CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-081

CORRESPONDENCE

RECORD OF TELEPHONE CONVERSATION/MEETING	**Date:** June 4, 1999
Re: 4/9/99 submission I called Dr. Patton and conveyed the following request from Dr. Wei. These requests were included in Dr. Wei's 6/2/99 memorandum. 1. Please submit Section 6 summary (Human Pharmacokinetics and Bioavailability) on disc in MS Word format. 2. Submit on disc individual study summaries (text and tables) in Section 6 in MS Word format. I asked Dr. Patton to use either Office 97 or 6.0 Word format. Dr. Patton agreed to get back to me with a timeline when we could expect the requested Word documents. cc:OrigNDA HFD-510/DivFile HFD-870/Wei p.s. The package insert was submitted on a disc as Word document. /S/ --- **Name: Julie Rhee**	**NDA #: 21-081** **Telecon/Meeting initiated by:** FDA **By:** Telephone **Product Name:** LANTUS™ **Firm Name:** Hoechst Marion Roussel, Inc **Name and Title of Person with whom conversation was held:** Lavonne Patton, Ph.D. Regulatory Affairs Quintiles US agent for Hoechst **Phone:** (816) 767-6674

ORIGINAL

MEMORANDUM OF FILING MEETING MINUTES

Meeting Date: June 2, 1999
Application: NDA 21-081 Lantus (insulin glargine injection [rDNA origin])
Sponsor: Hoechst Marion Roussel, Inc.
Attendees:

Solomon Sobel, M.D., Director, DMEDP
Robert Misbin, M.D., Medical Officer, DMEDP
Ronald Steigerwalt, Ph.D., Pharmacology Team Leader, DMEDP
Herman Rhee, Ph.D., Pharmacology Reviewer, DMEDP
Todd Sahlroot, Ph.D., Statistical Team leader, DOB II
Jonathan Ma, Ph.D., Statistician, DOB II
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DPE II
Jim Wei, Ph.D., Biopharm reviewer, DPE II
Julie Rhee, Project Manager, DMEDP

Discussion Points:

Clinical:

1. The NDA is fileable as a standard application.
2. Advisory Committee meeting is not necessary.
3. Statistical review is needed for type 1 indication only.
4. Dr. Misbin is amenable to have the Division of Scientific Investigation choose the clinical audit sites from Study 3001 or Study 3004.

Pharmacology:

The application is fileable.

Statistical:

1. The application is fileable.
2. There are five Phase 3 studies (three studies for type 1 and two studies for type 2 indication). Medical Officer agreed that review of only type 1 indication would be acceptable.
3. Ask the sponsor to submit study reports from studies 3001, 3004, and 3005 in Word format.
4. Ask the sponsor to submit a hard copy of carcinogenicity study reports.

Biopharm:

The application is fileable.

Chemistry:

Dr. Berlin was not able to attend the filing meeting but informed me that the NDA is fileable by e-mail (attached).

Microbiology:

Dr. Stinavage informed me that the NDA is fileable by e-mail (attached).

Conclusion:

1. The NDA is filed as a standard application.
2. Advisory Committee meeting is not necessary for this NDA. machang
3. Statistical review of type 1 indication only would be acceptable.
4. Clinical audit sites are to be chosen by DSI from either Study 3001 or 3004.
5. The NDA is NME with UF_{10} due date of February 23, 2000. The following is a list of target dates:
   - January 7, 2000: Final review with team leader's concurrence
   - January 18, 2000: Action package to Dr. Sobel
   - January 31, 2000: Action package to Dr. Jenkins
6. The company's Information Technology contact person is ——— at

/S/ 6-21-99
Julie Rhee

Attachments: 1. Summary of studies prepared by Dr. Jonathan Ma, HFD-715
2. E-mail from Dr. Berlin
3. E-mail from Dr. Stinavage

cc:OrigNDA
HFD-510/DivFile
HFD-510/Malozowski/Misbin/Moore/Berlin/Steigerwalt/HRhee
HFD-715/Sahlroot/Ma
HFD-870/Ahn/Wei
HFD-160/Cooney/Stinavage
R/D by: JRhee 6/3/99
Concurred by: Steigerwalt 6-4-99/Sahlroot 6-4-99/Ahn 6-17-99/Ma 6-18-99/Wei 6-18-99/Misbin 6-21-99/HRhee 6-21-99
F/T by: JRhee 6-21-99

Meeting Minutes

NDA 21-081
Drug name: Lantus (insuline glargine injection)
Applicant: Hoechst Marion Roussel, Inc.
Indication: Treatment of —— diabetes
User fee date: 23 February 2000
Statistics reviewer: Z. Jonathan Ma, Ph.D.

Date6/2/99

Summary of Pivotal Studies: 3001 and 3004		
	3001	3004
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III	
Study Treatment	HOE 901 once daily, individually titrated, plus regular insulin injections.	
Control Treatment	NPH once or twice daily, individually titrated, plus regular insulin injections.	
Duration of Treatment	28 weeks	
Patient Population	Type 1 diabetic subjects: >1 yr insulin trt; C-peptide<0.5 nmol/L; GHb≤12%	
Primary Efficacy Endpoint	GHb: change from baseline to 28 weeks or study endpoint	
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose. (3001 had nocturnal bood glucose)	
Sample Size	585 (292 HOE 901, 293 NPH)	534 (264 HOE 901, 270 NPH)
No. of Centers	63 in 12 European countries	49 in US
Primary Efficacy Analysis		
ANCOVA model	Change in GHb at endpoint = treatment + (pooled) center + baseline GHb	
ITT population	557 (283 HOE 901, 274 NPH)	518 (256 HOE 901, 262 NPH)
GHb (%): adj mean chg from baseline at endpoint	0.21 (0.053) vs 0.10 (0.053)	-0.16 (0.05) vs -0.21 (0.049)
Difference in adj mean chg	0.11	0.05 (0.069)
95% Confidence Interval	(-0.03, 0.24)	(-0.08, 0.19)

Summary of Study 3005	
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, plus regular insulin injections.
Control Treatment	NPH once or twice daily, individually titrated, plus regular insulin injections.
Duration of Treatment	16 weeks
Patient Population	Type 1 diabetic subjects: >1 yr daily insulin and NPH and Lispro for 3 months; C-peptide<0.5 nmol/L; GHb≤12%
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); 24-hr blood glucose profile; variability of fasting glucose; insulin dose.
Sample Size	619 (310 HOE 901, 319 NPH)
No. of Centers	60 in US and Canada

Summary of Study 3006	
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, with/without regular insulin injections.
Control Treatment	NPH once or twice daily, individually titrated, with/without regular insulin injections.
Duration of Treatment	28 weeks
Patient Population	Type 2 diabetic subjects: >3 months insulin; GHb 7-12%; BMI<40 kg/m2
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); variability of fasting glucose; fasting serum C-peptide; fasting serum insulin; insulin dose.
Sample Size	518 (259 HOE 901, 259 NPH)
No. of Centers	60 in US and Canada

Summary of Study 3002	
Overall Design	Multi-center, Active-Controlled, Randomized, Open-label, Parallel-Group, Phase III
Study Treatment	HOE 901 once daily, individually titrated, combined with OAD.
Control Treatment	NPH once or twice daily, individually titrated, combined with OAD.
Duration of Treatment	20 weeks
Patient Population	Type 2 diabetic subjects: >1 yr OAD; inadequate for >3 months with current OAD or insulin treatment; GHb 7.5-12%; BMI<40 kg/m2
Primary Efficacy Endpoint	GHb: change from baseline
Secondary Efficacy Endpoints	Hypoglycemia; fasting glucose (FPG;SMBG); nocturnal bood gucose; 24-hr blood glucose profile; variability of fasting glucose; fasting serum C-peptide; fasting serum insulin; insulin dose.
Sample Size	570 (289 HOE 901, 281 NPH)
No. of Centers	57 in 14 European countries

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

Sensitivity: COMPANY CONFIDENTIAL

Date: 15-Jun-1999 02:20pm EDT
From: William Berlin
BERLINW
Dept: HFD-510 PKLN 14B31
Tel No: 301-827-6370 FAX 301-443-2356

TO: Julie Rhee (RHEEJ)

Subject: NDA 21-081

Julie,
I have reviewed the contents of the above NDA and have concluded that adequate information has been provided for the CMC section to permit filing.
D

APPEARS THIS WAY
ON ORIGINAL

Printed by Julie Rhee

Electronic Mail Message

.ivity: COMPANY CONFIDENTIAL

Date: 02-Jun-1999 03:18pm
From: Paul Stinavage
STINAVAGEP
Dept: HFD-160 PKLN 18B08
Tel No: 301-827-7340 FAX 301-443-9281

O: Julie Rhee (RHEEJ)

ubject: FWD: Re: NDAs 21-081 filing meeting

hey're both (NDA's 21-081 filable.

aul

APPEARS THIS WAY
ON ORIGINAL

AC meeting was not held for Lantus

QUINTILES

Quintiles
10245 Hickman Mills Drive
P. O. Box 9708
Kansas City, MO 64134-0708

Tel (816) 303-6000
Fax (816) 966 3594

US Drug Regulatory Affairs

MERC Team (Metabolism, Endocrinology, Rheumatology, Cardiovascular)

MERC Team Members: Carol Blanton, Marguerite Enlow, Sharon Huffman, Philip Kastner, Michelle Kliewer, Lavonne Patton, Cindy Vick, Susan Zordan

To:	Julie Rhee	From:	Susan Zordan
Company:	FDA	Date:	March 15, 2000
Fax No:	301 443-9282	Page 1 of :	12

Comments: Copies of three submissions to NDA 21-081

Julie,
Attached are copies of the three submissions to NDA 21-081 which we discussed earlier today:

1. [redacted] withdrawal - Mailed 3/13/2000
2. Precautionary statement for mixing of Lantus with Regular Insulin – Mailed 3/15/2000
3. Outline of the educational program for health care professionals and patients – Mailed 3/15/2000

Sue

APPEARS THIS WAY
ON ORIGINAL

Jenkins/Malozowski/Misbin

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.	3/13/2000
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
withdrawal.

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 Lavonne Patton, Ph.D. Director, Regulatory & Technical Services (Quintiles)	DATE 3/13/2000
ADDRESS *(Street, City, State, and ZIP Code)* P.O. Box 9708, Mail Station: F3-M3026 Kansas City, MO 64134-0708		Telephone Number (816) 767-6000

QUINTILES

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

March 13, 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

[redacted] Withdrawal

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 requested by the Division of Metabolic and Endocrine Drug Products, Aventis Pharmaceuticals Inc., is withdrawing from consideration for approval [redacted] as part of HOE 901 NDA 21-081. The OptiPen™ [redacted] device will remain in the file being reviewed.

Please let me know if you have any comments or concerns regarding this request.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, Regulatory and Technical Services
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

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
Aventis Pharmaceuticals Inc.

DATE OF SUBMISSION
3/15/2000

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) 767-6670 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)*
insuline glargine injection

PROPRIETARY NAME *(trade name)* IF ANY
LANTUS™

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

CODE NAME *(If any)*
HOE 901

DOSAGE FORM
Injection

STRENGTHS
100 U/mL

ROUTE OF ADMINISTRATION
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
Holder of Approved Application

TYPE OF SUBMISSION
check one

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ RESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION
Provide precautionary statement for mixing of Lantus with Regular Insulin

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
Susan Jordan for Lavonne Patton	Lavonne Patton, Ph.D. Director, Regulatory & Technical Services (Quintiles)	3/15/2000
ADDRESS *(Street, City, State, and ZIP Code)* P.O. Box 9708, Mail Station: F3-M3026 Kansas City, MO 64134-0708	Telephone Number (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.

QUINTILES

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

March 15, 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

Precautionary Statement for Mixing of Lantus with Regular Insulin

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.

During our teleconference with the FDA on March 14, 2000, the Sponsor was provided two options for approaching the issue of "mixing" HOE 901 with other insulins.

[ ]

The second option was to put appropriate precautionary statements in the labeling based on the dog study to address what a patient may expect if HOE 901 is mixed with regular insulin. If this statement is placed into the precautions section of the labeling, no additional studies would be needed.

The Sponsor has determined that Option #2 above would be preferred. To that end, attached please find the statement that the Sponsor is proposing to be added to the labeling for Lantus®.

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

Sincerely,

Susan Jordan for Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, Regulatory and Technical Services
Quintiles, Inc (Mail Stop: F3-M3026; Phone: 816-767-6674)

smh/Attachment

Proposal for Modifications to Mixing Statements in the LANTUS™ Package Insert

The following four changes, regarding not mixing Lantus with other insulins or solutions, are being proposed to be made to the sponsor's draft package insert dated February 29, 2000:

1. **PRECAUTIONS: General**, second paragraph changed to read:

   LANTUS™ must not be diluted or mixed with any other insulin or solution. [redacted]. When LANTUS™ and regular human insulin were mixed immediately before injection in dogs, a delayed onset of action and time to maximum effect for regular human insulin was observed. The total bioavailability of the mixture was also slightly decreased compared to separate injections of LANTUS™ and regular human insulin.

2. **PRECAUTIONS: Information for patients**, add a new second paragraph to read:

   Patients must be advised that LANTUS™ must not be diluted or mixed with any other insulin or solution.

3. **DOSAGE AND ADMINISTRATION: Preparation and handling**, third paragraph changed to read:

   Mixing and diluting. LANTUS™ must not be diluted or mixed with any other insulin or solution (See PRECAUTIONS: General).

4. **DOSAGE AND ADMINISTRATION: Preparation and handling**, fourth paragraph starting with [redacted] to be deleted.

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 Pharmaceutcals Inc.	3/15/2000
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
Provide Outline of the Educational Program for Health Care Professionals and Patients

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
Susan Jordan for Lavonne Patton	Lavonne Patton, Ph.D. Director, Regulatory & Technical Services (Quintiles)	3/15/2000

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.

QUINTILES

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

March 15, 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

Outline of the Educational Program for Health Care Professionals and Patients

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.

At the teleconference with the FDA on March 14, 2000, the FDA asked that the Sponsor provide a summary of the educational program currently being planned to educate health care professionals and patients regarding non-mixing of Lantus with other insulins. The attached document contains the Sponsor's current plan to address the educational aspects.

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

Sincerely,

Susan Jordan for Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, Regulatory and Technical Services
Quintiles, Inc. (Mail Stop: F3-M3026; Phone: 816-767-6674)

smh/Attachment

WITHHOLD 1 PAGE (S)

Draft

ORIG AMENDMENT
BC

ORIGINAL

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

February 28, 2000

John Jenkins, MD
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 Fischers Lane
Rockville, MD 20857

WAT
/S/
3/1/00

/S/
3/10/00

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

Amendment: Response to CMC questions from Dr. Moore received 2/22/2000

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.

We are submitting the enclosed response in reply to a request received February 22, 2000 from Dr. Stephen Moore. (Please see the attached list of questions received by fax from the Agency.)

A summary of the Phase IV commitments made in this response is as follows:

1. [redacted]

2. The 24 month data from the primary stability studies for drug substance will be available in May 2000. That data will be submitted to the NDA and the specification limits for HOE [redacted] will be reevaluated based on 90% content, that data.

3. [redacted]

If you require any additional information, please do not hesitate to contact me.

Sincerely,

Susan M. Zordan

Susan M. Zordan
Assistant Director, Regulatory & Technical Services
Quintiles, Inc. (Mail Stop: F3-M3026; Phone: (816) 767-6673)

smh/Attachments

/S/
3/9/00

REVIEWS COMPLETED

/S/

QUINTILES

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

March 2, 2000

Julie Rhee
Project Manager
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

OptiPen™

Dear Julie:

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

As you requested, I have enclosed two samples of the OptiPen insulin injection device.

Currently, Marketing plans to bring the OptiPen insulin injection device to the US market

Please let me know if you require any additional information.

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

Enclosure

APPEARS THIS WAY
ON ORIGINAL

Quintiles
10245 Hickman Mills Drive
P. O. Box 9708
Kansas City, MO 64134-0708

Tel (816) 767-6000
Fax (816) 767-7373

US Drug Regulatory Affairs

MERC Team: Metabolism, Endocrinology, Rheumatology, Cardiovascular

MERC Team Members: Carol Blanton, Marguerite Enlow, Sharon [illegible], Philip Kastner, Michelle Krewer, Lavonne Patton, Cindy Vick, Susan Zordan

To:	Julie Rhee	From:	Lavonne Patton
Company:	FDA	Date:	2-9-00
Fax No:	301-443-9282	Page 1 of:	3

NDA 21-081

Comments:

Julie -

Here is some background information for our teleconference tomorrow. I have confirmed it on our side.

Please let me know if you have any questions.

Thank you.

Lavonne

APPEARS THIS WAY
ON ORIGINAL

Mixing HOE 901 (pH ≈ 4.0) with a neutral buffered solution of regular insulin will increase the pH of the entire solution. At approximately pH 5.1 - 5.3 precipitation of HOE 901 will begin to occur. Exploratory studies show that this process of an almost complete HOE 901 precipitation starts at a ratio of 95% HOE 901 and 5% regular insulin. As a result of this precipitation, the clear solution in the vial will turn into a cloudy suspension. Depending on the mixing ratio, a partial precipitation of the added regular insulin is also found.

Mixing Ratio HOE901/Insulin	pH	Visual Inspection	HPLC Analysis HOE 901 % of total amount found in:		HPLC-Analysis Human Insulin % of total amount found in:	
			Supernatant	Precipitate	Supernatant	Precipitate
96.80 / 3.20	4.5	Clear solution	n.d.	n.d.	n.d.	n.d.
95.00 / 5.00	5.1	Slightly opaque solution	100	0	100	0
85.00 / 15.00	5.5	Suspension	1	99	38	62
50.00 / 50.00	6.9	Suspension	1	99	55	45
30.00 / 70.00	7.1	Suspension	1	99	78	22
2.90 / 97.10	7.3	Slightly opaque solution	100	0	100	0

Solutions with 100 IU/ml human insulin or HOE901 have been used. Insulin means our commercial regular human insulin preparation. The HOE 901 solution contains 30 µg/ml zinc.

For theoretical reasons, the same should hold true for insulin lispro added in increasing concentrations to HOE 901. Similar results to those reported above for human insulin, were found with insulin lispro for visual inspection and pH measurement (no HPLC analysis was performed). This significant co-precipitation of the added soluble insulin may be explained by the fast exchange of the different insulin molecules between hexamers before or during pH-induced precipitation.

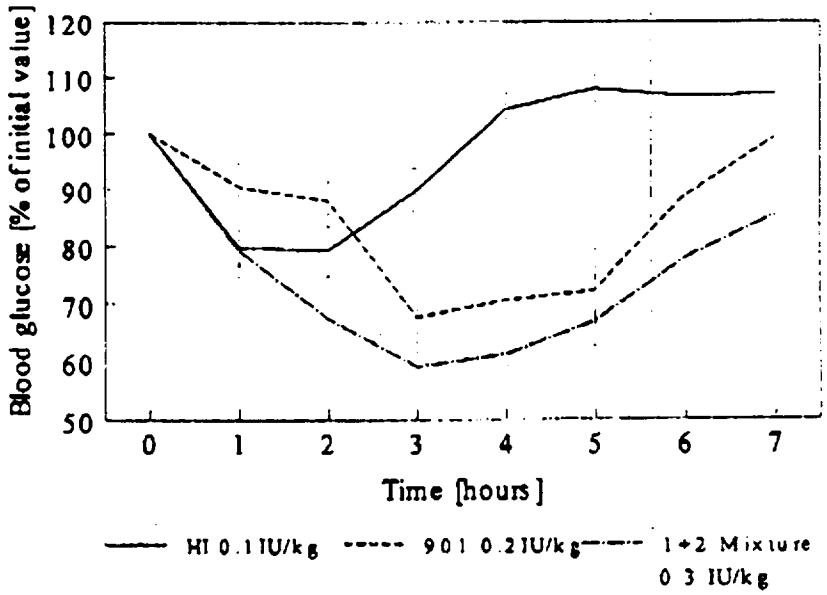
Precipitation of insulin may alter the pharmacokinetic behavior of an insulin but not its biological activity. A precipitation of HOE 901 in the vial is not expected to change its PK profile since this is what occurs at the injection site, too.

For the regular insulin a more delayed onset of action as a consequence of the co-precipitation could be expected. However, exploratory studies in dogs did not show a major change in onset of action with a mixture of HOE 901 and regular insulin in comparison to the individual injections of both insulins. Moreover, no significant decrease in total hypoglycemic effect was indicated (see Figure on next page).

HOE 901 is given at bedtime when the simultaneous injection of regular insulin or insulin lispro is very unlikely. In the very unlikely case of mixing both insulins with HOE 901 the worst case scenario would be a delayed onset to the regular insulin component. This situation is comparable to the injection of zinc-containing lente insulins with regular insulin.

Mixture (1+2) of H-Insulin and HOE 901

Dogs (n=7-8), s.c.



HOE 901 is a formulation containing 40 IU/kg HOE 901 and ~ µg/ml zinc.
HI = regular human insulin (our commercial U40 formulation).

APPEARS THIS WAY
ON ORIGINAL

QUINTILES

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

January 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** **NDA Amendment**
insulin glargine injection

Response to question raised by Dr. Komanduri on January 11, 2000

Attention: Dr. Pardha Komanduri

Dear Dr. Jenkins:

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

The attached response is provided to address a question raised by Dr. Pardha Komanduri in our conversation of January 11, 2000. If you require any additional information, please do not hesitate to contact me at the number listed below, or Susan Zordan at (816) 767-6673.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, Regulatory and Technical Services
Quintiles, Inc.
P.O. Box 9708 --F3-M3026
Kansas City, MO 64134-0708
(816) 767-6674

APPEARS THIS WAY
ON ORIGINAL

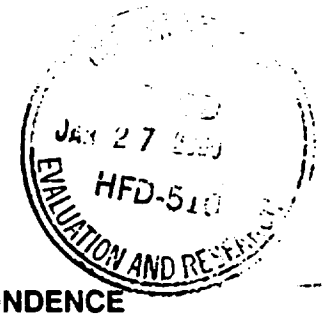
sh
Enclosure

Aventis Pharmaceuticals

NEW CORRESP
NC

Aventis

January 17, 2000



Food and Drug Administration
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 21-081
LANTUS™
(insuline glargine injection)

GENERAL CORRESPONDENCE
Company Name Change

Dear Sir/Madam:

A letter was recently forwarded to your attention regarding a name change for our corporation. "Inc." was inadvertently omitted. This letter is to inform you that the name of the corporation sponsoring the above-captioned application has been changed recently from Hoechst Marion Roussel, Inc. to Aventis Pharmaceuticals Inc. There has been no transfer of ownership of this application. Enclosed is an updated FDA Form 356h reflecting the name change.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

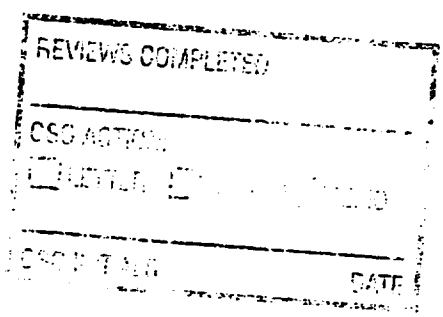
If you should have any questions or comments concerning this submission, please contact the undersigned at:

AVENTIS PHARMACEUTICALS INC.
P.O. Box 9627
Kansas City, Missouri 64134-0627

Sincerely,

J Michael Nicholas

J. Michael Nicholas, PhD
Director, US Regulatory Affairs
Marketed Products
816-966-5720



QUINTILES

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

ORIGINAL

NDA SUPP AMEND

N. BM

January 13, 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

mailed
/S/
1/20/2000

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

Response to questions raised by Dr. Robert Misbin on December 28, 1999

Attention: Dr. Robert Misbin

Dear Dr. Jenkins:

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

We are submitting the enclosed response in reply to a request received December 28, 1999, from Dr. Robert Misbin.

Please let me know if you require any additional information.

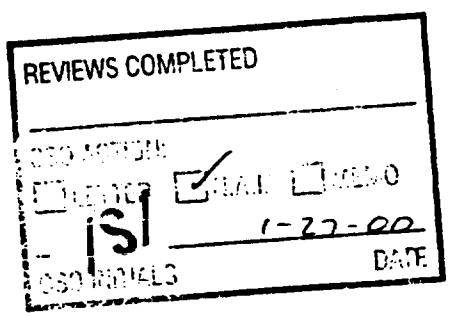
Sincerely,

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

Enclosure

cc: Julie Rhee, Project Manager



Aventis Pharmaceuticals

NEW CORRESP
NC

Aventis

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JAN 11 2000
HFD-510

January 10, 2000

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products (HFD-510)
Document Control Room 14B-03
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 21-081**
LANTUS™
(insuline glargine injection)

GENERAL CORRESPONDENCE
Company Name Change

Dear Sir/Madam:

This letter is to inform you that the name of the corporation sponsoring the above-captioned application has been changed recently from Hoechst Marion Roussel to Aventis Pharmaceuticals. There has been no transfer of ownership of this application. Enclosed is an updated FDA Form 356h reflecting the name change.

Please be advised that there have been no other changes in relation to the studies ongoing or the responsible individuals. You will be advised if any changes occur as appropriate.

If you should have any questions or comments concerning this submission, please contact the undersigned at:

AVENTIS PHARMACEUTICALS
P.O. Box 9627
Kansas City, Missouri 64134-0627

Sincerely,

J. Michael Nicholas, PhD
Director, US Regulatory Affairs
Marketed Products
816-966-5720

REVIEWS COMPLETED
CSO A
EMO
DATE
CSO

APPEARS THIS WAY
ON ORIGINAL

QUINTILES

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

NEW CORRESP

BP

January 6, 2000

Solomon Sobel, M.D.
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

/S/
1/14/2000

Subject: **NDA 21-081**
insulin glargine injection
Response to question received January 5, 2000 regarding incidence of hepatocellular adenomas in male NMRI mice

Attention: Herman Rhee, Ph.D.

/S/
1/14/2000

Dear Dr. Sobel,

The following information is being provided in response to a question raised by Dr. Herman Rhee, on January 5, 2000, regarding the incidence of hepatocellular adenomas in male NMRI mice.

In the HOE 901 mouse carcinogenicity study, hepatocellular adenomas were observed in the HOE 901 vehicle control (6/50) and in the low (5/50) and intermediate (5/50) HOE 901 dose groups. In the high dose group the incidence was 1/50. The HOE 901 mouse carcinogenicity study was the first study performed in our testing facility with NMRI mice from the breeder ———

In the meantime a second study was conducted with the test compound ——— The incidence of hepatocellular adenoma in the two control groups of 50 male NMRI-mice (breeder: ———— , each was: 3/50 and 1/50.

As mentioned in the original HOE 901 carcinogenicity study report in mice, the historical control data for male NMRI-mice received from the Registry of Industrial Toxicology Animal (RITA) database showed a range of 2.0% - 16.0% for hepatocellular adenomas (5 studies with 248 control animals). Only in one of these studies were NMRI-mice from the breeder ———— used (study performed by another pharmaceutical company). The incidence of hepatocellular adenoma in the control group in this study was 6/50.

APPEARS THIS WAY
ON ORIGINAL

In conclusion, although the database is limited, the incidence of hepatocellular adenomas in male mice in the HOE 901 carcinogenicity study is considered to be a random event, reflecting the normal biological variation of this spontaneously occurring tumor in NMRI-mice.

Please let me know if you require any additional information.
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

cc: Julie Rhee

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

/S/ 1-21-00
CSO INITIALS DATE

/S/
1/19/00

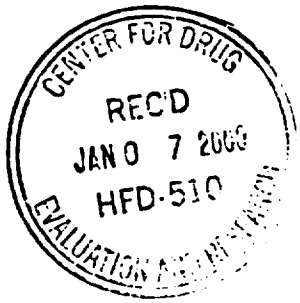
APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

QUINTILES

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

January 6, 2000



Ms. Julie Rhee
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

Dear Julie,

In our telephone conversation of January 4, 2000, you requested that we provide samples of the vials that will be used to supply insulin glargine (Lantus). Enclosed you will find three samples of the 5 mL and 10 mL vial packages as you requested.

Please note that the plastic flip caps for the actual Lantus vials will be lavender instead of the colors on the enclosed vials. The sealing discs in the 10 mL vials are the new proposed sealing disc and the sealing discs in the 5 mL vials are the current sealing disc.

Also enclosed are copies of the labels, which will be used on the vials. The labels will be printed on clear stock so that the patients will be able to visually examine the insulin solution before use. The area behind the text (shown as shaded gray on these labels) will be opaque so that the printing is more legible.

Please let me know if you require any additional information.

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

Enclosures

WITHHOLD 2 PAGE (S)

Draft

Labeling

QUINTILES

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

SV

December 22, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
DEC 23 1999
HFD-510

Solomon Sobel, M.D.
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

Attention: Julie Rhee

Subject: **NDA 21-081**
Insulin glargine injection
Final Safety Update

Dear Dr. Sobel:

In accordance with 21 CFR 314.50(d)(5)(vi)(b), Quintiles Inc, the US Agent for Hoechst Marion Roussel, Inc, is submitting a 2-volume Final Safety Update for NDA 21-081, insulin glargine injection. A diskette containing the updated unannotated labeling is included for your convenience.

The original NDA was received by the Agency on April 23, 1999. The 120-day Safety Update was submitted to the Agency on July 6, 1999. This Final Safety Update includes new safety information on the — ongoing clinical trials. The safety update includes data through November 24, 1999.

Please call me if you have any questions regarding this submission.

Sincerely,

Lavonne Patton

Lavonne Patton, Ph.D. (816) 767-6674
Director, US Drug Regulatory Affairs
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

REVIEWS COMPLETED
/S/ 12/30/99

Biometrics has green jacket
/S/ 12/29/99

/S/ 12/29/99

/S/ 12/29/99

QUINTILES

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

ORIGINAL

BM

December 2, 1999

Solomon Sobel, M.D.
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

NAI
/S/
12/14/99

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

Amendment to a pending application
Response to the request for additional clinical information

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

The following document is being submitted in response to the request for additional clinical information received by fax on November 18, 1999, from Julie Rhee (see attached).

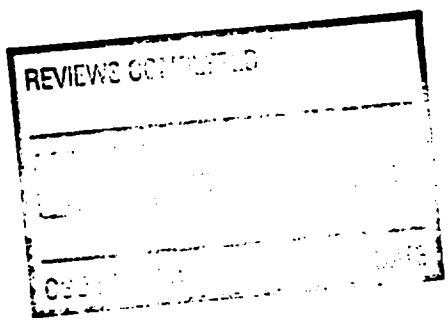
Please let me know if you require any additional information.

/S/ 1/15/00

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

QUINTILES

ORIGINAL

ORIG AMENDMENT
BI

November 22, 1999

Solomon Sobel, MD
Food and Drug Administration
Division of Metabolism and Endocrine Drug Product (HFD-510)
Center for Drug Evaluation and Research
Document Control Room 14B-04
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 21-081
insulin glargine injection

Amendment – Response to List of Microbiology Deficiencies

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

The following document is being submitted in response to the list of microbiology deficiencies received by fax from Julie Rhee on October 28, 1999 (see attached).

If you require any additional information, please contact me at (816) 767-6673 or Lavonne Patton at (816) 767-6674.

Sincerely,

Susan M. Zordan

Susan M. Zordan
Assistant Director, US Drug Regulatory Affairs
Quintiles, Inc.

smh
Attachment

REVIEWS COMPLETED
ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO
/S/ 12-8-99
CSO INITIALS DATE

Micro consult requested

A6.1 c Ng
12-10-99

DUPLICATE

QUINTILES

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

NDA SUF

EP

October 21, 1999

Solomon Sobel, M.D.
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**
Insluin glargine injection

NDA Amendment
Mouse Carcinogenicity Codes on Diskette

Attention: Julie Rhee

Dear Dr. Sobel,

It was brought to my attention by the Statistical Reviewer, Dr. Moh Jee Ng, that some of the codes for the Tumor Type and Organ-Tissue Type data were missing from the preclinical carcinogenicity package provided to the FDA on April 27, 1999, in support of the HOE 901 NDA submission. All of the codes for the rat data were provided in this submission, however the codes for the mouse data were not included. To correct this oversight, I am enclosing a virus-scanned diskette and hard copy of the missing mouse tumor and organ/tissue codes.

Please let me know if you have any questions.

Sincerely,

Lavonne Patton

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

APPEARS THIS WAY
ON ORIGINAL

List of Tumor Type Codes
Mouse

060008	Osteoma
080006	Papilloma
090025	Adenoma bronchiolo-alveolar
090026	Carcinoma bronchiolo-alveolar
090040	Papilloma bronchial
150105	Papilloma squamous cell
150207	Adenoma
170106	Schwannoma benign
170107	Sarcoma not otherwise specified
170203	Haemangioma
180025	Haemangioma
180026	Adenoma hepatocellular
180027	Carcinoma hepatocellular
180028	Haemangiosarcoma
180045	Histiocytoma fibrous malignant
200024	Adenoma acinar cell
200026	Carcinoma islet cell
230010	Papilloma transitional cell
230011	Submucosal mesenchymal tumour of the urinary bladder
230014	Carcinoma transitional cell
280009	Tumour granular cell benign
280013	Haemangioma
320011	Tumour sex cord stromal mixed benign
320012	Tumour granulosa cell benign
320014	Cystadenoma
320015	Haemangioma
320017	Adenoma tubulostromal
320024	Tumour sertoli cell benign
340013	Polyp stromal
340014	Polyp glandular
340016	Schwannoma benign
340021	Schwannoma malignant
340025	Tumour granular cell benign
340028	Sarcoma endometrial stromal
340030	Leiomyosarcoma
340031	Histiocytoma fibrous malignant
340032	Adenocarcinoma
410005	Adenoma pars distalis
410010	Adenoma pars intermedia
440113	Adenoma subcapsular cell mixed type
440114	Adenoma subcapsular cell type A
440115	Adenoma subcapsular cell type B
450001	Lymphoma malignant
450002	Tumour mast cell malignant
450003	Histiocytic sarcoma
460014	Haemangioma
460015	Haemangiosarcoma
470009	Haemangioma
500009	Thymoma benign
560005	Adenocarcinoma

560007	Adenoacanthoma malignant
570010	Haemangioma
570011	Schwannoma malignant
570013	Carcinoma basal cell
570017	Carcinoma sebaceous
570018	Carcinoma squamous cell
570021	Keratoacanthoma
570022	Histiocytoma fibrous malignant
570023	Haemangiosarcoma
580011	Sarcoma NOS
680009	Histiocytoma fibrous malignant
720004	Chondroma
760013	Lipoma
760018	Histiocytoma fibrous malignant
760028	Tumour granular cell benign

List of Organ/Tissue Type Codes
Mouse

0101	CEREBRUM
0102	CEREBELLUM
0103	BRAIN STEM
0104	MEDULLA OBLONGATA
0211	SPINAL CORD, CERVIC
0212	SPINAL CORD, THORAC
0213	SPINAL CORD, LUMBAR
0520	AORTA
0600	NOSE
0800	TRACHEA
0900	LUNGS
1501	FORESTOMACH
1502	STOMACH, GLANDULAR
1601	DUODENUM
1602	JEJUNUM
1603	ILEUM
1701	CECUM
1702	COLON
1703	RECTUM
1800	LIVER
1900	GALLBLADDER
2000	PANCREAS
2300	URINARY BLADDER
2600	EPIDIDYMIDES
2700	PROSTATE
2800	SEMINAL VESICLES
3200	OVARIES
3400	UTERUS
4100	PITUITARY GLAND
4401	ADRENAL CORTEX
4500	HAEMOLYMPHORET. SYS.
4600	SPLEEN
4700	BONE MARROW
5000	THYMUS
5104	MESENT. LYMPH NODE
5106	ILIAC LYMPH NODE
5600	MAMMARY GLAND
5700	SKIN/SUBCUTAN.TISSUE
5800	SKELETAL MUSCLE
6500	EYES
6510	OPTIC NERVES
6900	BODY CAVITIES
7200	STERNUM
7600	INJECTION SITE

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 last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	10/21/99
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	CODE NAME *(If any)*
insuline glargine injection	**LANTUS™**	**HOE 901**

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

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
In response to FDA request, provide missing codes for Tumor Type and Organ-Tissue Type data from preclinical carcinogenicity package provided 4/27/99.

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 314.5 (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 knowlege 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, Drug Regulatory Affairs (Quintiles)	10/21/99

ADDRESS (Street, City, State, and ZIP Code)	Telephone Number
P.O. Box 9708, Mail Station ~~FS-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.

FORM FDA 356h (4/97)

BC

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

ORIGINAL

March 6, 2000

John Jenkins, MD
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 Fischers Lane
Rockville, MD 20857

Subject: NDA 21-081
insulin glargine injection

Amendment –Phase IV CMC Commitments

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.

The sponsor agrees to the following Phase IV CMC commitments in reply to a request received March 3, 2000 from Dr. Stephen Moore. (Please see the attached fax from the Agency.)

1. The sponsor will re-evaluate the ——— for the HOE 901 content, ——— when the 24-month stability data on the primary stability lots of HOE 901 drug substance is available.
   - Protocol Submission: Submitted in the original NDA
   - Study Start: Study on-going
   - Final Report Submission: No later than May 31, 2000

2. The sponsor will re-evaluate the ——— related to the drug substance, when the 24-month stability data on the primary stability lots of HOE 901 drug substance is available.
   - Protocol Submission: Submitted in the original NDA
   - Study Start: Study on-going
   - Final Report Submission: No later than May 31, 2000

If you require any additional information, please contact me.

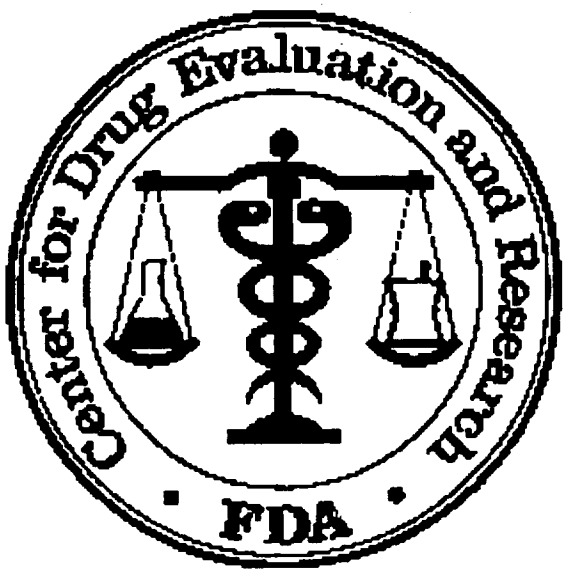
Sincerely,

Susan M. Zordan

Susan M. Zordan
Assistant Director, Regulatory & Technical Services
Quintiles, Inc. (Mail Stop: F3-M3026, Phone: (816) 767-6673)

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

DATE: March 3, 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 Lantus

Please provide your Phase 4 CMC commitments. Thank you.

Cc : Orig NDA 21-081
HFD-510/Div File
HFD-510/Moore/Komanduri

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

Date of submission: February 28, 2000

Chemistry, Manufacturing, and Controls Requests

Please provide your Phase 4 commitment for the following:

1. To re-evaluate the [redacted] for the HOE 901 content, [redacted] when the 24-month stability data on the primary stability lots of HOE 901 drug substance is available.

Protocol Submission:	Submitted in the original NDA
Study Start:	Study on-going
Final report submission:	No later than May 31, 2000

2. To re-evaluate the [redacted] related to the drug substance, when the 24-month stability data on the primary lots of HOE 901 drug substance is available.

Protocol Submission:	Submitted in the original NDA
Study Start:	Study on-going
Final report submission:	No later than May 31, 2000

Cleared for faxing by: /S/ 3/3/2005

Stephen Moore, Ph.D., Chemistry Team Leader I, DMEDP

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)

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

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.

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

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

QUINTILES

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

ORIGINAL

September 2, 1999

cc

[redacted]

Solomon Sobel, M.D.
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** **CMC Amendment**
insulin glargine injection

Dear Dr. Sobel:

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

This amendment contains the sterilization validation report for insulin glargine cartridges which was discussed at the pre-NDA teleconference with the FDA on December 17, 1998 and in telephone conversations with Dr. William Berlin on June 14-15, 1999. The sterilization validation report for cartridges was not available when the initial NDA was submitted [redacted] It was agreed with the Division that the information for cartridges could be filed as an amendment to the NDA no later than September 7, 1999.

The sterilization validation report for vials has been updated to include the installation of a [redacted]. A revised version of this report for vials is also included in this amendment.

The vial and cartridge sterilization validation reports are in Volume 2 of this submission. An extra copy of this volume is included for the convenience of the chemistry and microbiology reviewers. Volume 1 of the submission contains several new or updated reports, which are described in more detail in the Introduction section of the submission.

If you have any questions, please contact me at (816) 767-6673.

Sincerely,

Susan M. Zordan

Susan M. Zordan
Assistant Director, Drug Regulatory Affairs
Quintiles, Inc.
P. O. Box 9708, Mail Station F3-M3026
Kansas City, MO 64134-0708

smh

QUINTILES

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

DUPLICATE

NEW CORRESP
NSC

June 10, 1999

Solomon Sobel, M.D.
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

Attention: **Julie Rhee, Project Manager**

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

Request for Marketing Exclusivity for insulin glargine

Dear Dr. Sobel,

Quintiles Inc. as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

Enclosed is a letter from Hoechst Marion Roussel, Inc. requesting extended marketing exclusivity for insulin glargine.

If you have any questions regarding the attached document, please do not hesitate to contact me at (816) 767-6674.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, U.S. Drug Regulatory Affairs
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137

APPEARS THIS WAY
ON ORIGINAL

Enclosure

Letter from Hoechst Marion Roussel requesting Marketing Exclusivity

Hoechst Marion Roussel

June 4, 1999

Hoechst Marion Roussel, Inc.

10236 Marion Park Drive
Mail P.O. Box 9627
Kansas City, MO 64134-0627
Telephone (816) 966-5000
U.S. Web site www.hmri.com

Solomon Sobel, M.D.
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

Request for Marketing Exclusivity

Dear Dr. Sobel,

This letter serves as an official request for a period of extended marketing exclusivity under 21CFR 314.50(j) and 21CFR 314.108(b)(2), for insulin glargine (New Drug Application April 9, 1999 and submitted to the Agency on April 22, 1999). As a new chemical entity, insulin glargine is entitled to five (5) years of exclusivity pursuant to 505(j)(4)(D)(ii) of the Federal Food. Drug and Cosmetic Act (21 U.S.C. 355). If you have any questions concerning this request, please contact:

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
U.S. Regulatory Affairs
Hoechst Marion Roussel, Inc.
Kansas City, MO 64137

APPEARS THIS WAY
ON ORIGINAL

Hoechst

Hoechst Marion Roussel
The Pharmaceutical Company of Hoechst

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 last page

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Hoechst Marion Roussel, Inc.	6/10/99
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)

FOR ANDA: IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

FOR 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
Request for Marketing Exclusivity for insulin glargine

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

NUMBER OF VOLUMES SUBMITTED_____ 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 314.5 (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 knowlege 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 M Patton	Lavonne Patton, Ph.D. Director, Drug Regulatory Affairs (Quintiles)	6/10/99

ADDRESS (*Street, City, State, and ZIP Code*)	Telephone Number
P O Box 9708, Mail Station: ~~P2-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.

FORM FDA 356h (4/97)

ORIGINAL

NEW CORRESP

C

QUINTILES

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

June 4, 1999

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

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

Attention: **Julie Rhee**

NDA 1
/S/
6/10/99

Dear Dr. Sobel,

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel. has been authorized to communicate with the FDA on NDA 21-081.

Enclosed please find a copy of the diskette containing the proposed text of the labeling for HOE 901 in Word 6.0, originally submitted on April 27, 1999. I am enclosing a copy of the memo outlining the contents of this diskette for your information.

Please let me know if you require additional information.

Sincerely,

Lavonne Patton

Lavonne M. Patton, Ph.D.
Director, U.S. Drug Regulatory Affairs
Quintiles, Inc.
10245 Hickman Mills Drive
Kansas City, MO 64137
Phone: (816)-767-6674

/S/
6/11/99

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Enclosure

Diskette containing the proposed text of the labeling for HOE 901
Original letter and memo from the April 27, 1999 submission

NDA 1
/S/
6/11/99

QUINTILES

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

May 13, 1999

Solomon Sobel, M.D.
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
Amendment to Pending Application:
SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED

Dear Dr. Sobel,

Quintiles, Inc., as the US Agent for Hoechst Marion Roussel, has been authorized to communicate with the FDA on NDA 21-081.

As discussed and agreed with the Agency (verbal contact of February 4, 1999), Hoechst Marion Roussel is submitting the report of the Pediatric Study (3003) conducted with insulin glargine for review with the original NDA dated April 9, 1999 and submitted on April 22, 1999.

This Pediatric Study is being supplied to the Agency in accordance with the Written Agreement from the Agency dated May 12, 1999 (copy attached). We understand that the submission of this study report makes the product eligible for FDAMA exclusivity of 6 months.

As noted in the cover letter of the original submission, the applicant has shown advantages in adults of insulin glargine compared to NPH in the frequency of the occurrence of clinically important severe and nocturnal hypoglycemic episodes. In the pediatric study 3003, equal maintenance of glycemic control (glycohemoglobin) and better fasting blood glucose control was also achieved in subjects treated with insulin glargine compared with NPH. As in the adult population, fewer subjects treated with insulin glargine reported nocturnal hypoglycemia, although the difference did not reach statistical significance in this smaller study. Therefore, the results observed in the pediatric population are consistent with the results of the adult population and represent a meaningful therapeutic benefit of insulin glargine.

The available treatment options to provide a basal insulin supply for children with diabetes are limited. The available treatments often provide inadequate glycemic control *and are not currently labeled for pediatric use*. We believe the results of our clinical studies and the need for additional treatment options for children with diabetes justifies consideration by the Agency to give insulin glargine priority review in accordance with the Center for Drug Evaluation and Research Priority Review Policy and the final Pediatric Rule.

The labeling currently submitted to the Agency regarding pediatrics will be reviewed based on the results of this study and proposed changes to the initially wording in the labeling will be submitted to the Agency for their consideration.

The pediatric study report is being submitted in triplicate, including an archival copy, medical review officer copy and statistical copy. A CD containing the PDF based electronic review aid is also being supplied with the report for the reviewer's convenience. The study report consists of 23 volumes with the pagination reflecting the volume number and page number. Item 16 (Debarment certification) and Item 19 (Financial Disclosure) on the 356h form are covered by the original NDA submission dated April 9, 1999 and submitted on April 22, 1999. The list of investigators associated with the financial disclosure statement can be found in Appendix A.2 (Volume 3) of the report.

Sincerely,

Lavonne M Patton

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

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

Hoechst Marion Roussel, Inc.
Attention: Lavonne Patton, Ph.D.
Director, Drug Regulatory Affairs at Quintiles, Inc.
U.S. Agent for Hoechst Marion Roussel, Inc.
P.O. Box 9708
Kansas City, MO 64134-0708

MAY 12 1999

Dear Dr. Patton:

Reference is made to your correspondence dated March 19, 1999, requesting a change to FDA's December 23, 1998, Written Request for pediatric studies for HOE 901 (insulin analog [rDNA origin] injection).

We have reviewed your proposed change and are amending the Written Request regarding the age groups accordingly. All other terms stated in our Written Request issued on December 23, 1998, remain the same.

Age groups in which study will be performed:
Ages 6 through 11 years
Ages 12 through 15 years

Reports of the studies that meet the terms of the Written Request dated December 23, 1998, as amended by this letter must be submitted to the Agency on or before June 30, 1999, in order to retain eligibility to qualify for pediatric exclusivity extension under Section 505A of the Act.

Reports of the studies should be submitted as an amendment to your pending application with the proposed labeling changes you believe would be warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF PEDIATRIC STUDY REPORTS – PEDIATRIC EXCLUSIVITY DETERMINATION REQUESTED**" in large font, bolded type at the beginning of the cover letter of the submission and include a copy of this letter. Please also send a copy of the cover letter of your submission, via fax (301-594-0183) or messenger to the Director, Office of Generic Drugs, HFD-600, Metro Park North II, 7500 Standish Place, Rockville, MD 20855-2773.

If you wish to discuss any amendments to this Written Request, please submit proposed changes and the reasons for the proposed changes to your application. Submissions of proposed changes to this request should be clearly marked "**PROPOSED CHANGES IN WRITTEN REQUEST FOR PEDIATRIC STUDIES**" in large font, bolded type at the beginning of the cover letter of the submission. You will be notified in writing if any changes to this Written Request are agreed upon by the Agency.

We hope you will fulfill this pediatric study request. We look forward to working with you on this matter in order to develop additional pediatric information that may produce health benefits to the pediatric population.

If you have any questions, contact Julie Rhee, Regulatory Project Manager, at (301) 827-6424.

Sincerely yours,

/S/

John K. Jenkins, M.D., F.C.C.P.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

QUINTILES

Quintiles, Inc
Post Office Box 9708
Kansas City, MO 64134-0708
816 767 6000
http://www.cro.quintiles.com

April 9, 1999

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

Attention: Central Document Room
Park Building, Room 214
1240 Parklawn Drive
Rockville, MD 20852

Subject: New Drug Application
insulin glargine injection
NDA 21-081

Dear Dr. Sobel,

In conformance with 21 CFR 314.1, Hoechst Marion Roussel, Inc. is submitting a New Drug Application for insulin glargine injection. The development of insulin glargine has been a collaborative effort between the applicant and the Reviewing Division at the FDA. This NDA provides support for the use of insulin glargine injection once-daily by subcutaneous administration for patients with diabetes mellitus who require a basal insulin for the control of hyperglycemia. The submission is 479 volumes in length.

In the analysis of the Phase III study results, the applicant has identified an advantage of insulin glargine compared to NPH human insulin in the frequency of the occurrence of clinically important hypoglycemic episodes. With equal maintenance of glycemic control (glycohemoglobin) and equal or better fasting glucose control in subjects treated with insulin glargine compared with NPH, significantly fewer subjects treated with insulin glargine reported severe and nocturnal hypoglycemia. A rationale for the observed advantage in clinical hypoglycemia is based on the smooth, peakless time-action profile of insulin glargine compared to that of NPH observed in Phase I studies. We believe these results justify consideration by the Agency to give insulin glargine priority review.

The applicant is cognizant in making this request for priority review of the discussions held with the Agency regarding the practical limitations of the reporting of admittedly subjective hypoglycemic symptoms by subjects in an open study design. However, in the process of data collection and analysis this limitation in the data has been taken into account and an attempt has been made to make the data as objective as possible. Several measures of hypoglycemia are reported, including all symptomatic hypoglycemic events with subsets of severe symptomatic hypoglycemia, using the DCCT definition of the patient requiring assistance of another person, and nocturnal symptomatic hypoglycemia. In addition, subjects were requested to determine blood glucose values at the time of the episode and episodes with blood glucose values less than 50 mg/dL and less than 36 mg/dL are presented. Furthermore, we have identified a subgroup of subjects reporting severe neurologic symptoms of hypoglycemia, including coma, convulsions and syncope. With progressively more restrictive and more clinically important definitions of hypoglycemia, the advantage of insulin glargine compared to NPH is more apparent. Finally, we have compared the frequency of hypoglycemic episodes to those reported in major clinical trials