CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-146

Administrative Documents

Section VI. Patent Certification

Appended are the Patent Certification and Exclusivity Statements per 314.94(a)(12) and 314.94(a)(3), respectively, for the subject drug.

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

PATENT AND EXCLUSIVITY INFORMATION

1. Active Ingredient(s): Atropine Sulfate

2. Strength(s): 0.1 mg/ mL and 0.05 mg/mL

3. Trade Name: Atropine Sulfate Injection, USP
(Atropine Sulfate Injection, USP in Plastic Syringe)

4. Dosage Form: Injectable solution
Atropine Sulfate, 5 mL and 10 mL

5. Route of Administration: Subcutaneous, Intramuscular and Intraveous administration

6. Applicant Firm Name: Abbott Laboratories

7. NDA Number: 21-146

8. Approval Date: To be determined.

9. Exclusivity - Date first NDA could be approved and length of exclusivity period:

None

10. Applicable patent numbers and expiration date of each:

None

Per 21 CFR 314.94 (a) (12), this is a "Paragraph II Certification" stating that the patent has expired.

Jessie Y. Lee 12/15/99

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-3537

Date

Section V. Patent Information

Per current edition of *Approved Drug Products with Therapeutic Equivalence Evaluations* (Orange Book), this drug product is not subject to patent and exclusivity.

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ON ORIGINAL

APPEARS THIS WAY
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EXCLUSIVITY SUMMARY FOR NDA # 21-146 SUPPL #_____

Trade Name _____ Generic Name Atropine Sulfate Injection, USP, Plastic Syringe

Applicant Name Abbott Laboratories HFD # 110

Approval Date If Known Not known

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /☒/ NO /☐/

b) Is it an effectiveness supplement?

YES /☐/ NO /☒/

If yes, what type? (SE1, SE2, etc.) _____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /☒/ NO /☐/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /☐/ NO /☒/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /☐/ NO /☒/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO- please indicate as such)

YES /☐/ NO /☒/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /☐/ NO /☒/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /☒/ NO /☐/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 17-106 Atropine

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /☐/ NO /☒/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # _____ YES /___/ ! NO /___/ Explain: _____
!
! _____

Investigation #2 !
!
IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____
!
!

Investigation #2 !
!
YES /___/ Explain _____ ! NO /___/ Explain _____
!
_____ ! _____
!
_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____ _____

Signature Date

Title: Consumer Safety Officer

_____ 12/18/00

Signature of Office Date

Division Director

cc: Original NDA Division File HFD-93 Mary Ann Holovac

FDA Links Tracking Links Check Lists Searches Reports Help

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements) View Word Document

NDA Number:	021146	**Trade Name:**	ATROPINE SULFATE INJ 0.1MG/ML(5/10ML)0.0
Supplement Number:	000	**Generic Name:**	ATROPINE SULFATE INJ 0.1MG/ML(5/10ML)0.0
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	AS AN ANTIISIALOGOGUE FOR PREANESTHETIC MEDICATION TO PREVENT OR REDUCE SECTIONS OF THE RESPIRATORY TRACT
Action Date:	12/20/99		

Indication # 1 Atropine Sulfate Injection, USP is indicated when excessive (or sometimes normal) muscarinic effects are judged to be life threatening or are producing sumptoms severe enough to call for temporary, reversible muscaminc blockade.

Label Adequacy: Does Not Apply

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date
0 years	18 years	Waived	12/20/00

Comments: The Division is waiving the pediatric requirement for all pediatric age groups. In his memo, Dr. Lipicky states" This is not a new chemical entity, and this NDA is not the culminiation of a modern development plan. The pediatric requirement should not be imposed upon what is simply a chemistry supplement, namely a change in container. Atropine was not included in this Division's list of drugs that needed pediatric trials."

Indication # 2 N/A. See above.

Label Adequacy: Does Not Apply

Forumulation Needed: NO NEW FORMULATION is needed

Comments (if any):

Lower Range	Upper Range	Status	Date

This page was last edited on 12/18/00

Signature _____ 12/18/00 Date

Section VIII. Debarment Certification

Attached are the debarment certification for this application and the list of relevant convictions for persons debarred or not debarred.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

ABBOTT

CERTIFICATION REQUIREMENT FOR ALL APPLICATIONS

FOR APPROVAL OF A DRUG PRODUCT

CONCERNING USING SERVICES OF DEBARRED PERSONS

Under the new law, any application for approval of a drug product submitted on or after June 1, 1992, must include:

"a certification that the applicant did not and will not use in any capacity the services of any person debarred under subsections (a) or (b) [section 306(a) or (b)], in connection with such application."

Abbott Laboratories hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

Jessie Y. Lee

12/15/99

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
D-389. AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

Date

ABBOTT

LIST OF RELEVANT CONVICTIONS FOR

PERSONS DEBARRED OR NOT DEBARRED

Per letter from the Office of Generic Drugs dated January 15, 1993, abbreviated applications must contain a list of relevant convictions, as described in section 306(a) and (b) of the GDEA*, of the applicant and affiliated persons (i.e., contractors, et. al.) responsible for the development or submission of the application, which have occurred within five years before the date of the application. Firms with no convictions to list should submit a statement to that effect.

Abbott Laboratories states that it has no such convictions to list.

*Generic Drug Enforcement Act of 1992
Section 306(k) (1) of the act (21 USC 335a(k) (1)).

Jessie Y. Lee

12/15/99

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Road
Abbott Park, Illinois 60064-3537

Date

ABBOTT

REQUEST FOR WAIVER

FINANCIAL DISCLOSURE

No specific clinical studies were sponsored or funded by Abbott Laboratories in support of NDA 21-146, Atropine Sulfate Injection, Plastic Syringe.

Jessie Y. Lee

5/9/00

Jessie Y. Lee, Ph.D.
Manager, Regulatory Affairs
Hospital Products Division
D-389, AP30
Abbott Laboratories
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION **Public Health Service**
Division of Cardio-Renal Drug Products

Memorandum

DATE : December 18, 2000

FROM : Raymond J. Lipicky, MD
Director, Division of Cardio-Renal Drug Products, HFD-110

SUBJECT: Approval of NDA 21-146, Atropine Sulfate in Plastic Syringes, Abbott Laboratories

TO : NDA File

Introduction

Abbott has marketed the identical drug and formulation since before 1938, however it initially was and still is marketed in glass syringes. Since initial marketing was prior to 1938, continuation of marketing did not require and still would not require submission of an NDA, provided the container (the syringe) remained glass.

Atropine has been and still is in common use in medical practice throughout the world. It is an alkaloid initially derived from belladonna plants and belongs to the pharmacological class of "belladonna alkaloids." Preparations of belladonna plants were used by ancient Hindus and have been in medicinal use for centuries. Initial studies of the pharmacology of purified atropine date back to 1831. Indeed, atropine and other belladonna alkaloids represent the oldest drugs in clinical medicine, and can hardly be considered a new molecular entity.

Atropine is a highly selective, reversible, competitive antagonist of acetylcholine at muscarinic receptors (hence the classification as an anti-muscarinic) existing on smooth and cardiac muscle and exocrine gland cells. Atropine also blocks muscarinic receptors in the central nervous system (CNS), but the overt CNS effects of atropine are complex and differ depending upon dose. Being a specific antagonist of muscarinic receptors, its pharmacology has been studied extensively and atropine was the drug that helped classify the autonomic nervous system. Atropine's use in clinical medicine has not been studied in clinical trials as we know them today, rather its use has been part of the evolution and culture of medicine for hundreds of years. The class of belladonna alkaloids has not been well studied through clinical trials, but there are at least 18 currently marketed products (a rough count from the PDR), for a variety of uses, that have atropine as one of the ingredients. For other examples, scopolamine, another belladonna alkaloid, is marketed as a transdermal formulation for the treatment of motion sickness, and homatropine, another belladonna alkaloid, is marketed for the treatment of cough.

The toxicity (safety) of atropine (and other belladonna alkaloids) is similarly well known, being one of the first syndromes taught in Pharmacology courses that I was responsible for, several decades ago. The syndrome is characterized by excitement and maniacal

tendencies, fever, hot and dry skin, dilated pupils and tachycardia. The full blown syndrome, usually not fatal, occurs at doses of several hundred milligrams (a non-fatal case from 1000 mg has been reported (Goth, Medical Pharmacology, 5th Edition). The usual dose of atropine is in the order of 0.5 mg, with doses as great as 6 mg recommended for the treatment of organophosphate poisoning. Safety is well established, based on common experience, the evident **200-fold** human safety margin, and the well described and easily recognized "textbook" syndrome of clinical toxicity.

The Current NDA

In NDA 21-146, Abbott proposes to market the identical formulation (the one marketed for over half a century) in plastic syringes (rather than the glass syringes currently marketed). The only change in the product is the container, from glass to plastic. Had Abbott's atropine been marketed under an approved NDA, to change the container of the formulation would not have required submission of an NDA. The change in container would have simply been a chemistry supplement, and would not have resulted in a change to labeling other than in the "How Supplied" section.

Since there is no existing approved NDA for the Abbott product, there could not be a chemistry supplement to the approved NDA. A new NDA (21-146) was the only vehicle available for Abbott's request for a container change.

That atropine causes dryness of the mouth (antisialagogue effect), an increase in heart rate (except at low doses, particularly when a slow heart rate is due to excess vagal tone), dilates pupils, produces decreased accommodation, and decreases sweating are all beyond reasonable question. Such effects are well documented by common experience (although incompletely documented by published systematic human study; but well documented in animal experimental literature - exception being sweating) and are the predominant signs and symptoms of atropine poisoning.

If one defines efficacy, for purposes here, as having shown that any of these pharmacological effects of atropine produce some form of clinical benefit, ordinarily one would depend upon results from some kind of clinical trial designed to evaluate the effects of atropine on clinical outcome. Such trials supporting use of atropine are not available, or at least were not found by either Dr. Fredd in his review or by the sponsor. For example, two common uses are briefly summarized, pre-operative use (antisialagogue effects) and cardiac rhythm effects.

Antisialagogue effects

Out of 10 articles submitted by Abbott, two controlled clinical trials (one published in 1976 and another in 1979) comparing atropine to placebo were identified. Each concluded that the routine use of atropine was not supported by the study results. The other 8 were review articles, recommendations or textbook citings.

Cardiac rhythm effects

Out of 26 articles submitted, one (published in 1997) compared atropine to placebo for prevention of vaso-vagal reactions during removal of femoral arterial sheaths (atropine was favored, p = 0.03), the remaining 25 articles simply made recommendations or were open-label, baseline-controlled studies of something or another.

The picture is much the same for each of the other indications currently in labeling.

Other Atropine-Approved NDAs

AtroPen is a parenteral atropine sulfate marketed in syringes for the treatment of organophosphorous or carbamazate insecticide poisoning. I am not familiar with the basis for that approval but know that it was the formulation used during the "Desert Storm" military venture several years ago.

Enlon-Plus is marketed as a parenteral fixed dose combination of edrophonium and atropine sulfate used to reverse the effects of nondepolarizing neuromuscular blocking agents. Atropine is present to reverse the muscarinic effects produced by edrophonium. I am similarly unfamiliar with the basis for that approval, but am confident that atropine would produce the anticipated effects and that it could be easily titrated to clinically measurable endpoints.

According to regulations, as pointed out by Dr. Fredd, should the same indications be sought, there is no need to support such uses by studies, only indications other than already approved indications need be championed. Thus, the glass syringe atropine sulfate proposed by Abbott is approvable for at least those two indications, without any need for thought or justification.

A "Usage" Problem

The proposed for marketing (plastic) and the currently marketed (glass) syringes and contents are as follows (3 different syringes):

Adult dosing forms

Syringe Volume	Atropine Concentration	Total Atropine Content
5 mL	0.1 mg/mL	0.5 mg
10 mL	0.1 mg/mL	1 mg

Pediatric dosing form

Syringe Volume	Atropine Concentration	Total Atropine Content
5 mL	0.05 mg/mL	0.25 mg

In practical use this translates to:

Adults

Usage	Usual Dose (mg)	Volume to Inject (cc)	
		5 mL syringe	10 mL syringe
Antisialagogue	0.5	5	5
BradyArrhythmia	0.5	5	5
Anticholinergic	2	20	20
Antidote (Organo-)	6	60	60

It appears from simple cursory examination of the above tables, that the concentrations in the adult syringes do not lend themselves to any convenient means of dosing (other than intravenously, where the volume infused is relatively unimportant, usually). How this formulation has survived the 30 odd years of marketing is not within my comprehension. Nonetheless, it has survived. Even more than that, it is the only formulation of atropine available, except for AtroPen (which has a concentration of 6 mg/cc, which is equally inconvenient).

I won't bother to comment upon the pediatric dosing. There is nothing but conventional usage to guide anyone here.

Pediatric Requirements

This is not a new chemical entity, and this NDA is not the culmination of a modern development plan. The pediatric requirement should not be imposed upon what is simply a chemistry supplement, namely a change in container. Atropine was not included in this Division's list of drugs that needed pediatric trials. Consequently, the pediatric requirement is hereby waived.

Summary and Action to Take

There is no clinical trial database that can be cited or analyzed in some innovative way that could form the basis of approval. Similarly, there is no clinical trial database that can be cited that demonstrates that the common clinical use of atropine is "unsafe". I cannot conceive of anyone thinking that atropine should be removed from the market (contained in glass or in plastic).

Nonetheless, with respect to this NDA (which is only sort of an NDA, had this formulation been previously approved this entire NDA would simply be a chemistry supplement), an action could be to issue a non-approvable letter. Of course, were we to do that, the very formulation we state is not approvable would continue to be marketed (in a less desirable container, namely glass). That would neither serve nor hinder any public health need. It would simply be a ridiculous action (in my judgement), but would be able to be defended from a strict interpretation of regulation.

Consequently, the action that should be taken is to approve this NDA, as suggested by the primary Medical reviewer, Dr. Fredd. Public health will certainly not be adversely affected. In fact public health may be favorably affected because there will be less glass to break (broken glass has a finite, but not clearly measurable, adverse effect). Atropine has been in use for centuries; I would declare it a medical necessity were its availability suddenly threatened by lack of supply. Consequently, a "medical need" will be satisfied.

The labeling is very old (pre 1938) and obviously needs "touching-up". I do not think it is worth our time, at the present time, to re-write the entire package insert. Perhaps this can be undertaken as some future date. There are some changes (see below) to the labeling proposed by Abbott.

Labeling

By section, my labeling comments:

Title and concentrations etc. in Bold on page 1

I have no changes I would make. If the chemists have suggestions, they should be incorporated (but please FAX those suggestions to me, so I know what they are).

Description page 1 and 2.

I have no changes I would make. If the chemists have suggestions, they should be incorporated (but please FAX those suggestions to me, so I know what they are).

Clinical Pharmacology pages 2 and 3

I do no wish to make any changes, at the present time. If Biopharmaceutics has anything they wish to add or modify, incorporate their suggestions (but please FAX those suggestions to me, so I know what they are).

Indications and Usage page 4

Should be replaced entirely by the following. Please note that I have not changed the formatting that they chose to use in their initial submission.

INDICATIONS AND USAGE.

Draft

DRAFT

Contraindications, Warnings, Precautions, Carcinogenesis, Mutagenesis, Impairment of Fertility pages 4 and 5

I have no changes I want to make. The pharamacologists may have thoughts that should be incorporated (but please FAX those suggestions to me, so I know what they are).

Pediatric Use

The proposed wording should be replaced entirely by the following.

Safety and effectiveness in pediatric populations have not been established.

Adverse Reactions and Overdosage pages 5 and 6

I have no changes that I would like to make.

Dosage and Administration page 7

Abbott's proposed labeling should be replaced in its entirety by what follows.

DOSAGE AND ADMINISTRATION

DRAFT

Adults

DRAFT

Titration intervals of one or two hours are recommended in circumstances that are not life-threatening.

Children

DRAFT

How Supplied (page 8)

I have no changes I would like to make. The chemists may have thoughts and such should be incorporated (but FAX me the suggestions).

The letter to the sponsor

This letter should be an Approvable letter, with send in final printed labeling like the enclosed marked-up draft clause.

It should also say:

> The DOSAGE AND ADMINISTRATION section needs some input from you. The draft labeling we have attached is being supplied as an initial draft and outline of concept. Note that it has no specifics, it contains ranges and guides only. The pediatric dosing is very difficult to get out of your submission; none-the-less some such instructions should be included. Please point out, in your response, where in your submission you find the information that leads to your choices. I recommend that you contact the Division to arrange a teleconference before you try to re-write the DOSAGE AND ADMINISTRATION section.

APPEARS THIS WAY
ON ORIGINAL

TELEPHONE MEMORANDUM

DATE:	July 6, 2000 and July 11, 2000
NDA:	21-146
APPLICANT:	Abbott Laboratories, Hospital Division
CONTACT PERSON	Jonathan Dohnalek Ph.D., Regulatory Affairs
INITIATED BY	Abbott (847)-937-3413

Dr. Dohnalek replaces Jessie Lee as manager of NDA 21-146. Jessie Lee has left Abbott.

Empathizes was placed on the importance of expediting the submission of CMC information by to update the DMF. CMC information and Abbott to update the impurity method(s) for the API and drug product in NDA 21-146.

FDA does not know what information will be sent and what revisions will make in manufacturing and controls. A letter was issued informing them that the DMF is deficient and should be updated. An acceptable review of the DMF is necessary for the approval of the NDA 21-146. Previous T. Com contact was with Abbott a month ago concerning these issues as well as on May 7, 2000 and July 6, 2000 which Jonathan Dohnalek was a participant. FDA is concerned about meeting their required time goals.

Dr. Dohnalek will not be able to contact Abbott purchasing until July 12, 2000 to request they contact the DMF holders. Abbott will work out the details.

NDA 21-146 Atropine Sulfate Injection, Abbott Laboratories Inc., and DMF( ) API supplier July 11, 2000

Abbott should be requested to address the issues

1- The type II DMF Holder that is referenced for the drug substance is currently deficient and needs to be updated.

   The DMF Holder has stated that they will amend the DMF but has not given specifics or a timeframe for this amendment.

   Since approval of the NDA depends on a satisfactory DMF, please request the DMF Holder to submit the amendment ASAP so we can continue our review.

2- Abbott's specifications for drug substance and drug product should include acceptance criteria for impurity/ degradation products using more sensitive methods than presently submitted as discussed with Jonathan Dohnalek, Ph. D. The drug product specification for degradation products should be valid over the shelf life of the product and be reflected in the stability protocol.

Please refer to the February 2000 Final Guidance

Guidance for Industry NDA's Impurities in Drug Substances

Telecon 7/13/2000 -

CSO Package Overview

Date:	July 5, 2001
Application:	NDA 21-146 Atropine Sulfate Injection, USP, Plastic Syringe
Applicant:	Abbott Laboratories
Classification:	5S
User Fee Goal Dates:	October 20, 2000 (primary) December 20, 2000 (secondary)

Background

This is a new NDA submission where Abbott Laboratories, Inc. is seeking approval for Atropine Sulfate Injection, USP, Plastic Syringes (0.1 mg/mL in a 5 or 10 mL plastic syringe, and 0.05 mg/mL in a 5 mL syringe). Since Atropine is a pre-1938 drug, Abbott has been marketing Atropine Sulfate Injections in a glass syringe without an approved NDA. The change to a plastic container does require NDA approval. An approvable letter was sent to the Sponsor on December 19, 2000.

Labeling

Since the approvable letter of December 19, 2000, the sponsor submitted final printed labeling (package insert and immediate container and carton labels) on March 30, 2001. This labeling incorporates changes requested by the Division in the approvable letter and further changes requested by the Sponsor as documented in a memo dated January 23, 2001.

CSO Summary

I have completed review of the final printed label and circulated the results of this review to the appropriate technical reviewers (Drs. Robbie, Srivivasachar, and Fredd). To my knowledge, there are no outstanding issues that would preclude taking an action on this application. An "approval" letter has been completed, reviewed, and approved by Dr. Lipicky.

RPHM Review of Final Printed Labeling
NDA 21-146

Date of Submission:	March 30, 2001
Date of Review:	June 6, 2001
Product:	Atropine Sulfate Injection (Ansyr® Plastic Syringe)
Sponsor	Abbott Laboratories

Introduction

This final printed labeling was submitted in response to the "Approvable" letter issued on December 19, 2000, with suggested revisions to the draft labeling submitted with the original NDA submission.

On January 9, 2001, the Sponsor submitted a FAX with draft labeling for Dr. Lipicky's review that contained all of the suggested revisions from the December 19, 2000 letter, but included the following additions:

- "Dosage and Administration" section, first paragraph – The Sponsor replaced the first sentence of the FDA recommended text which stated, '

  with the following text, "Atropine Sulfate Injection, USP in the Ansyr Syringe is intended for intravenous use."

- "Dosage and Administration" section, second paragraph – After the second paragraph, the Sponsor added the following text,

  "When the recurrent use of atropine is essential in patients with coronary artery disease, the total dose should be restricted to 2 to 3 mg (maximum 0.03 to 0.04 mg/kg) to avoid the detrimental effects of atropine-induced tachycardia on myocardial oxygen demand. For patients with bradyasystolic cardiac arrest, a 1 mg dose of atropine is administered intravenously and is repeated every 3-5 minutes if asystole persists. Three milligrams (0.04 mg/kg) given IV is a fully vagolytic dose in most patients. The administration of this dose of atropine should be reserved for patients with bradyasystolic cardiac arrest. Administration of less than 0.5 mg can produce a paradoxical bradycardia because of the central or peripheral parasympathomimetic effects of low doses in adults. Endotracheal administration of atropine can be used in patients without IV access. The recommended adult dose of atropine for endotracheal administration is
  diluted to a total not to exceed 10 mL of sterile water or normal saline.

Dr. Lipicky approved these changes, but in response to the FAX of January 9th, Dr. Lipicky requested the Sponsor make the following additional changes:

- "Dosage and Administration" section, first paragraph – The Sponsor suggested the following statement, "Atropine Sulfate Injection, USP in the Ansyr Syringe is intended for intravenous use." Dr. Lipicky requested the statement to say, "Atropine Sulfate Injection, USP in the Ansyr Syringe is intended for intravenous use, but may be administered subcutaneously or intramuscularly."

- "Dosage and Administration" section, new paragraph – Add a paragraph break before the 6th sentence ("Endotracheal administration of atropine can be used...") of the new paragraph.

These requested changes were communicated to the Sponsor by phone, were agreed to, and documented in a memo dated January 23, 2001.

Evaluation

I have reviewed the package insert and found that all changes requested by the Agency were made. Also, the Sponsor made the following changes:

- The trademark symbol (™) was replaced with a registered trademark symbol (®) after the word "Ansyr" every time the word was utilized.
- Instead of the word " Abbott utilized the term "pediatric" or "pediatric population".

Recommendation:

I recommend that the Division issue an approval letter, as all changes made in the final printed labeling were minor.

/S/

{See appended electronic signature page}

John Guzman
Regulatory Health Project Manager

cc: orig NDA 21-146
HFD-110
HFD-110/Blount
HFD-110/Guzman

8 pages redacted from this section of the approval package consisted of draft labeling

MEMORANDUM

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

DATE: January 23, 2001

TO: NDA 21-146 File

FROM: John Guzman, Consumer Safety Officer, HFD-110

PRODUCT: NDA 21-146, Atropine Sulfate Injection, USP, Plastic Syringe

SUBJECT: **Labeling comments by Dr. Lipicky regarding Abbott's draft labeling.**

On January 9, 2001, Abbott Laboratories sent in a FAX with draft labeling in response to the "Approvable" letter with suggested labeling sent on December 19, 2000. Dr. Lipicky reviewed the draft labeling included in the January 9, 2001 FAX and requested two changes:

- DOSAGE AND ADMINISTRATION section:

  Abbott had suggested the following opening sentence:

  Dr. Lipicky requested the following change
  *"Atropine Sulfate Injection, USP in the Ansyr Syringe is intended for intravenous use, **but maybe administered subcutaneously or intramuscularly.**"*

- DOSAGE AND ADMINISTRATION section – 3rd paragraph:
  Dr. Lipicky requested that a paragraph break be inserted at the 6th sentence of this paragraph ("Endotracheal administration of atropine can be used...").

I contacted Jonathan Dohnalek at Abbott Laboratories (847.937.3413) and communicated these changes to him. When asked what to do next, I told him that Dr. Lipicky had requested that Abbott send in a copy of the labeling with these changes as an amendment to the NDA as "Final Printed Labeling." Mr. Dohnalek agreed and will be sending in a copy.

Signed By: /S/

CC: HFD-110/Guzman

Attachments: Dr. Lipicky's "marked-up" copy of the January 9, 2001 FAX.

ABBOTT LABORATORIES
Hospital Products Division

Date: January 9, 2001

To: John Guzman
Regulatory Health Project Manager

Fax: 301-594-5494

No. of Pages: 11 (including cover page)

From: Jonathan P. Dohnalek
Manager, Regulatory Affairs
Dept 0389, Bldg. AP30-1

Tel: (847) 937-3413
Fax: (847) 938-7867

Dear John,

Attached is some information for the discussion tomorrow on NDA 21-146, Atropine Sulfate Injection, USP, Plastic Syringe.

Please feel free to contact me if you have further questions.

Sincerely,

Dohnalek.

Jonathan Dohnalek

ABBOTT

Hospital Products Division
Abbott Laboratories
D-389, Bldg. AP30
200 Abbott Park Road
Abbott Park, Illinois 60064-6157

January 9, 2001

CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIO-RENAL DRUG PRODUCTS, HFD #110
5600 Fishers Lane
Rockville, Maryland 20857

ATTENTION: John Guzman
Regulatory Health Project Manager

RE: **NDA 21-146 Atropine Sulfate Injection, USP, Plastic Syringe**
1/10/01 Teleconference

FDA will call Abbott Laboratories (847-937-3413) at approximately 3:30 eastern time.

Participants from Abbott Laboratories will include:
(1) Mary B. Baker, Pharm. D., Senior Medical Manager, Critical Care Medicine
(2) Lisa K. Zboril, R.Ph., Associate Director, Regulatory Affairs
(3) Jonathan P. Dohnalek, Manager, Regulatory Affairs

For the discussion, we have attached our proposed packaged insert, clearly identifying all of the Agency's deletions and additions, along with new Dosage and Administration text.

We would like clarification from the Agency concerning the use of the term ' ' in the Dosage and Administration section. It is our understanding that this definition only covers the pediatric population aged 2-12. Although Safety and Efficacy have not been established in the pediatric population, Abbott Laboratories propose revising this section to include all pediatric populations.

We look forward to the scheduled discussion tomorrow. If there are any questions, please contact me.

Sincerely,

ABBOTT LABORATORIES

JPDohnalek

Jonathan P. Dohnalek
Manager, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-3413

29 pages redacted from this section of the approval package consisted of draft labeling

CSO Package Overview

Date:	December 15, 2000
Application:	NDA 21-146 Atropine Sulfate Injection, USP, Plastic Syringe
Applicant:	Abbott Laboratories
Classification:	5S
User Fee Goal Dates:	October 20, 2000 (primary) December 20, 2000 (secondary)

Background

This is a new NDA submission where Abbott Laboratories, Inc. is seeking approval for Atropine Sulfate Injection, USP, Plastic Syringes (0.1 mg/mL in a 5 or 10 mL plastic syringe, and 0.05 mg/mL in a 5 mL syringe). Since Atropine is a pre-1938 drug, Abbott has been marketing Atropine Sulfate Injections in a glass syringe without an approved NDA. The change to a plastic container does require NDA approval.

Labeling

The sponsor has provided draft labeling (package insert). A copy of the draft labeling that includes revisions made by Drs. Lipicky, Fadiran, Resnick, and Jongdyk have been added to the labeling and have been approved by Dr. Lipicky. A copy of the revised labeling is attached to this review.

Exclusivity

Per 21 CFR 314.94(a)(12), the sponsor has noted that patent for this drug has expired and therefore is not entitled to exclusivity for the proposed indications.

Pediatric Rule

This is not a new chemical entity, and this NDA is not the culmination of a modern development plan. The pediatric requirement should not be imposed upon what is simply a chemistry supplement, namely a change in container. Atropine was not included in this Division's list of drugs that needed pediatric trials. Per Dr. Lipicky, the pediatric requirement is hereby waived.

Financial Disclosure/Debarment Certification

Jessie Y. Lee, from Abbott Laboratories had a discussion with Ms. Linda Carter on May 18, 2000 to discuss this issue. Dr. Lee stated that the product is grandfathered and that the NDA is for a change from a glass to plastic syringe. Ms. Carter noted that the submitted published studies did not meet the definition of "covered clinical studies" therefore no financial information is required to be submitted for the investigators in any of the submitted studies.

DSI

Per Dr. Lipicky, no DSI audit is needed because all supporting data was obtained from published literature.

Chemistry

All issues that the chemist had have been resolved. Further, the Dr. Jongdyk had also requested the following labeling change to the storage statement:

> "Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]"

The sponsor had already made this change. Dr. Jongdyk had accidentally reviewed the wrong version of the label.

Statistical

No statistical review was conducted due to the fact that all data came from published literature.

Primary Medical Review

Dr. Fredd concluded that the application did not provide a basis for approving any of the requested indications. He did note that since an IM product was already approved for the treatment for organophosphorous poisoning, the Abbott product could be approved based on the previous approval.

Secondary Medical Review

In his December 18, 2000 memo, Dr. Lipicky stated that this application was "approvable" provided that the labeling be revised. He also noted that he was conflicted as to which (if any) indications would be approved. Dr. Lipicky also recommended that Abbott arrange a teleconference to discuss the DOSAGE AND ADMINISTRATION section before they begin writing the section.

Dr. Lipicky's labeling suggestions are included in his memorandum.

Safety Update

A safety update was not submitted for this application, as the studies submitted to support this application have been completed for some time. Therefore, there are no new safety data from these studies to review.

CSO Summary

All primary and secondary reviews have been completed. To my knowledge, there are no outstanding issues that would preclude taking an action on this application. An "approvable" letter has been completed, reviewed, and approved by Dr. Lipicky.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Meeting Minutes

Meeting Date:	16 February 2000
NDA#:	21-146
Submission Date:	16 December 1999
Sponsor:	Abbott Laboratories

FDA Participants

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Robert Fenichel, M.D., Ph.D.	Deputy Director, HFD-110
Stephen Fredd, M.D.	Deputy Director for Policy, HFD-110
Emmanuel Fadiran, Ph.D.	Biopharmaceutist Reviewer, HFD-860
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-???
Natalia A. Morgenstern	Chief, Project Management Staff, HFD-110

Abbott Laboratories

Marc Menkus	Director Device Program Management
Jessie Lee, Ph.D.	Manager, Regulatory Affairs
Thomas F. Willer, Ph.D.	Associate Director, Regulatory Affairs Hospital Products Division
Charles H McLesky, MD	Senior Director of Anesthesia

SUBJECT: NDA 21-146 Atropine Sulfate Injection

Background:
Abbott laboratories market a number of small and large volume parenteral products in glass containers. They now want to market these products in plastic containers, one of these, atropine sulfate, has been marketed in glass without an approved new drug application (NDA). Under 21 CFR 310.509, any parenteral drug product packaged in a plastic immediate container is considered an unapproved new drug and requires an approved NDA before it could be marketed. The firm sought guidance from Drs. Roger Williams and Murray Lumpkin on the process of submitting NDAs and on how to gain approval for changing packaging of parenteral drug products from glass to plastic containers. Among other things, they were advised that a 505(b)-application might be submitted for atropine. Although there is an approved NDA for atropine sulfate as a nerve gas antidote/adjunct, Abbott's drug is not eligible for an Abbreviated New Drug Application (ANDA) because the dosage strengths of their product is not the same as that approved. Dr. Lumpkin further advised Abbott that based on their description of this product including its apparent substantial marketing history, they might wish to consider the feasibility of an application under section 505(b)(2). As stated in Dr. Lumpkin's letter, applications under this section may sometimes consist only of simple literature references and text from medical textbooks to support safety and effectiveness.

Under a cover letter dated December 16, 1999, Abbott submitted a new drug application for atropine received in the Agency December 20, 1999. The submission consisted of the usual manufacturing control information and in support of safety and effectiveness, 19 literature references. There were no description or analysis of which of these references were pertinent to the 7 proposed indications. Instead, Abbott contended that atropine was on the market in 1938 and was grandfathered under the 1938 Food, Drug and Cosmetic Act.

At the filing meeting on February 11, 2000 the primary medical reviewer stated that there were no controlled clinical studies in the application to review and recommended that the Division refuse to file the NDA. Dr. Lipicky, however, was reluctant to do that and wanted to discuss the application with Abbott and asked that a meeting with the firm be scheduled.

Meeting

After regular introductions, Dr. Lipicky noted that at the filing meeting, reviewers recommended that the Division refuse to file the NDA because on its face there was insufficient information required under 505 (b). Nevertheless, he wanted to meet with them to discuss 3 items:

1. Based on the fact that there was not sufficient information to conduct a review he wanted to know whether Abbott wanted the application filed noting that even if we refuse to file the application, Abbott could still request that we a file the NDA over protest. Reviews would still need to be written before an action letter could be issued.

2. He asked whether Abbott would participate in an Advisory Committee meeting to discuss the requirement that an approved NDA is required for marketing to continue of products like atropine when packaging is changed from glass to plastic.

3. Dr Lipicky noted that obviously the seven indications desired by Abbott for this product could not all be approved in view of the paucity of the submitted data for approval of even only one of the indications proposed in the application. He asked whether they would be willing to work with Division reviewers to find a way of approving this application.

Most of the discussion centered on the content of the submission and the lack of sufficient information to support safety and effectiveness. Abbott candidly admitted that they were unable to locate the requisite information in their literature search but contended that the "grandfathered" status of atropine should take precedence and the NDA should not be subjected to rigorous standard of safety and effectiveness. In addition, they pointed out that Drs Williams' and Lumpkin's letters were encouraging.

Dr. Fredd suggested that Abbott might want to explore the possibility of submitting this NDA under 21 CFR 314.54 This section describes procedures for submission of an application requiring investigations for approval of a new indication or other change from a listed drug (a 505(b)(2) application). This application need contain only that information needed to support the modification(s) of the listed drug.

Dr. Lipicky requested that Abbott tell us of their decision on the three questions above prior to the filing date (February 18, 2000) of the NDA. Abbott will call Ms. Morgenstern with their decision next day (February 17, 2000).

Recorder: S

/Natalia A. Morgenstern
Chief, Project Management Staff

Chair: S

Director, Division of Cardio-Renal Drug Products.

ADDENDUM

Abbott called on 17 February 2000 and told Ms. Morgenstern the following:

1. Abbott wanted the Division to file the application.

2. They are not willing to participate in an Advisory Committee meeting to discuss atropine. They cannot defend the safety and effectiveness of this "old drug."

3. They are willing to cooperate with Division reviewers to find ways of approving NDA.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL