-45 of our December 19, 1996, amendment in Exhibit I.

COMMENT: **"In addition, the proposed limits for —— and —— are high. Please justify by demonstrating that similar levels are observed for the reference listed drug."**

RESPONSE: The current limits for ——(NMT —) and —— (NMT —) are based upon full term 24 months controlled room temperature stability data obtained for the drug product. (Please refer to our amendment dated September 4, 1997, Exhibit 3 for the up-to-date 24 month controlled room temperature stability data for the exhibit batch, PD4-712).

[redacted]

LABELING

Twelve copies of final printed labeling are provided to reflect a —— to Abbott Laboratories. See Exhibit II.

APPEARS THIS WAY
ON ORIGINAL

We trust that this information is complete and that this application may now be approved.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867
email: Leslie.Koehler@abbott.com

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APPEARS THIS WAY
ON ORIGINAL

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

AMENDMENT
N/AM

September 4, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD # 630
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ATTENTION: Douglas Sporn
Director

Re: ANDA 40-140: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL
MINOR AMENDMENT

Abbott Laboratories hereby amends the above-referenced abbreviated new drug application dated April 7, 1995 for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL Carpuject®. We are responding to the Agency's facsimile dated June 12, 1997, regarding our correspondence dated December 19, 1996. The following comments were made:

A. Chemistry Deficiencies

COMMENT: **"Please be advised that DMF # —— is currently deficient and the DMF holder has been advised of the deficiencies. A satisfactory resolution of the DMF deficiencies is required prior to the approval of this ANDA."**

RESPONSE: We acknowledge that DMF # —— for the drug substance, Diphenhydramine Hydrochloride USP, is deficient and that a satisfactory resolution of the DMF deficiencies is required prior to the approval of this ANDA.

We note that the DMF holder, ——————————, has responded to the deficiencies in the DMF. Their response is dated July 29, 1997.

COMMENT: **"The overall impurities/degradants limits of ——, for release and stability are unacceptable. The process related drug substance impurities in the drug product can not be higher than the related substance limits established in the drug substance. Please revise**

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GENERIC DRUGS

/S/

these limits, also revise the limits for the degradation products to be closer to the observed values."

RESPONSE: We have tightened the overall impurities/degradants limits for release and stability from NMT — to NMT —, based upon 24-month controlled room temperature stability data. (Please refer to Exhibit 1 and Exhibit 2.) The total limits of NMT — for impurities/degradants include — NMT —, — NMT — (which was tightened from NMT —, and other individual NMT — (which was tightened from NMT —.

[redacted] Therefore, the established limits for these impurities are set higher to allow limited degradation.

Exhibit 3 contains the up-to-date 24-month controlled room temperature stability data for the exhibit batch (PD4-712).

B. "In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

COMMENT: **The firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval. The evaluation report from the Division of Manufacturing and Product Quality is pending at this time."**

RESPONSE: We note and acknowledge that the firms referenced in the application relative to the manufacture and testing of the product must be in compliance with cGMPs at the time of approval. We also note and acknowledge that the evaluation report from the Division of Manufacturing and Product Quality is pending at this time.

Abbott Laboratories hereby certify that we have sent a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas FDA District Office.

We trust that this information is complete.

Sincerely,

ABBOTT LABORATORIES

Leslie Koehler
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 938-7873
FAX: (847) 938-7867

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APPEARS THIS WAY
ON ORIGINAL

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December 19, 1996

VIA FEDERAL EXPRESS

Mr. Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

NDA ORIG AMENDMENT
N/AC FPL

MAJOR AMENDMENT

Re: ANDA 40-140
Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (Carpuject®)

Dear Mr. Sporn:

Reference is made to our abbreviated new drug application dated April 7, 1995, as amended May 8 and 12, 1995, for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL Carpuject®.

Reference is also made to Dr. Rashmikant Patel's correspondence dated February 23, 1996. Contained herein, please find our reponse to Dr. Patel's letter in **comment**/response format. For your convenience, we have included a copy of the February 23, 1996 correspondence immediately following this letter.

A. Chemistry Deficiencies

1. **The DMF ' —— for the drug substance, Diphenhydramine Hydrochloride, is deficient. The DMF holder is being notified about the deficiencies. Please note that a successful resolution of the deficiencies is essential prior to the approval of your application.**

   We acknowledge that DMF —— for the drug substance, Diphenhydramine Hydrochloride USP, is deficient and that a successful resolution of the deficiencies is essential prior to the approval of our application.

   We note that the DMF holder ——————————————— ——————————), has responded to the deficiencies in the DMF and amended DMF # ——. Copies of the cover letters to the Agency are contained in Attachment 1.

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GENERIC DRUGS

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7. **The stability report does not list the batch number of the product placed on stability. Please provide this information.**

The product batch number placed on stability is identified on the stability summary forms as "Control Number". The batch number of the product placed on stability is PD4-712. The suffixes " [redacted] ' distinguish the type of [redacted] used for the stability study.

Updated controlled room temperature stability data for the test batch, PD4-712, is provided in Attachment 9.

B. Labeling Deficiencies

[redacted]

Carton: (Box of 10s)
In accordance with the Agency's request, the statement "Retain in carton until time of use" has been added to the carton labeling in conjunction with the "Protect from light" statement. Please refer to Attachment 11 for the revised final printed carton labeling; twelve copies are provided.

Insert
Regarding the innovator's warning statement about manufacturing with [redacted] in the manufacturing of this proposed product.

The *contraindications* and *dosage and administration* sections of the package insert labeling have been revised in accordance with the Agency's comments. Twelve copies of final printed insert labeling are contained in Attachment 12.

[redacted] hereby certifies that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA District Office, and a true copy of this submission to Mr. W. Michael Rogers of the Lenexa, Kansas, FDA District Office, as per Mr. Warner's instructions.

This document consists of Confidential and/or Trade Secret information subject to 18 U.S.C. 1905 and to which all claims of Privilege and Confidentiality are asserted in both statutory and common law.

If you require any clarification or further information, please call Mr. Yau-Kit Lam, Manager CMC, at (212)-551-4219.

Sincerely,

Yau Kit Lam

for Gilbert W. Adelstein, Ph.D.
Associate Director, CMC
Drug Regulatory Affairs

APPEARS THIS WAY
ON ORIGINAL

4/0140

ANDAs (see attached list)

Abbott Laboratories
Attention: David T. Guzek
D-389, Bldg, AP30
200 Abbott Park Road
Abbott Park, IL 60064-3537

JUL 29 1997

Dear Sir:

We acknowledge receipt of your communications dated June 18, 1997, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the attached list of abbreviated applications.

Your letters detail the [redacted] of these pending unapproved applications [redacted], to Abbott Laboratories.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of these applications once they become approved.

The material submitted is being retained as part of your applications.

Sincerely yours,

/S/ 7/29/97

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ATTACHMENT

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ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

June 18, 1997

NEW CORRESP
NC

Noted:
NAE /S/
7/29/97

CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF GENERIC DRUGS, HFD #630
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855

ATTENTION: Douglas Sporn, Director

RE: ANDA 40-140 Diphenhydramine HCl Injection, USP, 50 mg/mL

Abbott Laboratories hereby provides notification per 21 CFR 314.72 that on June 10. 1997, [redacted] of the subject approved application has taken place. As of that day, the [redacted] to Abbott Laboratories, North Chicago, Illinois.

Per 21 CFR 314.72(a)(2), Abbott Laboratories commits to agreements, promises, and conditions made by the [redacted] and has obtained and has on file, a copy of the application including supplemental applications.

Please use the address below for further correspondence:

David T. Guzek, Director HPD Regulatory Affairs
Abbott Laboratories
200 Abbott Park Road, D-389, AP30
Abbott Park, IL 60064

We trust that this information application is complete.

Sincerely,

ABBOTT LABORATORIES

David T. Guzek

David T. Guzek, Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3216
FAX: (847) 938-7867

DTG/dg
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Attachment

RECEIVED
JUN 20 1997
GENERIC DRUGS

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ANDA 40-140

FEB 23 1996

Dear Madam:

This is in reference to your abbreviated new drug application dated April 7, 1995, submitted pursuant to Section 505(j) of the Federal food, Drug, and Cosmetic Act, for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL carpuject.

Reference is also made to your amendments dated May 8 and 12, 1995.

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

A. Chemistry Deficiencies

1. The DMF # ——— for the drug substance, Diphenhydramine Hydrochloride, is deficient. The DMF holder is being notified about the deficiencies. Please note that a successful resolution of the deficiencies is essential prior to the approval of your application.

2.

In addition, please add specifications for the residual solvents to your release specifications for the drug substance.

3. You have not provided any particulate matter specification for the release of drug product. Please add the particulate matter specification to

your release specifications.

4. Please provide individual and total impurities limits for the release and stability of the drug product.

5. The stability protocol (page 469) provides for testing of the first three production lots using containers provided with stoppers either from [redacted] or [redacted] Please revise your stability protocol to include testing for both. Similarly, the yearly testing should be conducted on containers with stoppers [redacted] by [redacted]

6. We note that the stability report contains test results for description, assay and pH, but the stability test protocol (p 470) does not include testing for these parameters. Please revise your stability protocol in conformance with the stability report.

   In addition, please specify in your stability protocol the position in which the carpujects are to be stored for stability studies.

7. The stability report does not list the batch number of the product placed on stability. Please provide this information.

B. Labeling Deficiencies

Container: (1 mL Carpuject®)

Carton: (Box of 10s)

Add the following statement to appear in conjunction with the "Protect from light" statement: "Retain in carton until time of use".

Insert:

1. GENERAL

   Please note, a **WARNING** about manufacturing with labeling. If there is a need for such a warning with your product, please include and/or comment.

2. CONTRAINDICATIONS

   Revise the subsection heading to read " rather than "**Nursing Mothers.**"

3. DOSAGE AND ADMINISTRATION

   In line 9, "**Adults**" is to appear in bold to be consistent with

Please revise your container labels, carton labeling, and package insert labeling, then prepare and submit final printed labels and labeling.

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. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

Sincerely yours,

/S/ 2/23/96

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

40-140

/S/

ANDAs See Attachment

DEC 22 1995

Dear Madam:

This is in reference to your supplemental new drug applications dated May 12, 1995, submitted pursuant to 21 CFR 314.70, regarding your abbreviated new drug applications for the products listed in the attachment.

The supplemental applications provide for the discontinuance of the use of [redacted] in the Carpuject [redacted]

We have completed the review of these supplemental applications and they are approved.

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

The material submitted is being retained in our files.

Sincerely yours,

/S/ 12/19/95

Frank O. Holcombe, Jr., Ph.D.
Director
Division of Chemistry II
Office of Generic Drugs
Center for Drug Evaluation and Research

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pages of trade secret and/or confidential commercial information

ANDA 40-140

[ ] JUN 2 1995

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to our "Refuse to File" letter dated April 28, 1995, and your amendment dated May 8, 1995.

NAME OF DRUG: Diphenhydramine Hydrochloride Injection USP, 50 mg/mL (syringe)

DATE OF APPLICATION: April 7, 1995

DATE OF RECEIPT: April 10, 1995

DATE ACCEPTABLE FOR FILING: May 9, 1995

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

James Wilson
Consumer Safety Officer
(301) 594-0310

Sincerely yours,

6/2/95

/S/

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOAVAILABILITY

AMENDMENT

N/AC

MAY 0 8 1995

ANDA 40-140

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Sir/Madam:

Reference is made to our original Abbreviated New Drug Application for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL Carpuject®, submitted on April 7, 1995.

Reference is also made to your letter dated April 28, 1995, wherein you request a side-by-side comparison of our proposed formulation with that of the reference listed drug. Attached are the side-by-side formulations. There are no differences.

We hereby certify that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA district office, and a true copy of this correspondence to the Kansas City, KS FDA district office, as per Mr. Warner's instructions.

Your attention to this application is greatly appreciated. If you have any inquiries, please contact me at (212) 551-4219.

Sincerely,

RECEIVED

MAY 0 9 1995

GENERIC DRUGS

ANDA 40-140

APR 28 1995

Dear Madam:

Please refer to your abbreviated new drug application (ANDA) dated April 7, 1995, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, (syringe).

We have given your application a preliminary review, and we find that it is not sufficiently complete to merit a critical technical review.

We are refusing to file this ANDA under 21 CFR 314.101(d)(3) for the following reason:

> You must provide information demonstrating that the inactive ingredients in the proposed drug product are **qualitatively** and **quantitatively** the same as those in the reference listed drug. If any differences do exist, you must identify and characterize the differences and provide information demonstrating that the differences do not affect the safety of the proposed drug product [314.94(a)(9)(iii)]. This information to demonstrate safety should include, but is not limited to: (a) examples of approved drug products administered by the same route of administration which contain the same inactive ingredients, and that are within the same concentration range, (b) a description of the purpose of the inactive ingredients when different inactive ingredients are included in the proposed drug product, (c) a comparison of the physical and chemical properties (e.g. pH, osmolarity, tonicity) of the proposed drug product with that of the reference listed drug, and (d) information to show that the inactive ingredients do not adversely affect these properties. Please include a side-by-side comparison of your proposed formulation with that of the reference listed drug.

Thus, it will not be filed as an abbreviated new drug application within the meaning of Section 505(j) of the Act.

Within 30 days of the date of this letter you may amend your application to include the above information or request in writing an informal conference about our refusal to file the application. To file this application over FDA's protest, you must avail yourself of this informal conference.

If after the informal conference, you still do not agree with our conclusion, you may make a written request to file the application over protest, as authorized by 21 CFR 314.101(c). If you do so, the application shall be filed over protest under 21 CFR 314.101(b). The filing date will be 60 days after the date you requested the informal conference. If you have any questions please call:

William Russell
Consumer Safety Officer
(301) 594-0315

Sincerely yours,

/S/ 4/28/95

Yana Ruth Mille
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-140
cc: DUP/Jacket
Division File
HFD-82
Field Copy
HFD-600/Reading File
HFD-615/MBennett

Endorsement: HFD-615/PRickman, Acting Chief /S/ 4/20/95 date
HFD-615/WRussell, CSO /S/ 4/20/95 date
HFD-610/JPhillips, Chief, LRP /S/ 4/20/95 date
HFD-623/RKishore, Sup.Chem. /S/ 4/24/95 date
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F/T by CMI 4-20-95
ANDA Refuse to File!

APR 07 1995

MICRO/STERILITY ASSURANCE INFORMATION ENCLOSED

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, Maryland 20855-2773

Dear Sir/Madam:

Submitted herewith in duplicate, under 21 CFR 314.50 is an original Abbreviated New Drug Application for Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL Carpuject®.

Diphenhydramine Hydrochloride Injection is listed in "Approved Drug Products with Therapeutic Equivalence Evaluations," 14th Edition, page 3-99. A copy appears in Section II.

The active ingredient, indications, concentration, route of administration, and conditions of use for Diphenhydramine Hydrochloride Injection, are the same as those of the innovator's product, Benadryl®, manufactured by Parke-Davis, Division of Warner-Lambert Co. Comparative information is attached in Section IV.

The labeling is the same in content as that of the innovator's drug Benadryl®, except for changes that are necessary due to a change in manufacturer and editorial changes. A copy of the innovator's package insert is provided in Section V for your convenience.

The first — production batches of Diphenhydramine Hydrochloride Injection USP, 50 mg/mL, 1 mL fill in 2 mL Carpuject®, will be placed into our stability program and reported at regular intervals for as long as necessary to support the proposed 24-month expiration date. Furthermore, we agree to withdraw from the market any batch found to fall outside the specifications for this product.

The Sponsor of this Abbreviated New Drug Application is [redacted]. The product is manufactured at the [redacted], which is registered under the name [redacted]. However, the product, when approved, will be marketed by [redacted] which is an affiliate of [redacted] The labeling included in this application reflects the name [redacted] There may be internal documents and correspondence to/from vendors and contract facilities that reflect the old name [redacted] and the name [redacted] which is an affiliate of [redacted] Please be aware of this when reviewing the application.

RECEIVED
APR 10 1995
GENERIC DRUGS

We hereby certify that we have sent a true copy of this cover letter to Mr. Edward T. Warner, District Director of the New York FDA district office, and a true copy of this original submission to the Kansas City, KS FDA district office, as per Mr. Warner's instructions.

Any inquiries concerning this Abbreviated New Drug Application should be addressed to:

[ ]

Your attention to this application is greatly appreciated.

Sincerely,

[ ]

LLN/ST:ls