CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-038

CHEMISTRY REVIEW(S)

N21038 on #21-038 HFD-170 K1.3

DRUG NAME: Precedex (dexmedetomidine hcl injection)

APPLICANT: ABBOTT LABORATORIES

REC. 12/28/99

CHEMICAL & THERAPEUTIC CLASS:1S

Review Cycles

Review Cycle: 1 **Submission Date:12-18-98** **Receipt Date:12-18-98** **Goal Date:12-18-99** **Action:AP**	**Review Cycle: 2** **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**
Review Cycle: 3 **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**	**Review Cycle: 4** **Submission Date:** **Receipt Date:** **Goal Date:** **Action:**

CORE REVIEW TEAM MEMBERS

PROJECT MANAGER/ CSO :Susmita Samanta **Phone # & Office Room #:301-827-7410, 9B-45**
MEDICAL:Patricia Hartwell, M.D., M.B.A.
CHEMISTRY:Michael Theodorakis, Ph.D.
PHARM/TOX:Harry Geyer, Ph.D.
BIOPHARMACEUTICS:Suresh Doddapaneni, Ph.D.
BIOMETRICS: Z.Jonathan Ma, Ph.D.
ABUSE LIABILITY: BeLinda A. Hayes, Ph.D.
MICROBIOLOGIST: Patricia Hughes, Ph.D.

Volume 3 of 4

Administrative volume #(s): 1
Clinical volume #(s): 2
CMC volume #(s): 3
Pharmacology/Toxicology volume #(s): 4

ODE II ACTION PACKAGE TABLE OF CONTENTS

Application #21-038

Drug Name: Precedex (dexmedetomidine Hydrochloride injection), 2 mL ampule/2 mL vial, 100 mcg/mL

Applicant: Abbott Laboratories Chem./Ther. Type:1S

CSO/PM: Susmita Samanta Phone: 301-827-7410 HFD-170

Original Application Date: December 18, 1998 Original Receipt Date: December 18, 1998

CURRENT USER FEE GOAL DATE: December 18, 1999 DateTableofContentsCompleted:9/13/99

Section A:	Administrative Information	**X** (completed), **N/A** (not applicable), or Comment
Tab A-1	Action Letter(s) Current Action:AP	X
Tab A-2	Phase 4 Commitments:	
	a. Copy of applicants communication committing to Phase 4	NA
	b. Agency Correspondence requesting Phase 4 Commitments	NA
Tab A-3	FDA revised Labels & Labeling and Reviews: (Separate each version/cycle with a colored sheet)	
	a. Package Insert	X
	b. Immediate Container and Carton Labels	NA
Tab A-4	Original Proposed Labeling	X
Tab A-5	Foreign Labeling:	
	a. Foreign Marketing History	NA
	b. Foreign Labeling and Review(s)	NA
Tab A-6	Labeling and Nomenclature Committee's Tradename Review	X
Tab A-7	Summary Memoranda (e.g., Division Director, Group Leader, Office)	X
Tab A-8	Copy of Patent Statement	X
	Exclusivity Checklist (and any requests for exclusivity)	X
	Debarment Statements	X
Tab A-9	Correspondences, Faxes, & Telecons	X
Tab A-10	Minutes of Meetings:	
	a. End-of-Phase II meeting	NA
	b. Pre-NDA meeting(s)	NA
	c. Filing meeting	X
	d. Other meetings	X
Tab A-11	Advisory Committee Meeting:	
	a. Questions Considered by the committee	NA
	b. List of Attendees	NA
	c. 24 hour alert memorandum	NA
Tab A-12	Project Management Administrative Information (optional)	

ODE II ACTION PACKAGE TABLE OF CONTENTS (continued)

Application #21-038 Drug Name: Dexmedetomidine HCL

Section B:	Clinical Information	X (completed), N/A (not applicable), or Comment
Tab B-1	Clinical Reviews and Memoranda	X
Tab B-2	Safety Update Reviews	X
Tab B-3	Pediatric Page	X
Tab B-4	Statistical (Clinical) Review and Memoranda	X
Tab B-5	Biopharmaceutics Review and Memoranda	X
Tab B-6	Abuse Liability Review	X
Tab B-7	DSI Audits	X
Tab B-8	Summary of Efficacy (from the summary volume of the application)	NA
Tab B-9	Summary of Safety (from the summary volume of the application)	NA

Section C:	Chemistry, Manufacturing, and Controls (CMC) Information	X (completed), N/A (not applicable), or Comment
Tab C-1	CMC Reviews and Memoranda	X
Tab C-2	DMF Reviews	X
Tab C-3	EA Reviews/FONSI	X
Tab C-4	Micro Review (validation of sterilization)	X
Tab C-5	Statistical Review of drug stability	NA
Tab C-6	Inspection of facilities => Decision:_____ Date:_____	X
Tab C-7	Methods Validation Information	PENDING

Section D:	Pharmacology/Toxicology Information	X (completed), N/A (not applicable), or Comment
Tab D-1	Pharmacology/Toxicology Reviews and Memoranda	X
Tab D-2	Carcinogenicity Review (statistical)	NA
Tab D-3	CAC/Executive Committee Report	NA

ADDITIONAL NOTES:

ABBOTT

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

REQUEST FOR A CATEGORICAL EXCLUSION

OF THE REQUIREMENTS OF AN ENVIRONMENTAL IMPACT REPORT

Abbott Laboratories hereby requests a CATEGORICAL EXCLUSION of the requirements of an Environmental Impact Report under the provisions of 21 CFR 25.24.

A CATEGORICAL EXCLUSION may be granted if the drug product will not be administered at higher dosage levels, for longer duration, or for different indications than were previously in effect and if data available to the Agency do not establish that at the expected level of exposure, the substance may be toxic to organisms in the environment.

We attach a certification of environmental compliance on the following page.

ABBOTT LABORATORIES

Thomas F. Willer

Thomas F. Willer, Ph.D.
Associate Director, Regulatory Affairs
Hospital Products Division
Phone: (847) 937-6845
Fax: (847) 938-7867
Internet: WILLETF@hpd.abbott.com

12-99f.ttw/35

CERTIFICATION OF COMPLIANCE
Rocky Mount, North Carolina Facility

Abbott Laboratories certifies that it is in compliance with, or on an enforceable schedule to be in compliance with, all emission requirements set forth in permits, consent decrees, and administrative orders applicable to solution preparation and filling of Dexmedetomidine Hydrochloride Injection at its facility in Rocky Mount, North Carolina as well as emission requirements set forth in applicable federal, state, and local environmental and occupational exposure statutes and regulations applicable to solution preparation and filling of Dexmedetomidine Hydrochloride Injection at its facility in Rocky Mount, North Carolina.

Signature: John Robbins

John Robbins
Principal Environmental Specialist
Abbott Laboratories,
Hospital Products Division

Date: December 9, 1999

APPEARS THIS WAY
ON ORIGINAL

5

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: November 29, 1999

/S/

FROM: **Albinus M. D'Sa, Ph.D.**

TO: **Cynthia McCormick, M.D.**

SUBJECT: NDA 21-038, CMC review status

I am writing this memo to inform you that currently all CMC issues are resolved and that the NDA from the CMC stand point is recommended for approval.

Previously, our recommendation in the CMC review #1, dated June 30, 1999, was approvable. This was because the Office of Compliance recommendation was pending and the EES indicated that

Upon talking with the compliance officer, Mr. Richard Friedman and the inspector. Mr. Thomas Arista, I was informed that . The applicant was working on the deficiencies listed in the form-483, as listed by the inspector. All of these issues pertained to Current Good Manufacturing Practice. However, the inspection deficiencies only applied to drug substances that were to be used in manufacturing a drug product via an aseptically filled sterile process. Dexmetatomidine HCl, is a terminally sterilized product and therefore the issues in the form-483, did not apply to this particular NDA. The drug product manufacturing facility was found to be acceptable from the CGMP perspective. The office of compliance could not however provide an acceptable recommendation to the EES request because of the pending CGMP issues at the firm.

A consult was initiated (based on an E-mail from Dr. Rappaport) to Microbiology to seek advice on the micro issues that compliance had raised in the form-483; the response is pending. However, in the interim, the firm has complied with all of the CGMP observations, and the Office of Compliance on November 19, 1999, reported an acceptable status for all the facilities in the EES request. Therefore from the CMC standpoint, this application is recommended for approval.

The other issues that needed clarification were as follows, however none of these are approvability issues:

Except for one, all issues raised in the NDA review pertain to labeling. On the one issue, the applicant has tightened the specs for endotoxin. The reviewer was asking for data to support the new specs. At this point this data may not be important because the marketed product will have to meet these new tighter specs.

The applicant has satisfactorily addressed the issues raised in DMF. The stability protocol for the drug substance is modified as requested, and applicant has agreed to perform acceptance testing of every lot of drug substance based on the specifications of the drug substance. The DMF holder will have an expiration date for the drug substance of 3 years, based on the stability data for the drug substance.

And finally, a standard statement should on methods validation should be included in the approval letter, because the FDA labs have not yet completed the validation.

FOOD and DRUG ADMINISTRATION
CENTER of DRUG EVALUATION and RESEARCH
DIVISION OF ANESTHETICS, CRITICAL CARE and ADDICTION DRUG PRODUCTS (DACCADP)
HFD-170

NDA:21-038 CHEMISTRY REVIEW #:1 REVIEW DATE: 30-JUN-99

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	18-DEC-98	18-DEC-98	23-DEC-98
AMENDMENT[AC]	09-FEB-99		
AMENDMENT[BC]	30-APR-99	03-MAY-99	

NAME & ADDRESS OF APPLICANT:

Abbott Laboratories
Hospital Products Division
D-389, Bldg. AP30200
Abbott Park Road
Abbott Park, Illinois 60064-3537

Attn: Thomas F. Willer, Ph.D.
Assistant Director, Regulatory Affairs
tel.: 874-937-6845

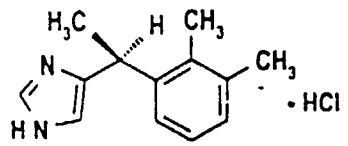
DRUG PRODUCT NAME

Proprietary: ———
Nonproprietary/USAN: dexmedetomidine HCl
Code Name/#:
Chem.Type/Ther.Class: 1 S

PHARMACOL.CATEGORY/INDICATION:

DOSAGE FORM: Injection
STRENGTHS: 100 µg/mL, 2 mL, in a 2 mL ampoule or vial
ROUTE OF ADMINISTRATION:
DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOL.WT:



(S)-4-[1-(2,3-dimethylphenyl)ethyl]-
1H-imidazole hydrochloride
DEXMEDETOMIDINE HYDROCHLORIDE

CONCLUSIONS & RECOMMENDATIONS:

a. No DMF reviews are pending.

b. The validation of the analytical methods is in progress.

c. Inspection of the facilities has been completed.

d All chemistry related consult reviews, namely the microbiology and tradename reviews, have been completed.

e. The comments and deficiencies listed in the Draft Letter must be conveyed to the Applicant.

f. This application is approvable from the chemistry standpoint pending satisfactory resolution of the issues related

/S/

Michael C. Theodorakis, Ph.D.
Senior Review Chemist

/S/

Albinus M. D'Sa, Ph.D.
Chemistry Team Leader

Sanofi

REVIEW FOR HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
ADDENDUM TO MICROBIOLOGIST'S REVIEW #1 OF NDA

November 23, 1999

A. 1. NDA 21-038

SPONSOR Abbott Laboratories

2. PRODUCT NAMES: [redacted] dexmedetomidine HCl) for Infusion

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile 2 mL vials and 2 mL ampules for infusion

4. METHOD(S) OF STERILIZATION: Terminal moist heat by autoclave. The ampule presentation is aseptically processed before the autoclave cycle.

5. PHARMACOLOGICAL CATEGORY: Sedative

6. DRUG PRIORITY CLASSIFICATION: 1S

B. 1. DATE OF INITIAL SUBMISSION: December 18, 1998

2. DATE OF AMENDMENT: N/A

3. RELATED DOCUMENTS: Microbiologist's Review #1 dated April 27, 1999, Inspection Report (FDA 483) dated March 6, 1999, and letter from Compliance to [redacted]

4. ASSIGNED FOR REVIEW: 11/12/99

C. REMARKS: The consult request asks for an evaluation of the inspection report of the [redacted]. The inspection evaluated [redacted] aseptic processing of finished small volume sterile solution products, and resulted in findings of cGMP deviations. Consequently, a letter was sent (November 1, 1999) from the FDA's Office of Compliance to notify the firm that it was not in a state of compliance. Microbiologist's Review #1 of the NDA was done by Dr. Patricia Hughes, and recommended approval of the finished product, which is manufactured at Abbott's facility in Rocky Mount, NC. Notes concerning the Investigator's findings, Compliance's

recommendation, and the Microbiologist's review are provided in the "Review Notes" that follow.

D. CONCLUSIONS: The application is recommended for APPROVAL. Additional considerations are discussed in section "E. Review Notes".

/S/ 11-23-99

David Hussong, Ph.D.

Date 11/23/99

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: HFD-160 (Division of Microbiology), Dr. Peter ey, Parklawn Rm 18B-08

FROM: HFD-170 (Division of Anesthetic, Critical Care, and Addiction Drug Products), Dr. Cynthia McCormick

	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
November 10, 1999		21-038	Conclusion of CGMP inspection of Dexmedetomidine facility in	November 1, 1999

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Dexmedetomidine	High	1-S	ASAP

NAME OF FIRM: Abbott Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ■ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ITROLLED STUDIES TOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

/10 /S/ 11/12/99

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISION RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the microbiology-related conclusions of the cGMP inspection of the facility for manufacturing the bulk drug substance, dexmedetomidine HCl, located in Espoo Finland. It should be noted that the bulk substance is shipped to US and the drug product, dexmedetomidine HCl injection, is manufactured by Abbott Labs and is terminally sterilized. The Abbott Labs facility was found to be acceptable by Compliance. Please indicate whether or not the approvable recommendation of your staff regarding this application is still valid. Please note that the SVT product (NDA 20-038) was not evaluated in this establishment inspection.

If you have any written comments, please provide a copy for Laura Governale, Regulatory Project Manager, HDF-170 and Joan Fuscher /S/ 11/10/99

TURE OF REQUESTER /S/	METHOD OF DELIVERY (Check one) ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH & HUMAN SERVICES

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

Division of Manufacturing and Product Quality, HFD-320
7520 Standish Place
Rockville, Maryland 20855-2737

TELEPHONE: (301) 594-0093
FAX: (301) 594-2202

NOV 1 1999

Dr. Jyrki Mattila
President
Orion Corporation,
Orion Pharma
Orionintie 2
02101 Espoo, Finland

Dear Mr. Mattila:

The Food & Drug Administration has completed its review of the March 1-6, 1999 inspection of your sterile pharmaceutical manufacturing facility in Espoo, Finland. The inspection revealed significant deviations from current good manufacturing practices (CGMP) in the manufacture of sterile pharmaceuticals. The deviations were presented to your attention on an FDA-483 List of Observations at the close of the inspection. The CGMP deviations cause these drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act.

Some notable deficiencies include:

1. No records that equipment was sterilized or disinfected. No record existed for materials/equipment including but not limited to: stopper bowl, stopper bowl plastic cover, RCS microbial sampler, and scissors.

It should be noted that sterilization and sanitization records are fundamental to a sterile drug product manufacturing operation. As part of your response to this issue, please specifically state whether stopper bowls (and associated covers) are sterilized or only disinfected.

2. Lack of reconcilability of vials discarded during the media fill operation.

3. Inadequate studies performed to evaluate laminarity of air in class 100 processing zone.

4. Failure to adequately control computer software used to record and process data for annual reports, complaint handling, raw material weighing, creating

batch record instructions (in some instances), and control/release of goods from raw material through finished stages.

5. A number of instances of failure to maintain either adequate or sufficient records, including validation documentation.

For example, autoclave load configurations and placement of thermocouples in autoclave chamber were not adequately described in SOPs. As another example, your firm did not document which aerosol compound was used for performing integrity tests of HEPA filters in the aseptic processing area.

With regard to computers, we note that there was no record of original system requirements or design. In addition, the previous software version/s/ for significant programs were not retained. Version control should be practiced for software developed by firms for use in any CGMP application.

Within your response to this letter, please provide an update on your firm's progress toward retaining digital data (observations 23-26). The inspection found that many quality control laboratory digital data files were deleted.

6. Change control procedures were inadequate. As an example, significant water system changes (e.g., changes in major piping) were not the subject of increased testing for purposes of revalidation. In addition, when significant systems (e.g., air, water, etc.) undergo modifications, the updated configuration of the system should be promptly and adequately documented.

7. Water for injection (WFI) sampling was inadequate. Some points of use (approximately one-quarter of them) were not sampled, and only three samples were taken per week. Please note that at least one sample should be taken from the WFI system daily, and rotation of sampling to a given WFI takeoff point should generally occur more frequently than monthly (as stated in your FDA 483 response).

Please clarify each of the above items in your response and address your firm's efforts to handle these issues globally. Include a timetable of when corrections will be completed and supporting documents and translations in English. Specifically, we would prefer a *report updating the status of each commitment (e.g., creation or revision of an SOP; performing training)* included in your firm's April 20 and June 4, 1999 responses.

Finally, we would like to clarify one aspect of FDA 483 observation #20 and your associated written response. We consider the person performing the

validation studies to be responsible for the integrity of data generated. However, it is not a specific GMP requirement that the data must be otherwise "evaluated" by this specific individual. "Evaluation" can connote an assessment or interpretation of the data in order to reach a conclusion on process validity. FDA does not require conclusions on the validity of the process to be determined by the same person generating the actual data for the study. This critical responsibility is one which FDA expects to be properly discharged by specified personnel of the firm, including final review and approval by responsible officials of the quality control unit.

The CGMP deviations identified above are not to be considered an all inclusive list of the deficiencies at your facility. F DA inspection are audits which are not intended to determine all deviations from CGMPs that exists at a firm. We recommend that you continually evaluate the overall CGMP compliance of your facility.

Until FDA has confirmed that your firm is in CGMP compliance we will not recommend approval of any new drug applications for sterile drugs manufactured by this facility.

Please acknowledge your receipt of this letter. Facsimiles may be sent to (301) 827-0145. You may contact me at (301) 594-0095 with any questions.

Sincerely,

/S/

Richard L. Friedman
Compliance Officer
Investigations and Compliance Branch

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

DATE: December 1, 1999

FROM: **Albinus M. D'Sa, Ph.D.** /S/

TO: **NDA file # 21-038**

SUBJECT: NDA 21-038, CMC review status

I am writing this memo to document a telcon that occurred yesterday between David Hussong, Ph.D. (Acting Assoc. Director of Microbiology, Acting for Perter Cooney, Ph.D.).

I indicated to Dr. Hussong that the division was concerned and needed clarification on the comment made in the consult review (page 10, fourth paragraph). The review was done by Patrica Hughes, Ph.D., who I was informed no longer works in the Division of Microbiology. The comment related to the asceptic processing prior to the terminal sterilization of the product. The comment stated that this process was not validated and the filters have not been validated for microbial retentivity.

Dr. Hussong, said that the review conclusion are based on the terminal sterilization process and its validation. The lack of information in the asceptic processing such as filter retention is not critical. so this was not a problem that he was concerned about. The filtration step does not have to be validated because the materials are accepted with low bioburden.

I also inquired during the conversation on the status of the inspection consult that chemist had sent to Peter Cooney. He indicated that it was completed and we should have already received it.

APPEARS THIS WAY
ON ORIGINAL

APR 30 1999

REVIEW TO HFD-170
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY TEAM
MICROBIOLOGIST REVIEW OF A NDA
27 April 1999

A. NDA 21-038

PRODUCT NAME: ——— x (dexmedetomidine HCl) for Infusion

APPLICANT: Abbott Laboratories

DOSAGE FORM: Sterile aqueous solution in vials and ampoules for injection; List No. 1638, 2 mL vial, 100 µg/mL and List 3434 2 mL ampoule, 100 µg/mL

METHOD OF STERILIZATION: Terminal sterilization by autoclave

PHARMACOLOGICAL CATEGORY: Alpha-2 sedative with analgesic properties for use in an intensive care setting.

B. INITIAL APPLICATION DATE: 18 December 1998
ASSIGNED FOR REVIEW: 11 February 1999

C. REMARKS: A microbiology consult was requested to review the terminal sterilization process and the sterility test information. The drug product is a sterile aqueous solution filled in vials and ampoules. It is intended to be further diluted with 0.9% sodium chloride prior to intravenous infusion.

D. CONCLUSIONS: The NDA 21-038, which provides for ——— lexmedetomidine HCl) Injection is recommended for approval from the standpoint of product quality microbiology. Please see section E for Review Notes.

/S/ 4/30/99

Patricia F. Hughes, Ph. D.
Review Microbiologist

PFH 4/30/99

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
dical Imaging and Radiopharmaceutical Drug
lucts Dr. Peter Cooney HFD-160 Rm. 18B-08

FROM: **Michael Theodorakis, Reviewing Chemist**
Anesthetic, Critical Care & Addiction Drug Products
HFD-170 827-7410

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 5, 1999		21-038	**NDA**	12-18-98

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
(dexmedetomidine HCL) Injection	Routine		**May 30, 1999**

NAME OF FIRM: Abbott Laboratories

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- X PAPER NDA
- ☐ CONTROL SUPPLEM
- ESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- OTHER *(SPECIFY BELOW)*:

/S/ PITC 2/4/99

OMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
PE A OR B NDA REVIEW) OF PHASE II MEETING ONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

FILED FOR DRUG
FEB 10 99
HFD-160
EVALUATION AND RESEARCH

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RICK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This is a terminally sterilized small volume injection. Please review the sterilization process and sterility testing information.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one)
...ichael C. Theodorakis, Ph.D. /S/ 2/5/99	☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER /S/	SIGNATURE OF DELIVERER

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21038/000**
Stamp: **18-DEC-1998** Regulatory Due: **18-JAN-2000**
Applicant: **ABBOTT LABS**
200 ABBOTT PARK RD D389 BLDG A
ABBOTT PARK, IL 600643537

Priority: **1S** Org Code: **170**
Action Goal: District Goal: **19-NOV-1999**
Brand Name: **EXMEDETOMIDINE HCL)100MCG/ML I**
Established Name:
Generic Name: **DEXMEDETOMIDINE HCL**
Dosage Form: **INJ (INJECTION)**
Strength: **100 MCG/ML**

FDA Contacts: **S. SAMANTA (HFD-170)** **301-827-7410 , Project Manager**
M. THEODORAKIS (HFD-170) **301-827-7425 , Review Chemist**
A. D SA (HFD-170) **301-827-7443 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 19-NOV-1999 by M. EGAS (HFD-322) 301-594-0095

Establishment: **1021343**
ABBOTT LABORATORIES
HWY 301 NORTH
ROCKY MOUNT, NC 27804

DMF No:
AADA No:

Profile: **SVT** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **20-MAY-1999**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE MANUFACTURER**

Establishment: **1411365**
ABBOTT LABORATORIES
1401 14TH & SHERIDAN ROAD
NORTH CHICAGO, IL 60064

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **03-FEB-1999**
Decision: **ACCEPTABLE**
Reason: **BASED ON PROFILE**

Responsibilities: **FINISHED DOSAGE STABILITY TESTER**

Establishment: **9610102**
ORION CORP LTD
FERMION KOIVUMANKKAANTIE 6
ESPOO, , FI

DMF No:
AADA No:

Profile: **CSS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **19-NOV-1999**

Responsibilities: **DRUG SUBSTANCE MANUFACTURER**

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Decision: **ACCEPTABLE**

Reason: **DISTRICT RECOMMENDATION**

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

Date: June 4, 1999

To: Food and Drug Administration, Pre-approval Laboratories

1st Laboratory

Division of Testing and Applied Analytical Development, HFD-920
1114 Market Street, Room 1002
St. Louis, MO 63101
Attention: Harry Coffman

2nd Laboratory

Philadelphia District Laboratory, HFR-MA160
US Customhouse
2nd and Chestnut Streets, Room 900
Philadelphia, PA 19106
Attention: Nicholas Falcone

From: Michael Theodorakis, Ph.D. Senior Review Chemist, HFD-170, MCT 6/4/99
Division of Anesthetic, Critical Care, and Addiction Drug Products, CDER

Through: Albinus D'Sa, Ph.D., Chemistry Team Leader, HFD-170, MCT for DSA 6/4/99
Division of Anesthetic, Critical Care, and Addiction Drug Products, CDER

Subject: Laboratory Assignments for NDA Methods Validation (MV)

NDA No: 21-038

Product: [redacted] (dexmedetomidine HCl) Injection

Applicant: Abbott Laboratories,
200 Abbott Park Road
Abbott Park, IL 600064-3537
Attn: Thomas F. Willer, Ph.D., Assistant Director, Regulatory Affairs,
tel. 847-937-6845

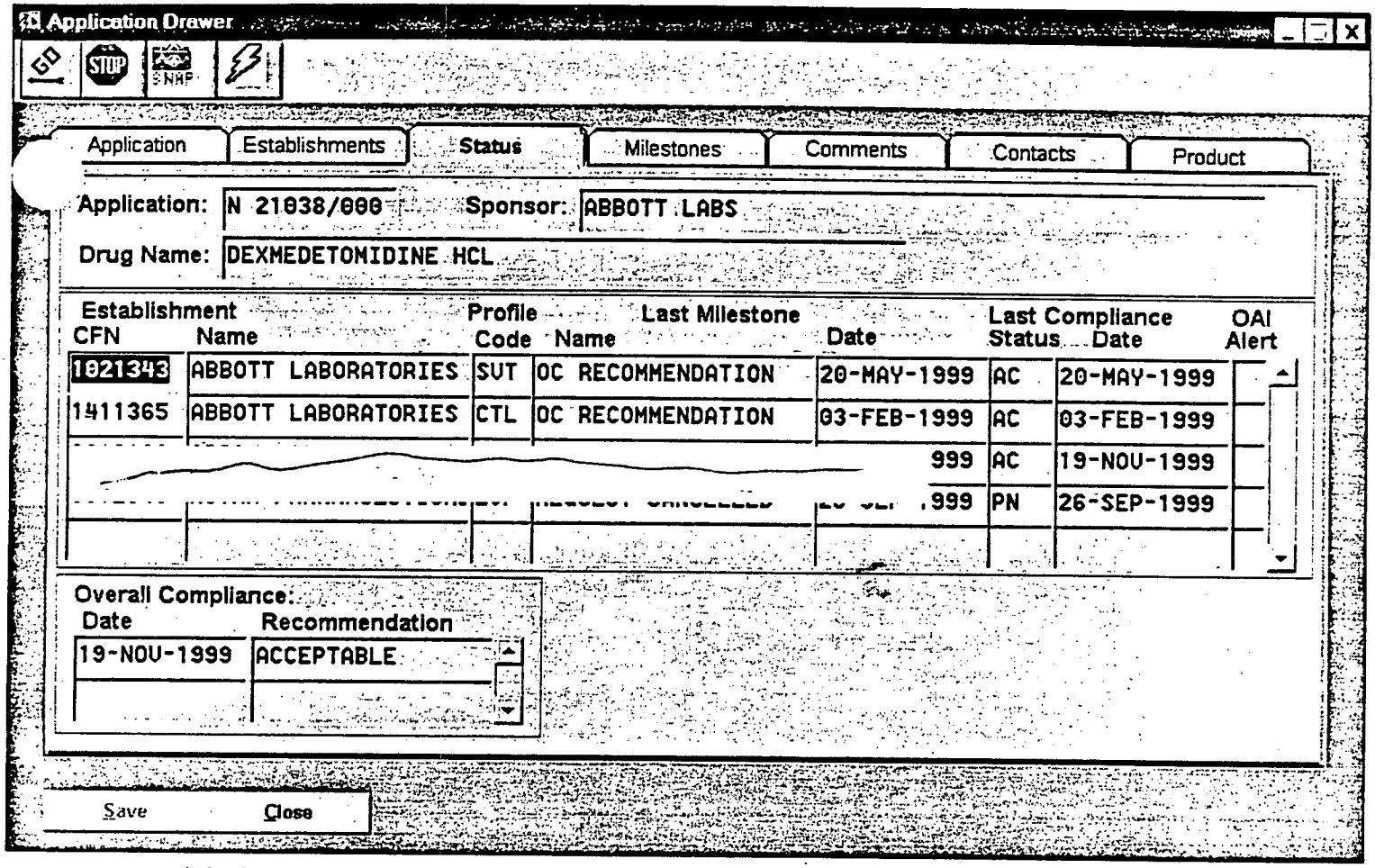
Please find attached an amendment to NDA 21-038 that contains revisions for the following analytical procedures:

a. 74762 Dexmedetomidine HCl
b. C-1681 Determination and Identification of Dexmedetomidine and Related Substances in Bulk Drug and Injection.

This amendment should become part of the MV package for NDA 21-038 that was mailed to your labs on March 17, 1999.

Enclosures
cc: Original NDA 21-038
HFD-170 Division File

APPEARS THIS WAY
ON ORIGINAL



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