of subjects with type 1 and type 2 diabetes. The rates of severe hypoglycemia in subjects with type 1 diabetes are comparable to those reported in the DCCT and in subjects with type 2 diabetes the rates are comparable to those reported in the UKPDS. Therefore, we believe the results are objective and represent a real clinical advantage of insulin glargine that justifies consideration to make insulin glargine available to patients with diabetes as quickly as possible.

Based on the above, the applicant requests priority review and approval of insulin glargine.

The following components make up the NDA submission for insulin glargine. All applicable 356h items, except Item/Section 12 are being submitted as a paper archival copy. Item 12 is being submitted as an electronic archival copy in compliance with the September 1997 electronic guidance. In addition to the paper copy, an electronic review aid is being supplied on six compact discs to allow electronic review and hypertext linking of the NDA. An aid for the reviewer follows this letter.

Item/Section	Volume(s)
1) Index	1.1
2) Labeling	1.1
3) Summary	1.2
4) Chemistry, manufacturing and controls	1.3 – 1.15
5) Nonclinical pharmacology and toxicology	1.16 – 1.59
6) Human pharmacokinetics and bioavailability	1.60 – 1.59
7) Microbiology – not applicable	
8) Clinical data	1.160 – 1.476
9) Safety summary – not applicable	
10) Statistical section	1.477
11) Case report tabulations	1.478
12) Case report forms – submitted electronically	1.479
13/14 Patent information/certification	1.1
15) Establishment description – not applicable	
16) Debarment certification	1.1
17) Field copy certification	1.1
18) User fee cover sheet	1.1
19) Financial disclosure	1.1

This submission is paginated to reflect the section number, followed by the volume number (v) and the page number (p).

A separate identical copy of Section 4. Chemistry, manufacturing and controls, has been sent to Alan Mehl at the Kansas City District Office. A statement certifying this is provided in Item 17 of this submission.

Over the course of the development of insulin glargine, the following agreements have been made between the Agency and the applicant:

- The Agency agreed to accept the 12-month safety data from study 3002 after the submission and filing of the initial NDA for insulin glargine.
- If any additional CRFs are requested by the Agency for the ex-US studies (other than those required in the initial submission) the Agency agreed to accept a by-subject database printout of the case report form data.

- The Agency agreed to the applicant's proposal for collection of financial disclosure information from Phase III and Phase I studies.
- The Agency agreed to the applicant's proposal to provide tabulation reports for Section 11 in Sections 6 and 8 of the NDA. The tabulations for each report are presented as data listings located with the reports in sections 6 and 8. A cross-reference table is provided in Section 11 to these listings. The table of all clinical studies also contains this cross-reference.
- The Agency agreed the sponsor could submit the 120-day safety update at day 75 after the initial submission.
- The electronic version of the NDA will be provided to the Agency within two weeks of the initial submission.
- After conversations with Enid Galliers and Julie Rhee the pediatric report will be submitted to the Agency before the filing meeting for the NDA. This should allow time for the pediatric report to be considered at the filing meeting for HOE 901.

Additional agreements regarding the CMC and clinical sections of the submission are provided in those respective sections.

Under separate cover, the User Fee for this NDA has been submitted according to the Prescription Drug User Fee Act (see Item 18 of this submission [User Fee ID No. 3691]).

Please address any comments or questions regarding this application to Lavonne Patton, authorized representative for Quintiles, the U.S. Agent for Hoechst Marion Roussel, Inc. the official applicant of the NDA.

Lavonne Patton, Ph.D.
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
Phone: 816-767-6674

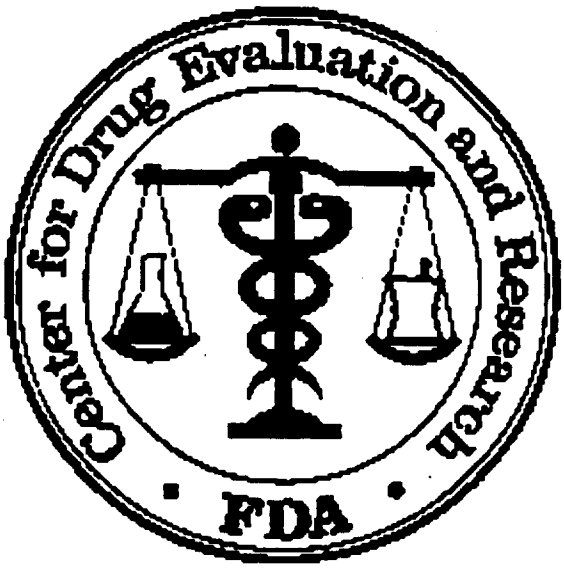
Sincerely,

J. Michael Nicholas, Ph.D.
Director, Marketed Products
US Regulatory Affairs
Hoechst Marion Roussel

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: November 18, 1999



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee.

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 2

COMMENTS:

NDA 21-081 Lantus™

Additional information requests. Please submit your response by 12/3, if it's possible at all. Thank you.

cc: Orig NDA
HFD-510/Div File
HFD-510/Misbin

NDA 21-081 Lantus™

Date of submission: April 9, 1999

Additional information requests (clinical)

1. The definition of nocturnal hypoglycemia is not clear. How were the data collected. If patients were asleep how is it known that they were hypoglycemic?

2. The disparity between fasting plasma glucose and fasting blood glucose seems larger than what one generally expects. Please explain.

3. Please give details of the methods for measuring antiinsulin antibodies. Was bound/free corrected for nonspecific binding? If so, how?

4. Were insulin levels in study 3006 free or total?

5. What is the outcome of the pregnancy in study 3004? The expected due date was Oct 23, 1999.

Cleared for faxing by:

/S/

Robert Misbin, M.D.
Medical Officer

/S/ 11/18/99

Saul Malozowski, M.D.
Acting Medical Team Leader

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 8, 1999
Dr. Misbin and I called Dr. Patton and asked to include "Do not mix" statement on a vial and carton. We also asked to include the same statement prominently on top of physician/patient package inserts. I also asked they submit the draft labeling after they incorporate the statement. She agreed. cc:OrigNDA HFD-510/DivFile HFD-510/Misbin APPEARS THIS WAY ON ORIGINAL /S/ 10-8-99 Name: Julie Rhee	**NDA#:** 21-081 **Telecon/Meeting initiated by:** FDA **By:** Telephone **Product Name:** Lantus™ **Firm Name:** Hoechst Marion Roussel **Name and Title of Person with whom conversation was held:** Lavonne Patton, Ph.D. Regulatory Affairs, Quintiles (Consultant to Hoechst) **Phone:** (816) 767-6674

PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION /S/ 9/17/99

TO (Division Office) Paul Stinavage, Ph.D., HFD-160			FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee	
pt 16, 1999	IND NO.:	NDA NO.: 21-081	TYPE OF DOCUMENT: Micro Amendment	DATE OF DOCUMENT: Sept 2, 1999
NAME OF DRUG: Insulin glargine injection	PRIORITY CONSIDERATION:		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: Dec 31, 1999
NAME OF FIRM: Hoechst Marion Roussel				

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	☐ CHEMISTRY REVIEW
☐ END OF PHASE II MEETING	☐ PHARMACOLOGY
☐ CONTROLLED STUDIES	☐ BIOPHARMACEUTICS
☐ PROTOCOL REVIEW	☐ OTHER:
☐ OTHER	

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 RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
SEP 17 1999
HFD-510

COMMENTS/SPECIAL INSTRUCTIONS:

Paul,

Please review this submission which provides for the sterilization validation report for vials and cartridges. Thanks.

cc: Original NDA 21-081
HFD-510 Div. Files
HFD-510/

SIGNATURE OF REQUESTER: /S/ 9-17-99

METHOD OF DELIVERY (Check one): ☐ MAIL ■ HAND

SIGNATURE OF RECEIVER: /S/

SIGNATURE OF DELIVERER: /S/

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: October 28, 1999

TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 4

COMMENTS:

NDA 21-081 Lantus

Microbiology review comments on the 9/2/99 submission. Please submit your response to Dr. Sobel no later than 11/30/99. Thank you.

cc. Orig NDA
HFD-510/Div File
HFD-160/Shinavage

WITHHOLD 3 PAGE (S)

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 22, 2000

TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 3

COMMENTS:

NDA 21-081 Lantus™ (insulin glargine [rDNA origin] injection)

Additional CMC information request. Please let me know when we could expect your response. Thank you.

cc. Orig NDA 21-081
HFD-510/Div File
HFD-510/Moore/Komanduri

NDA 21-081 LantusTM (insulin glargine [rDNA origin] injection)

Date of Submission: April 9, 1999

Chemistry, Manufacturing, and Controls Requests

Please provide your response to the following additional CMC information request:

Drug Substance:

[

]

Drug product:

[

]

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

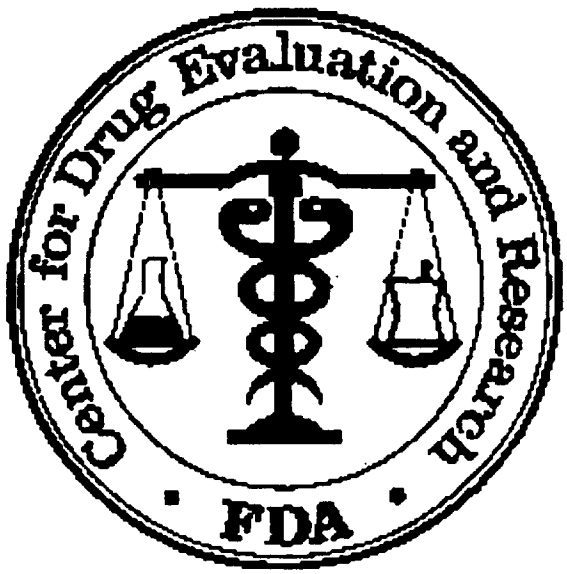
APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by: /S/ 2-22-00
Stephen Moore, Ph.D., Chemistry Team Leader I, DMEDP

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: January 12, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 3

COMMENTS:

NDA 21-081 Lantus (insulin glargine [rDNA origin] injection)

CMC review requests. Please let me know how soon we could expect your response. Thank you.

NDA 21-081 Lantus™ (insulin glargine [rDNA origin] injection)

Date of Submission: April 9, 1999

Chemistry, Manufacturing, and Controls Requests

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application. If you respond to these issues during

this review cycle, depending on the timing of your response, and in conformance with the user fee reauthorization agreements, we may not be able to consider your response before we take an action on your application during this review cycle.

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by: /S/ 1-12-00
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP

APPEARS THIS WAY
ON ORIGINAL

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

Date: 19-Mar-2000 11:44am EST
From: John Gibbs
GIBBS
Dept: HFD-820 PKLN 14B31
Tel No: 301-827-6420 FAX 301-827-0878

TO: Leah Ripper (RIPPER)
TO: Julie Rhee (RHEEJ)

CC: Stephen Moore (MOOREST)

Subject: NDA 21-081 (LANTUS) Tertiary Chem Review

NDA #21-081
Drug: Lantus (insulin glargine [rDNA origin] injection).

Type of Letter: APPROVAL Drug Classification: 1S

Chemistry Tertiary Review:

A: Applicant has claimed Categorical Exclusion. ACCEPTABLE to Chemistry Reviewer. See Chem. Rev. dated 29 Feb 2000.

ER: Overall Recommendation of ACCEPTABLE per EES dated 8 Feb 2000.

TORO: ACCEPTABLE per Microbiologist's Review #2 by P. Stinavage, Ph.D dated 19 Jan 2000.

RADENAME: ACCEPTABLE per CDER Labeling and Nomenclature Committee consult #1203 dated 8/9/99 and OPDRA consult dated 29 Feb 2000.

EVICE CONSULT: Per CDRH Consult from Von Nakayama dated 14 Sept 99, there are no objections to using OptiPens for administering Lantus.

MC: Found ACCEPTABLE in Chemistry Review #1 dated 29 Feb 2000.

John J. Gibbs, Ph.D.

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 8, 2000

TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 21

COMMENTS:

NDA 21-081 Lantus

Physician PI (FDA revision #1). Please note the "Note to the sponsor" on pages 19 and 20.

Cc: Orig NDA
HFD-510/Div File

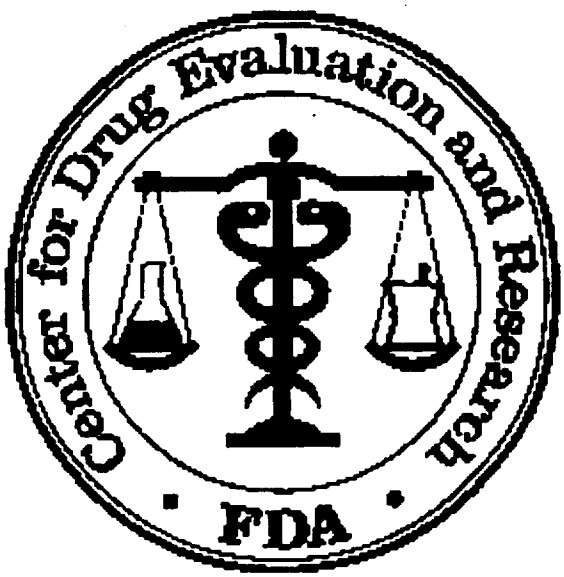
WITHHOLD 20 PAGE (S)

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 11, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 2

COMMENTS:

NDA 21-081 LantusTM (insulin glargine [rDNA origin] injection)

Clinical recommendations.

cc: Orig NDA
HFD-510/DivFile
HFD-510/Misbin

NDA 21-081 Lantus™ (insulin glargine [rDNA origin] injection)

Clinical comment

As discussed during our February 10, 2000, telephone conversation, the following is our recommendation on the mixing experiment for Lantus:

Use dogs that have been fasted at least 4 hours and remain fasting throughout sampling, at least 10 dogs per group. Sampling for blood glucose before injection (zero time) and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24 hours

Group A: 0.1 U/kg HOE 901 (U100) + 0.1U/kg regular insulin (U100) given as two separate subcutaneous injections.

Group B: 0.1U/kg HOE 901 (U100) + 0.1U/kg regular insulin (U100) injected together two minutes after mixing in the same syringe.

Cleared for faxing by:

/S/

Robert Misbin, M.D.
Medical Officer, DMEDP

/S/ 2/11/00

Saul Malozowski, M.D.
Medical Team Leader, DMEDP

/S/ 2/11/00

John Jenkins, M.D.
Acting Director, DMEDP

NDA Review (~~supplement~~)
NDA-21-081 Insulin Glargine

The financial disclosure document submitted with the original application on April 9, 1999 appears adequate.

The information in the safety update was already covered in the NDA review that I submitted January 24, 2000.

/S/

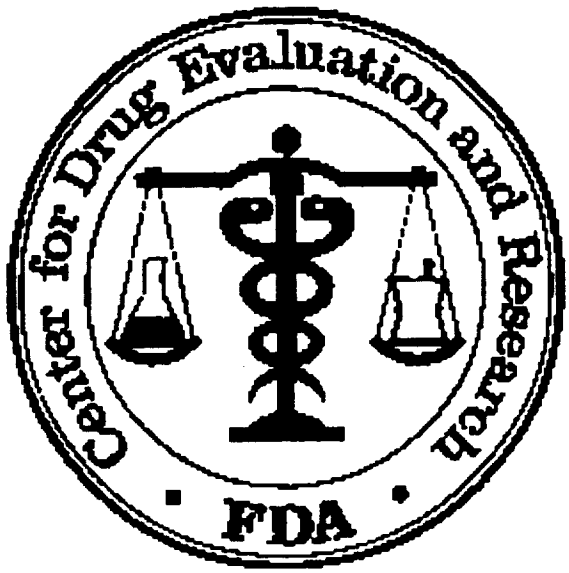
Robert I Misbin MD
Medical Officer
February 10, 2000

cc: Orig NDA 21-081
HFD-510/Div File
HFD-510/Misbin

APPEARS THIS WAY
ON ORIGINAL

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 3, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles (agent for Aventis)

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

COMMENTS:

NDA 21-081 Lantus

Please provide your commitment for the Phase 4 study concerning the progression of retinopathy in patients with type 2 diabetes by February 10, 2000. Thank you.

NDA 21-081 Lantus

Request for Phase 4 study commitment

Please provide your commitment to conduct a Phase 4 study to further evaluate the increased progression of retinopathy. The Phase 4 study should be a large simple trial in patients with type 2 diabetes with little or no background retinopathy. It should compare daily Lantus with twice daily NPH and should be powered to detect a two-fold increase in three step progression of retinopathy over one year with 90% power. The study should also include retinal photographs of all patients at baseline and at every 3-6 months in follow-up.

Please use the following timeline format for your commitment:

Protocol Submission:	X months after the approval
Study Start:	Y months after the approval
Final Report Submission:	Z months after the approval

Please submit your proposed commitment by February 10, 2000.

Cleared for faxing by: /S/ 2/3/00
John Jenkins, M.D., Acting Director, DMEDP

APPEARS THIS WAY
ON ORIGINAL

Explanation of Major Labeling Revisions – Lantus NDA 21081

Since the trials were unblinded we do not accept claims of superiority with respect to NPH insulin. The label should be revised to delete references to ——— . The table should include changes in GHb and total insulin dose. The text should explain that total insulin dose is the sum of basal and regular insulin and give any pertinent differences.

Lantus cannot be mixed with regular insulin. Inadvertent mixing of Lantus with regular insulin could cause precipitation of the regular insulin. This could constitute a safety hazard. ———

The retinopathy findings should be discussed in the Adverse Events section.

The claim that Lantus ——— should be deleted. The data were not corrected for non-specific binding and are probably of no clinical importance.

It is confusing to describe the PK data as "peakless" but give values for T max.

Phase 4

Required for approval:

The two major safety issues are concerns about the progression of retinopathy and the consequences of inadvertent mixing. To address the retinopathy issue, the Sponsor should perform a large simple trial in patients with type 2 diabetes with little or no background retinopathy. It should compare once daily HOE 901 with twice daily NPH and should be powered to detect a two-fold increase in three step progression of retinopathy over one year with 90% power. The need to include retinal evaluation was faxed to HMR on November 23, 1999 as part of comments on protocol 4002. ———

[ ]

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

February 29, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081** **NDA Amendment**
insulin glargine injection **Revisions to Proposed Labeling**

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

Enclosed please find our response to the changes you have requested regarding the HOE 901 labeling. The labeling is being provided as two documents:

- Revised proposed labeling with all changes marked (Additions made in blue and strikeouts in red. All new changes have been highlighted in yellow.)
- Revised proposed labeling with changes incorporated

In addition to several minor changes, there are four changes for which we have provided additional information in support of our position. These sections are identified by a "Tab number" in the text of the labeling, with the supporting information under the specific tab.

1) Rationale for the terms "smooth and peakless"
2) Rationale for the inclusion of fasting glucose and hypoglycemia results in the clinical section
3) Rationale for the rewording under "Carcinogenesis, mutagenesis, impairment of fertility
4) Background information to support the wording for the retinopathy section of the label under "Adverse Events"

The information on the 10 mL vials has not been included in this version of the revised proposed labeling, but will be added once the results of the dog study, currently being conducted, are available. We plan to provide these results to the Agency on March 3, 2000, as previously agreed.

As requested, we are providing diskettes containing the labeling described above. The diskettes have been scanned for viruses using a standard program.

Please let me know if you have any questions regarding this information.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals Inc.	2/29/2000
TELEPHONE NO. *(Include Area Code)* (816) 966-5000	**FACSIMILE (FAX) Number** *(Include Area Code)* (816) 966-6794

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
10236 Marion Park Drive
Kansas City, Missouri 64134-0627

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
Quintiles, Inc. (816) 767-6674 or FAX: (816) 767-7373
P.O. Box 9708
Kansas City, MO 64134-0708

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-081

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
insuline glargine injection	LANTUS™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
21^{A}-Gly-30^{B}a-L-Arg-30^{B}b-L-Arg-human insulin	HOE 901

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Injection	100 U/mL	Subcutaneous

(PROPOSED) INDICATION(S) FOR USE:
LANTUS™ is an insulin analog indicated for once-daily subcutaneous administration in the treatment of patients with type 1 or type 2 diabetes mellitus who require basal (long-acting) insulin for the control of hyperglycemia.

APPLICATION INFORMATION

APPLICATION TYPE (check one)
☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Response to FDA, providing revisions to proposed labeling

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See original New Drug Application dated 4/09/99

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

See original New Drug Application dated 4/09/99

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Lavonne Patton	Lavonne Patton, Ph.D. Director, Regulatory & Technical Services (Quintiles)	2/29/2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
P.O. Box 9708, Mail Station: F3-M3026 Kansas City, MO 64134-0708	(816) 767-6000

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

WITHHOLD 18 PAGE (S)

Draft

Labeling

Note to the sponsor:

Explanation of Major Labeling Revisions:

Clinical section:

1. Since the trials were unblinded, the Agency does not accept claims of superiority with respect to NPH insulin.

2. The label should be revised to delete references to [redacted]

3. The table should include changes in GHb and total insulin dose. The text should explain that total insulin dose is the sum of basal and regular insulin and give any pertinent differences.

4. Lantus cannot be mixed with regular insulin. Inadvertent mixing of Lantus with regular insulin could cause precipitation of the regular insulin. This could constitute a safety hazard. [redacted]

5. The retinopathy findings should be discussed in the Adverse Events section.

6. The claim that Lantus [redacted] should be deleted. The data were not corrected for non-specific binding and are probably of no clinical importance.

7. It is confusing to describe the PK data as "peakless" but give values for T max.

Pharm/Tox section:

Relative exposures are expressed based on body surface area comparisons.

Carcinogenicity: In male rats, there were findings of injection site histiocytomas in groups treated with vehicle or vehicle plus LANTUS. This did not occur in female rats, the saline control or an insulin comparator group in which the vehicle was similar, but a different pH. This was not dose related, but appeared to be related to the presence of vehicle. This cannot be clearly attributed to the vehicle alone, however, since the finding was not evident in females. The significance of this finding to humans in not known, but the executive CAC expressed concern when the results were presented to the committee and recommended that the findings be described in the label.

In mice, there were no tumor findings in males or females related to treatment. However, due to excessive mortality in the female arm of the study (apparently not related to drug toxicity since there was high mortality in the control group), the data could not be interpreted.

Since standard 2 year studies in two species are not generally recommended for insulin analogs, this is not a deficiency in the safety evaluation package, but the e-CAC again recommended that the label reflect that the female arm of the study was inconclusive.

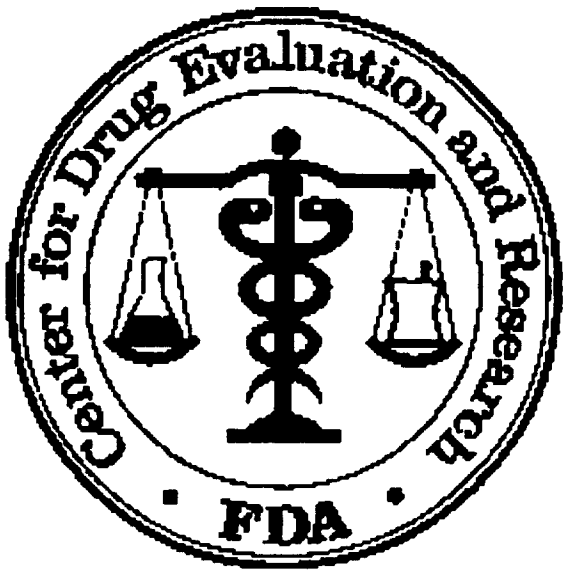
APPEARS THIS WAY
ON ORIGINAL

(this page is for my information only)

cc:Sahlroot 1-28-99/Misbin 1-28-99/Malozowski 1-28-99/Haidar 1-28-99/HRhee 1-28-99/Steigerwalt 1-28-99/Steigerwalt 2-3-00/Malozowski 2-4-00

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 8, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 21

COMMENTS:

NDA 21-081 Lantus

Physician PI (FDA revision #1). Please note the "Note to the sponsor" on pages 19 and 20.

Cc: Orig NDA
HFD-510/Div File

WITHHOLD 18 PAGE (S)

Draft

Labeling

Note to the sponsor:

Explanation of Major Labeling Revisions:

Clinical section:

1. Since the trials were unblinded, the Agency does not accept claims of superiority with respect to NPH insulin.

2. The label should be revised to delete references to ———

3. The table should include changes in GHb and total insulin dose. The text should explain that total insulin dose is the sum of basal and regular insulin and give any pertinent differences.

4. Lantus cannot be mixed with regular insulin. Inadvertent mixing of Lantus with regular insulin could cause precipitation of the regular insulin. This could constitute a safety hazard. ———

5. The retinopathy findings should be discussed in the Adverse Events section.

6. The claim that Lantus ——— should be deleted. The data were not corrected for non-specific binding and are probably of no clinical importance.

7. It is confusing to describe the PK data as "peakless" but give values for T max.

Pharm/Tox section:

Relative exposures are expressed based on body surface area comparisons.

1. Carcinogenicity subsection:
   In male rats, there were findings of injection site histiocytomas in groups treated with vehicle or vehicle plus LANTUS. This did not occur in female rats, the saline control or an insulin comparator group in which the vehicle was similar, but a different pH. This was not dose related, but appeared to be related to the presence of vehicle. This cannot be clearly attributed to the vehicle alone, however, since the finding was not evident in females. The significance of this finding to humans in not known, but the executive CAC expressed concern when the results were presented to the committee and recommended that the findings be described in the label.

   In mice, there were no tumor findings in males or females related to treatment. However, due to excessive mortality in the female arm of the study (apparently not related to drug

toxicity since there was high mortality in the control group), the data could not be interpreted. Since standard 2 year studies in two species are not generally recommended for insulin analogs, this is not a deficiency in the safety evaluation package, but the e-CAC again recommended that the label reflect that the female arm of the study was inconclusive.

2. Pregnancy subsection:
In rabbits, there were findings of ventricular dilatation in 5 fetuses in 2 litters of rabbits at a dose approximately twice human exposure based on surface area (mg/m2) comparisons. These appear to be similar (but not identical) to findings reported for human insulin when tested in animal models. The clinical significance would appear to be the same as for insulin. However, according to 21 CFR 201.57(f)(6)(c) this is an adverse effect in the fetus and thus justifies a category C for the pregnancy category.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: March 13, 2000 /S/

FROM: Karen Lechter, ~~HFD~~-42

TO: Julie Rhee, HFD-510

SUBJECT: Lantus Vial Patient Package Insert
NDA 21-081

Attached is my suggestion for the PPI for the vial form of Lantus. It is almost identical to the cartridge version I sent you earlier. I have indicated changes from the vial version by strike-outs and highlighting.

Please let me know if you have any questions.

cc:
HFD-42/Lechter/Ostrove/Tabak/Askine/Reading
NDA 21-081

KLechter 3/13/00

NON-RELEASABLE

cc: Jenkins/Mroczkowski/Miller

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 8 PAGE (S)

Draft

Labeling

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: April 20, 2000
Re: 4/18/00 submission (patient PI for vial and cartridge) I called Dr. Patton and requested the following changes be made on the patient PI for vial and cartridge: 1. Page 4, line 3: Add a comma between "antidiabetic pills" and "or ACE inhibitors". 2. Page 4, line 11: Add a comma between "alcohol" and "talk to your. . ." 3. Page 4: Change the following subheading [redacted] that are in the "What are the possible side effects of insulins?" heading section to as follow: 1. Allergic reactions: 2. Hypoglycemia: 3. Hyperglycemia: 4. Possible reactions on the skin at the injection site: 4. Page 6, "How should I store LANTUS?" Once a vial or cartridge is opened, the instruction should state to keep the vial or cartridge as cool as possible (not greater than 86°F [30°C]. cc:OrigNDA HFD-510/DivFile /S/ Name: Julie Rhee	NDA#: 21-081 **Telecon/Meeting initiated by:** O FDA **By:** Telephone **Product Name:** Lantus™ (insulin glargine [rDNA origin] injection) **Firm Name:** Aventis Pharmaceuticals, Inc. **Name and Title of Person with whom conversation was held:** Lavonne Patton, Ph.D. Quintiles (agent for Aventis) **Phone:** (816) 767-6674

APPEARS THIS WAY
ON ORIGINAL

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: April 20, 2000
Re: 4/18/00 submission I called Dr. Patton and conveyed the following changes, requested by Dr. Jenkins, on their 4/18/00 submission for physician PI: 1. Page 5, line 103: Add "In these studies," before the sentence starting with "LANTUS and NPH human . . . ." 2. Page 9, line 218: Add a colon between "hypoglycemia" and "oral antidiabetic" 3. Page 9, line 221: Add "of insulin:" after "effect" at the end of the line. 4. Page 9, line 232: Add a comma between "0.455 mg/kg" and "which is". 5. Page 12, line 335: Delete "s" from "antidiabetics" and add "drugs" at the beginning of the line. I asked Dr. Patton to send me the revised PI as an attachment to an e-mail and follow it with a hard copy. Dr. Patton agreed to do so. cc:OrigNDA HFD-510/DivFile	**NDA#:** 21-081 **Telecon/Meeting initiated by:** □□□FDA **By:** Telephone **Product Name:** Lantus™ (insulin glargine [rDNA origin] injection) **Firm Name:** Aventis Pharmaceuticals, Inc. **Name and Title of Person with whom conversation was held:** Lavonne Patton, Ph.D. Quintiles (agent for Aventis) **Phone:** (816) 767-6674
APPEARS THIS WAY ON ORIGINAL /S/ **Name: Julie Rhee**	

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

April 18, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081**
insulin glargine injection

NDA Amendment
Revisions to Proposed Labeling

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

Enclosed please find our response to the changes you have requested regarding the HOE 901 labeling based on the comments we received on April 17 and April 18, 2000. The following items are included in this submission (Additions made in blue and strikeouts in red. All new changes have been highlighted in yellow).

- Physician's Package Insert (clean copy)
- Physician's Package Insert (changes marked)
- Patient Information Leaflet – Vial (clean copy)
- Patient Information Leaflet – Vial (changes marked)
- Patient Information Leaflet – Cartridge (clean copy)
- Patient Information Leaflet – Cartridge (changes marked)
- OptiPen™ One User Manual (clean copy) with revised Figures as requested by the Division (Gatefold diagram, Figure A, Figure D and Figure E)
- OptiPen™ One User Manual (changes marked)
- Label and carton for the 5 mL vial and 10 mL vial; and label, carton and blister for the 3 mL cartridge (As requested by the Division the established name will be rewritten as "insulin glargine (rDNA origin) injection" on all labeling components.)
- Carton for the OptiPen™ One device.

We would like to provide the following comment to the Package Insert. On page 4 of the clean copy (lines 92-94), the Division had added the following wording, "The overall rate of hypoglycemia did not differ between patients ——— diabetes treated with Lantus compared with NPH human insulin." In reading this statement it was felt it could be misinterpreted to mean that the rate of hypoglycemia ——— diabetic patients was the same. Therefore, we have rewritten this statement to read, ""The overall rate of hypoglycemia did not differ between patients with diabetes treated with Lantus compared with NPH human insulin."

All of the labeling files listed above have been sent to Ms. Julie Rhee electronically, except the new Figures being supplied for the OptiPen™ One User Manual. In addition, we are providing a desk copy to Ms. Julie Rhee including diskettes containing the labeling described above. The diskettes have been scanned for viruses using a standard program.

Please let me know if you have any questions regarding this information.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

APPEARS THIS WAY
ON ORIGINAL

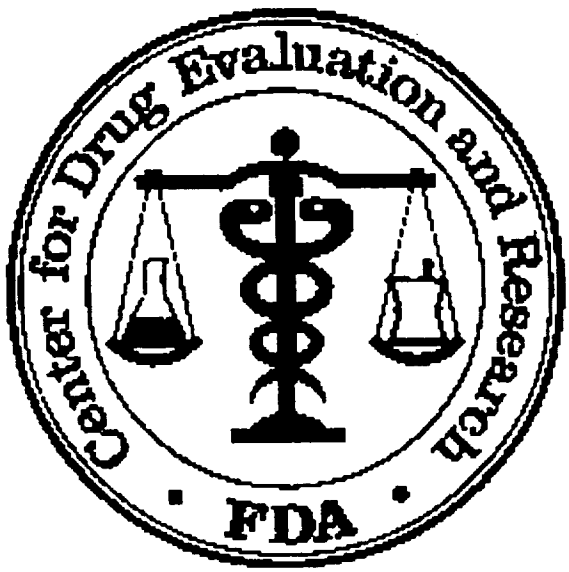
WITHHOLD 102 PAGE (S)

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: April 18, 2000



TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 18

COMMENTS:

NDA 21-081 Lantus™

Draft FDA revision (dated 4/18/00) OptiPen One Insulin Delivery Device User Manual

cc: Orig NDA
HFD-510/Div File

WITHHOLD 17 PAGE (S)

Draft

Labeling

FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: April 17, 2000

TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 32

COMMENTS:

NDA 21-081 Lantus

Draft FDA revision (dated 4/17/00) physician and patient PI for vial and cartridge.

cc: orig NDA
HFD-510/Div File

WITHHOLD 31 PAGE (S)

Draft

Labeling

March 27, 2000

Memo to the file

NDA 21-081 LantusTM (insulin glargine [rDNA origin] injection)

Sponsor: Aventis Pharmaceuticals, Inc.

The attached draft package inserts were forwarded to Lavonne Patton, Ph.D., Regulatory Affairs, at Quintiles (US agent for Aventis) today by e-mail. The documents were saved with the password ———

These draft PIs include the following:

1. Physician PI (FDA revision #2),
2. Patient PI for Vial (FDA revision #1),
3. Patient PI for Cartridge (FDA revision #1), and
4. OptiPen User Manual (FDA revision #1).

/S/

Julie Rhee
Regulatory Project Manager

cc:OrigNDA
HFD-510/DivFile

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 46 PAGE (S)

Draft

Labeling

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

April 20, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081** **NDA Amendment**
insulin glargine injection **Revisions to Proposed Labeling**

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

Enclosed please find our response to the changes you have requested regarding the HOE 901 labeling based on the comments we received on April 20, 2000, on the Physician's Package Insert and the Patient Information Leaflet for the vial and carton. The following items are included in this submission (additions made in blue and strikeouts in red).

- Physician's Package Insert (clean copy)
- Physician's Package Insert (changes marked)
- Patient Information Leaflet – Vial (clean copy)
- Patient Information Leaflet – Vial (changes marked)
- Patient Information Leaflet – Cartridge (clean copy)
- Patient Information Leaflet – Cartridge (changes marked)

All of the labeling files listed above have been sent to Ms. Julie Rhee. In addition, we are providing a desk copy to Ms. Julie Rhee including diskettes containing the labeling described above. The diskettes have been scanned for viruses using a standard program.

Please let me know if you have any questions regarding this information.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

WITHHOLD 14 PAGE (S)

Draft

Labeling

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

April 21, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081**
insulin glargine injection

NDA Amendment
General Correspondence

Attention: Ms. Julie Rhee

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

This letter is to inform you that we received both faxes dated April 21, 2000, regarding the approval of NDA 21-081 for Lantus™ (insulin glargine [rDNA origin] injection) and the OptiPen™ One Insulin Delivery Device.

Thank you for your support during the review of this NDA.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

APPEARS THIS WAY
ON ORIGINAL

Aventis Pharmaceuticals

Aventis

April 21, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081**
insulin glargine injection

NDA Amendment
General Correspondence

Attention: Ms. Julie Rhee

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081. As such, Aventis Pharmaceutical Inc., has also agreed that Quintiles, Inc., can receive the action letter from the Division of Metabolic and Endocrine Drug Products for NDA 21-081 for insulin glargine injection (Lantus™).

If you have any questions, please do not hesitate to contact me at 816-966-5721.

Sincerely,

J. Michael Nicholas, Ph.D.
Vice President, Marketed Products
U.S. Regulatory Affairs
Aventis Pharmaceuticals Inc.

APPEARS THIS WAY
ON ORIGINAL

WITHHOLD 14 PAGE (S)

Draft

Labeling

QUINTILES

Quintiles, Inc.
Post Office Box 9708
Kansas City, MO 64134-0708
(816) 767-6000

ORIGINAL

NEW CORRESP

NV

March 14, 2000

John Jenkins, M.D.
Acting Director, Division of Metabolic and Endocrine Drug Products
Center for Drug Evaluation and Research (HFD-510)
Food and Drug Administration
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081**
insulin glargine injection

Phase IV Clinical Commitment

Dear Dr. Jenkins:

Quintiles, Inc., as the US agent for Aventis Pharmaceuticals Inc., has been authorized to communicate with the FDA on NDA 21-081.

On February 3, 2000 we received a request from the Division for a commitment to conduct a Phase IV study "concerning the progression of retinopathy in patients with type 2 diabetes" (see attached FAX). The Sponsor is agreeing to the requested Phase IV clinical commitment based on our understanding from the Agency that vials will be approved in the U.S. for marketing as part of the HOE 901 NDA 21-081 application. Please note that while the initial date for response to this request was February 10, 2000, the response time was extended to March 14, 2000, after discussions with Julie Rhee, Project Manager.

Our commitment to conduct a Phase IV study along with a brief description of the study and proposed timing is included in the attached document.

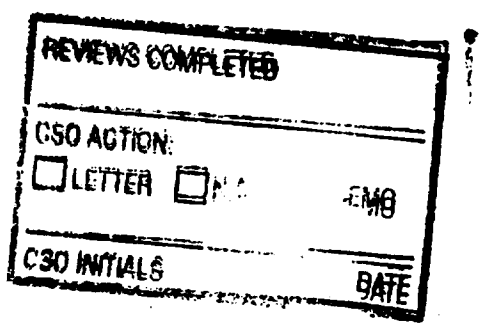
Please let me know if you have any questions or concerns.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D. (816) 767-6674
Director, Regulatory and Technical Services
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

Enclosures



FOOD AND DRUG ADMINISTRATION
DIVISION OF METABOLIC AND
ENDOCRINE DRUG PRODUCTS
5600 FISHERS LANE, HFD-510
ROCKVILLE, MARYLAND 20857-1706

DATE: February 3, 2000

TO:

Name: Lavonne Patton, Ph.D.

Fax No: (816) 767-7373

Phone No.: (816) 767-6674

Location: Quintiles (agent for Aventis)

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

COMMENTS:

NDA 21-081 Lantus

Please provide your commitment for the Phase 4 study concerning the progression of retinopathy in patients with type 2 diabetes by February 10, 2000. Thank you.

NDA 21-081 Lantus

Request for Phase 4 study commitment

Please provide your commitment to conduct a Phase 4 study to further evaluate the increased progression of retinopathy. The Phase 4 study should be a large simple trial in patients with type 2 diabetes with little or no background retinopathy. It should compare daily Lantus with twice daily NPH and should be powered to detect a two-fold increase in three step progression of retinopathy over one year with 90% power. The study should also include retinal photographs of all patients at baseline and at every 3-6 months in follow-up.

Please use the following timeline format for your commitment:

Protocol Submission:	X months after the approval
Study Start:	Y months after the approval
Final Report Submission:	Z months after the approval

Please submit your proposed commitment by February 10, 2000.

APPEARS THIS WAY
ON ORIGINAL

Cleared for faxing by: /S/ 2/3/00
John Jenkins, M.D., Acting Director, DMEDP

APPEARS THIS WAY
ON ORIGINAL

HOE 901 Clinical Phase IV Commitment

Background

At an 8 August 1996 Agency-Sponsor meeting, the Agency recommended that ophthalmologic assessments in some of the Phase III studies be conducted. It was suggested that these assessments be done by fundus photography, so that if an issue arose the photographs could be evaluated by an independent panel.

To address this request of the Agency, the Sponsor collected fundus photographs in 4 (3001, 3002, 3004 and 3006) of the 6 Phase III studies (fundus photographs were not collected in study 3005 due to its short duration of treatment, i.e., 16 weeks, or in study 3003 that was conducted in children). Specifically, seven-standard field fundus photography was used to document the diabetic retinopathy status in the applicable HOE 901 studies. The fundus photographs were taken at baseline and end study. In addition, fundus photographs were taken at week 12 in subjects with moderate non-proliferative retinopathy with a high risk of progression.

Before coming to a final conclusion on the methodology and study design of Phase III studies for evaluation of diabetic retinopathy, we had several discussions with experts. We were advised that the sample size and study duration was adequate to identify a marked toxic effect, but would be inadequate to identify a difference in the rate of retinopathy progression such as that seen between the conventional and intensive treatment groups in the DCCT. Because of the small number of events expected, there was a risk we could see an excess of events in either treatment group that was not clinically relevant. However, clinical data from adverse event reports and ophthalmological examinations in support of the fundus photography in all adult subjects at baseline and endpoint was believed to provide the best clinical and scientific assessment possible to evaluate the clinical relevance of any finding.

On 11 March 1998, following initiation of the HOE 901 Phase III studies, a joint meeting of the Ophthalmic Drugs Subcommittee of the Dermatologic and Ophthalmic Drugs Advisory Committee and the Endocrine and Metabolic Drugs Advisory Committee was held to discuss diabetic retinopathy clinical trial endpoints. The retinopathy experts at this meeting emphasized the need to document a sustained change in retinopathy to establish progression. Another point made by the experts was that they had learned that the ETDRS endpoint of clinically significant macular edema was not suitable for evaluating progression of macular edema and they proposed a new endpoint, retinal thickening that involves the center. Finally, the overall conclusion of the advisory committee was that studies should be of adequate long-term duration to evaluate progression of retinopathy. These discussions emphasized that evaluation of retinopathy in studies such as the HOE 901 Phase III studies was not ideal because the treatment duration was a year or less. In the original evaluation of the studies, center involvement for macular edema was not analyzed. However, it was included in the later analyses discussed below.

Upon completion of all retinopathy evaluations in the HOE 901 Phase III trials, we convened a group of experts to review the data, advise us on additional analyses and to help us interpret the outcome. Two observed differences in the multiple treatment group comparisons were noted and evaluated by the group. In study 3002 (1-year duration), there was an excess of patients who developed CSME according to the photographic gradings in the HOE 901 group than in the NPH group (26/233, 11.2% versus 14/214,

6.5%). In study 3006 (6-month duration), there was an excess of patients with a ≥3-step change in retinopathy in the fundus photographs (16/213, 7.5% versus 6/220, 2.7%). Their interpretation of the data, including adverse events, ophthalmological exam, visual acuity and photocoagulation events in addition to the fundus photography results, has been submitted to the agency in the "HOE 901 Retinopathy Expert Statement" submitted as a NDA Amendment on October 18, 1999. The expert group's conclusion was, "Taken in its totality the evidence does not demonstrate adverse retinopathy treatment effects due to HOE 901. Importantly, disc swelling, which had been observed in prior studies of IGF-1, was not observed in any patient. Although there are individual comparisons favoring one group or the other, our conclusion is strongly influenced by (1) the large number of statistical comparisons that have been made, increasing the probability of chance findings, (2) the lack of consistency among multiple measures of the disease process within each study, (3) the lack of consistency in findings between the studies, and (4) the lack of consistent differences for the most clinically important outcomes (development of proliferative retinopathy, photocoagulation for proliferative retinopathy, clinical exam data on macular edema involving the center of the macula, photocoagulation for macular edema, and visual acuity)."

The rigorous evaluation and considered opinion of these experts leaves no doubt that HOE 901 does not pose a retinopathy hazard in clinical use. However, the Agency has determined that the statistically significant difference in 3-step progression in one study must be evaluated further. Therefore, the sponsor commits to conduct a specific Phase IV evaluation of retinopathy in patients with type 2 diabetes mellitus with little or no retinopathy at baseline treated with HOE 901 or NPH human insulin.

Retinopathy Study Proposal

Primary objective

To compare the percentage of subjects with ≥3 step progression in the ETDRS retinopathy scale during treatment with insulin glargine or NPH human insulin

Design

This is an open-label, NPH human insulin-controlled, randomized (1:1), parallel-group study. The study consists of a 1- to 4-week screening phase and a treatment phase with a fixed end-date to provide an average three-year treatment period. Subjects will undergo seven standard field fundus photography at baseline, 6 months, 1 year and annually until endstudy.

Population

Subjects, age 30 to 70 years, with type 2 diabetes with little or no retinopathy (ETDRS score 43/<43 or lower) treated with stable doses of oral agents alone or in combination with NPH insulin for at least 3 months prior to study entry and a baseline HbA_{1c} ≤10.0%.

Sample Size

It is planned to treat 1060 subjects, 530 subjects in each group.

The primary efficacy variable for the comparison between HOE 901 and NPH insulin is the percentage of patients with a ≥3-step progression in the ETDRS retinopathy scale at the study endpoint.

The hypothesis to be tested:

H_0: There is no difference between the percentage of patients with ≥3-step progression in the HOE 901 and NPH treatment groups in the population,

(HOE 901 = NPH)

against the alternative:

H_1: There is a difference between HOE 901 and NPH treatment groups in the percentage of patients with ≥3-step progression.

(HOE 901 ≠ NPH)

From Phase III studies with HOE 901 [redacted] the expected annual event rate for ≥3-step progression in patients with no or minimal retinopathy (ETDRS 43/<43) is estimated to be 2.5%. Based on 1:1 randomization, a total number of 800 subjects (400 subjects for each group) is required to detect a two-fold difference between HOE 901 and NPH with a type I error of α = 5% and a statistical power of 90%.

With an expected drop-out rate of 25% during the course of the study, a total number of 1060 subjects (530 subjects in each group) should be enrolled in order to have 800 subjects (400 subjects in each group) evaluable at endstudy.

Rationale for a 3-year Study Duration

The sponsor is proposing a 3-year study rather than the 1-year study suggested by the Agency for a number of reasons.

In the target patient population the event rate is expected to be low. Factors such as treatment group imbalances in baseline risk factors, the treatment of co-morbid conditions, the quality of the photographs and confounding treatment effects such as improved glycemic control can influence the outcome of the study. A 1-year study will only answer whether HOE 901 is associated with a toxic effect on retinopathy, an assessment which could be confounded by early worsening associated with improved control. A longer study can be conducted in fewer patients with better logistical management of a technically complex study. Furthermore, a longer study can answer not only whether HOE 901 is associated with a toxic effect on retinopathy, but can also balance early worsening and the long-term benefit of improved control.

Proposed Study Time Schedule

Final protocol:	October 2000
First patient randomized:	January 2001
Study end date:	October 2004
Final report:	April 2005