MEMORANDUM

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

DATE: May 25, 2007

TO: Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products (DMEP)

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D._____
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering NDAs 21-809 and 21-810, NovoLog Mixes 30/70 and 50/50, Insulin Aspart Protamine Suspension and Soluble, Sponsored by Novo Nordisk Pharmaceuticals, Inc.

At the request of DMEP, the Division of Scientific Investigations audited the clinical-pharmacodynamic and analytical-pharmacokinetic portions of the following study.

Study: **#BIAsp1746:** "A Double-blind, Randomized, Four-Period Crossover Trial Comparing the Pharmacodynamics and Pharmacokinetics after Single Dose of Biphasic Insulin Aspart 30, Biphasic Insulin Aspart 50, Biphasic Insulin Aspart 70 and Insulin Aspart in Subjects with Type 1 Diabetes"

The primary objective of the study was to assess the glucose infusion rate (GIR) profiles between 0 to 2 hrs following administration of the biphasic insulin aspart (i.e. BIAsp 30, BIAsp 50 and BIAsp 70) or soluble insulin aspart products using the euglycaemic clamp technique. Secondary end-points for the study included pharmacokinetics (PK) of serum insulin aspart (IAsp) concentrations, and the pharmacodynamics of serum non-esterified fatty acid (NEFA) concentrations.

The euglycaemic clamp experiments for the study were conducted at Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany, and the IAsp and NEFA concentrations from the study serum samples were analyzed at [redacted]

b(4)

Following the inspections at Profil GmbH (May 14-18, 2007) and [redacted] (May 22-25, 2007), Form 483 was issued at each site. Our evaluation of the significant findings follows:

Clinical Site: Profil Institute, Neuss, Germany

In the euglycaemic clamp technique, blood glucose (BG) is "clamped" at a preset target level (90 mg/dL in this study) and any BG lowering effect of insulin is countered by automatic infusion of glucose to maintain the target BG level. The glucose infusion rate (GIR) measured using this technique is a reflection of the BG lowering effect of insulin, and thus allows for quantification of the pharmacodynamics of the insulin products. The following are the significant findings of the conduct of the euglycaemic clamp experiments.

1. **Treatment administered to the study subjects cannot be assured to have followed the randomization code.**
   Profil failed to retain the sealed randomization code for this double-blind study. Profil returned the code to the sponsor following the study. Profil stated that the study was conducted according ICH guideline for Good Clinical Practice (ICH E6), which requires returning the sealed codes to the sponsor to document any decoding. Nonetheless, in the absence of the sealed codes, the treatments administered to the subjects could not be confirmed during the inspection.

2. **Biostator® blood glucose (BG) failed to match the external BG concentrations between 0 to 120 min in some euglycaemic clamp experiments.**
   In addition to the BG measured by the Biostator® (i.e. glucose clamp apparatus), Profil also measured BG concentrations externally, every 15 to 30 min. The external BG data were not provided with the NDA submission. Profil considered the external BG concentrations as the reliable measurement, and used the measurement to validate the Biostator BG measurement, as the Biostator's glucose sensor

was susceptible to drift. Therefore, the reliability of GIR measurements depends on how closely Biostator BG concentrations mimic the external BG measurement (Attachments 1, 1a and 2). During the inspection, Biostator and external BG measurements were compared for limited subject data. The comparison revealed that for some experiments Biostator BG concentrations consistently and significantly deviated from external BG measurements, particularly during 0 to 120 min. post-dose, the relevant time period for the primary end point (i.e. $AUC_{GIR\ 0\text{-}120\ min}$). For example, for Subject ID #25 (Visit 5), #35 (Visit 3) and #28 (Visit 5), the Biostator concentrations consistently deviated from the external BG concentrations between 0 to 120 min (see Table below and Attachment 2). In addition to the above referenced experiments, the OCP/DMEP reviewer should evaluate the reliability of Biostator GIR measurements between 0 to 120 min for Subject IDs #13 (Visit 2), #32 (Visit 4), #33 (Visit 4), and #43 (Visit 3). Similarly, reliability of GIR for time periods >120 min should be evaluated in the current study.

Time (min)	Subject 25, Visit 5	
post-dose	Ext. BG	Biost. BG
45	72	80
60	55	94
62	59	92
80	61	93
88	70	85
100	82	90
112	77	88
120	93	80

Time (min)	Subject 35, Visit 3	
post-dose	Ext. BG	Biost. BG
15	92	88
30	90	Hold
45	83	90
60	75	88
74	83	93
80	78	Hold
91	78	92
100	77	88
120	81	85

Time (min)	Subject 28, Visit 5	
post-dose	Ext. BG	Biost. BG
0	83	89
15	82	90
30	76	90
45	71	87
55	82	87
60	82	91
80	102	81
100	111	89
120	99	87

Profil's explanation during the inspection (Attachment 3) does not address the impact of the significant and consistent deviations between Biostator and external BG measurements on GIR between 0 to 120 min.

3. **Quality control checks for external BG measurement were performed only at the beginning of analysis.** Nonetheless, the firm demonstrated precision and accuracy of the glucose analyzers periodically (3 months) with blinded quality controls (QC). Since BG measurements were routinely performed for 12 to 28 hours, the firm should also include additional QCs during analysis in future studies to monitor accuracy and reproducibility during these time frames.

Analytical Site: [redacted] b(4)

4. **NEFA assay was deficient.**
   The NEFA assay was performed in a deficient manner in that QC levels employed were inadequate to cover the entire range of the reported serum concentrations. The firm failed to use the conventional 3 QC levels, instead used only 2 QC levels (0.44 and 0.71 mmol/L) covering only the low concentration range. Also, the firm failed to use proper calibration points in the assay. The preparation of calibration curve was deficient in that the true concentrations of the calibrators were not known and the calibrators were not independent.

5. **Failure of analytical runs for the IAsp.**
   The QC acceptance of the IAsp assay should have used a 20% criterion instead of 30%, based on assay accuracy and precision data from the study and pre-study validation. Based on 20% QC acceptance criterion, the following 8 of the 75 runs should have been excluded: analytical runs #73, #76, #82, #84, #87, #100, #115 and #136. The runs involved numerous samples from Subjects 14 and 21. During the inspection, bioequivalence was reanalyzed after excluding IAsp data from the above analytical runs. The reanalysis did not affect bioequivalence outcome. The results of reanalysis will be provided in the sponsor's response to the Form 483.

Conclusions

The Division of Scientific Investigations found the following:

a. Dosing of subjects cannot be assured to have followed the randomization code (Item 1).
b. For the experiments in the table below, the OCP/DMEP reviewer should evaluate the reliability of the GIRs between 0 to 120 min ($AUC_{GIR,0\text{-}120\ min}$), the primary end-point (Item 2).

Subject ID	Visit
#13	2
#35, #43	3
#32, #33	4
#25, #28	5

c. The NEFA concentration data are unreliable as the NEFA assay was found to be deficient (Item 4).

Following your review, please attach this transmittal memo to the original NDA submission.

Sriram Subramaniam, Ph.D.

DSI Final Classifications:
VAI - Profil GmbH, Neuss, Germany.
VAI - b(4)

List of Attachments

Attachment 1 - CD containing external BG data (Listing of Safety BG.pdf) and Excel files of glucose clamp data for Study BIAsp1746. Note: Profil Subject IDs in the Excel files differ from Sponsor's Subject IDs in the pdf file in Attachment 1. See Attachment 1a.

Attachment 1a - Table correlating Profil's Subject ID and Sponsor's Subject ID.

Attachment 2 - BG Profiles: Figures comparing Biostator and External (i.e. safety) BG concentrations for subject visits in Study BIAsp1746.

Attachment 3 - Profil's explanation dated 5/17/07 regarding deviations in BG concentrations between Biostator and Super GL Glucoseanalyzer.

Attachment 4 - Profil's data to show that "arterializing" the venous blood sample has no effect on BG concentrations.

Note:
Due to the number of pages involved, Attachments will be forwarded only to the HFD-870 reviewer. Additional copies will be available upon request.

cc:
HFA-224
HFD-45/RF
HFD-48/Subramaniam(2)/Himaya/CF
DCP2 HFD-870/Wei (WO21 Rm 4660)
DMEP HFD-510/Zawadzki/Galliers/NDAs 21-809, 21-810
HFR-PA2535/Hall
HFR-CE650/Sadiku
Draft: SS 5/24/07
Edit: MFS 5/24/07
DSI:5760; O:\BE\EIRCOVER\21809nov.ins07.doc

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/s/

Sriram Subramaniam
5/25/2007 11:49:35 AM
PHARMACOLOGIST
Attachments will be forwarded to OCP reviewer.

Jacqueline OShaughnessy
5/25/2007 12:23:05 PM
PHARMACOLOGIST
On behalf of Dr. Viswanathan

Galliers, Enid M

From: Galliers, Enid M
Sent: Thursday, April 19, 2007 12:09 PM
To: 'LIZD (Liz D'Amato)'
Cc: Parks, Mary H; Wei, Xiaoxiong; Sahajwalla, Chandrahas G
Subject: Info request re NDAs 21-809 & 21-810

Dear Liz:

Would you please provide the following information for Study BIAsp-1746 that has been requested by the clinical pharmacology reviewer - or tell us where the information can be found in previous submissions?

Please provide:

(1) analytical assay summary
(2) insulin antibody information
(3) analytical report including raw data.

As usual, please make an official submission regardless of whether you submit the information by secure email.

Regards,

Enid

Enid Galliers
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
Phone: 301-796-1211
Fax: 301-796-9712
email: enid.galliers@fda.hhs.gov

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/s/

Enid Galliers
4/19/2007 01:02:45 PM
CSO

9.5.06

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-809
NDA 21-810

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, New Jersey 08540

Dear Dr. McElligott:

Pease refer to your Investigational New Drug Application (IND) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

NDA 21-809 NovoLog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin]), and

NDA 21-810 NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]).

We also refer to the meeting between representatives of your firm and the FDA on July 12, 2006, and to our internal minutes sent to you on July 7, 2006. The purpose of our meeting was to discuss the outstanding approvability issues for these applications.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call me at 301-796-1306.

Sincerely,

{See appended electronic signature page}

Jena Weber
Regulatory Project Manager
Division of Metabolism & Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES
MEMORANDUM OF MEETING MINUTES

Meeting Date: Wednesday July 12, 2006
Time: 11:00 – 12:30 pm
Location: White Oak Building 22, Conference Room 1311
Applications: NDA 21-809 and NDA 21-810
Drug names: NovoLog® Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin]); Biphasic Insulin Aspart (BIAsp) 70; NovoLog® Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]); Biphasic Insulin Aspart (BIAsp) 50

Type of Meeting: Type C
Meeting Chair: Mary Parks, M.D., Director, Division of Metabolism & Endocrinology Products
Meeting Recorder: Joanna K. Zawadzki, M.D.

FDA attendees:

Mary Parks, M.D.	Director, Division of Metabolism & Endocrinology Products (DMEP)
Joanna Zawadzki, M.D.	Medical Officer, DMEP
Karen Mahoney, M.D.	Medical Officer, DMEP
Jena Weber, BS	Acting Project Manager

Office of Clinical Pharmacology (OCP):

Hae-Young Ahn, Ph.D.	Team Leader
Jim Wei, M.D., Ph.D.	Biopharmaceutics Reviewer

Novo Nordisk (US):

Elizabeth D'Amato	Senior Manager, Regulatory Affairs
Janet Overholt	Director, Regulatory Affairs
Mary Ann McElligott, Ph.D.	Associate VP Regulatory Affairs
Alan Moses, M.D.	Associate VP, Clinical Research-Medical Affairs

Novo Nordisk (Denmark):

Karin Kanc Hanzel, M.D., Ph.D.	Medical and Science Director, Global Development
Klaus Juel, MSc, Ph.D.	Statistician, Department of Biostatistics
Hanne Haahr, MSc, Ph.D.	Clinical Pharmacologist, Medicine and Science
Anders Dyhr Toft, M.D.	International Medical Affairs
Hans Friberg, M.Sc.	Clinical Team Leader, Clinical Research
Lene Garde Rasmusssen, M.Sc.	Global Regulatory Affairs Director
Lise Lundbeck	Quality Systems

b(4)

6 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Jena Weber
9/5/2006 02:37:08 PM

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/s/

Enid Galliers
9/4/2006 05:24:52 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-809
NDA 21-810

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

NDA 21-809	NovoLog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin])
NDA 21-810	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

We also refer to your April 27, 2006, correspondence, received April 28, 2006, requesting an end of review meeting for the NDAs mentioned above.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: July 12, 2006
Time: 11:00 – 12:30 pm
Location: White Oak Buliding 22, C/R 1311
CDER participants (tentative):
Mary Parks, M.D., Acting Director, Division of Metabolism and Endocrinology Products
Joanna Zawadzki, M.D., Medical Officer, DMEP
Karen Mahoney, M.D., Medical Officer, DMEP
Hae Young Ahn, Ph.D., Biopharm Team Leader, OCPB
Jim Wei, Ph.D., Biopharm Reviewer, OCPB
CT Viswanathan, Ph.D., Associate Director, Division of Scientific Investigations
Michael F. Skelly, Ph.D., Pharmacologist, Division of Scientific Investigations
Julie Rhee, Regulatory Project Manager, DMEP

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. If there are additional attendees, email that information to me at hjulie.rhee@hhs.fda.gov so that I can give the security staff time to prepare temporary badges in advance. Upon arrival at FDA, give the guards either of the following numbers to request an escort to the conference room: Julie Rhee, 796-1280; Nicole Cooper, the division secretary, 796-2290.

Provide the background information for this meeting (two copies to the NDAs and 10 desk copies to me) at least one month prior to the meeting. Please submit the desk copies to my attention at 10903 New Hampshire Avenue, Silver Spring, MD 20993. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by June 12, 2006, we may cancel or reschedule the meeting.

If you have any questions, call me at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolism
and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee
5/11/2006 04:01:26 PM

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/s/

Mary Parks
4/28/2006 07:16:04 AM

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/s/

Denise Toyer
3/6/2006 04:26:52 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/6/2006 04:30:27 PM
DRUG SAFETY OFFICE REVIEWER

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODEII

FACSIMILE TRANSMITTAL SHEET

DATE: March 1, 2006

To: Elizabeth D'Amato	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolism and Endocrinology Products
Fax number: 609-987-3916	**Fax number:** 301-796-9718
Phone number: 609-919-7789	**Phone number:** (301) 796-1280

Subject: NDA 21-809 NovoLog Mix 30/70 and
NDA 21-810 NovoLog Mix 50/50

Total no. of pages including cover: 4

Comments:

Attached is PPI review comments from ODS/DSRCS. Please revise PPI accordingly and submit the revised labeling to EDR.

Please include ODS/DMETS recommendation on PPI that was sent to you on January 30, 2006, when you revise PPI. Thank you.

Document to be mailed: ☐ **YES** ☑ **NO**

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NDA 21-809 NovoLog Mix 30/70
NDA 21-810 NovoLog Mix 50/50

Date of submission: June 22, 2005

ODS/DSRCS labeling comments for patient insert

Diabetes is a chronic medical condition in which patients are expected to perform complex self-management activities in order to avoid death and disability. Health-related materials including diabetes materials are often written at levels that far exceed many people's reading abilities.[1] An insufficient ability to comprehend health-related information can lead people to feel overwhelmed and unable to develop and integrate the necessary skills and knowledge for self-care of their condition.[1] Research[2,3] has shown that inadequate health literacy in diabetics is associated with worse glycemic control and higher rates of retinopathy and may contribute to more diabetes-related problems.

Approximately one half of U.S., English-speaking adults read and comprehend materials only when written at less than an 8th grade reading level. Approximately one third of adults in the U.S. cannot read and understand basic materials.[1] Health literacy is usually lower than general literacy because of the unfamiliarity with health-related and medical terminology.[4] The association between educational attainment and health literacy skills is poor.[1] It is difficult to identify people with low general or health literacy because they come from all walks of life. Patients with low literacy are often ashamed of the condition and are quite successful at hiding the limitation.

1. The submitted patient labeling with instructions for use have a Flesch-Kincaid Reading Level of 11.1 (approximating an 11th grade reading level) and a Flesch Reading Ease of 44.3%. These PPIs along with Novo Nordisk Pharmaceutical's other NovoLog product PPIs fail to address the health literacy needs for the majority of diabetic adults in the U.S. For optimal comprehension across a broad patient population, patient materials should be written at a 5th to 8th grade reading level and have a reading ease of at least 60% (60% corresponds to an 8th grade reading level).

- Revise PPIs and Instructions for Use to meet the comprehension needs of the majority of patients with diabetes.
  - o We recommend a question and answer format, such as that used for Medication Guides (see 21 CFR § 208). This format is voluntary for PPIs, but has research to support its effectiveness as a risk communication tool.
  - o Use simple, short sentences to enhance readability. Avoid the use of technical terms or define them in patient-friendly terms.
  - o Use cognitive accessibility principles such as "chunking" for comprehensibility. Chunking allows people to access and retrieve information more readily. (The chunking principle involves classifying items into groups to avoid information overload.)
  - o Use enhanced visuals in the instructions for use and write instruction steps using short, clear steps.

- Demonstrate good principles of type-size and design by using at least a 10-point font, serif type, and not using all upper case letters in the text.
- Demonstrate good principles of page layout and design by left justifying margins, using ample white space throughout the document and using good contrast between ink and paper colors.
- Keep information on diabetes brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Description of an underlying medical condition should be brief or placed in a separate sheet and provided as a separate educational material for the patient.

****

[1] Chew, LD. The impact of low health literacy on diabetes outcomes, Diabetes Voice 2004; 49: 30-32

[2] Williams MV, Baker DW, Parker RM, Nurss JR. Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. Arch Intern Med 1998; 158: 166-72

[3] Schillinger D, Grumback K, Piette J, Wang F, Osmond D, Daher C, Palacios J, Sullivan GD, Bindman AB. Association of health literacy with diabetes outcomes, JAMA 2002; 288: 475-82

[4] The National Academy of Sciences. Health Literacy: A Prescription to End Confusion, 2004

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/s/

Julie Rhee
3/1/2006 03:22:54 PM

2.27.06

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-809
NDA 21-810

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

NDA 21-809	NovoLog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin])
NDA 21-810	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

We also refer to your January 19, 2006, submissions proposing new proprietary tradenames for NovoLog Mix 30/70 and NovoLog Mix 50/50.

We have reviewed the referenced material and recommend that one proprietary name be used for all of your insulin aspart protamine suspension and insulin aspart combination products. The products should be further differentiated with a numerical modifier (e.g., 70/30) representing the concentration of each component.

Because of post-marketing confusion and medication errors with the proprietary names NovoLog, NovoLog Mix, and Novolin, please propose a root name that does not share orthographic or phonetic similarity with these names.

Furthermore, you should be aware of the potential for confusion if you plan to market concentrations that would require the use of reverse numerical modifiers (e.g., 70/30 vs. 30/70).

If you have any questions, call Julie Rhee, Regulatory Project Manager, at (301) 796-1280.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Acting Director
Division of Metabolism
and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
2/27/2006 03:47:00 PM

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

REQUEST FOR CONSULTATION

O *(Division/Office)*:
Mail: ODS (Room 15B-08, PKLN Bldg.)

FROM:
Julie Rhee, DMEP

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 27, 2006		21-809 21-810	Response to ODS comments	February 9, 2006

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
NovoLog Mix 30/70 (NDA 21-809) NovoLog Mix 50/50 (NDA 21-810)			March 24, 2006

NAME OF FIRM: Novo Nordsk

REASON FOR REQUEST

I. GENERAL

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

II. BIOMETRICS

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

III. BIOPHARMACEUTICS

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

IV. DRUG EXPERIENCE

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

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

The Feb 9, 2006, submission is in response to your review comments dated 12/23/05 (ODS consult #s 05-0164 [for NDA 21-809] and 05-0165 [for NDA 21-810]).

Please review to see if the sponsor's response is satisfactory. The submission is available in EDR. Please access EDR to retrieve the submission.
Thank you.

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Julie Rhee
2/27/2006 02:52:31 PM

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/s/

Tina Tezky
2/22/2006 05:31:44 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
2/22/2006 05:35:54 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
2/22/2006 05:45:35 PM
DRUG SAFETY OFFICE REVIEWER

and understand basic materials.[1] Health literacy is usually lower than general literacy because of the unfamiliarity with health-related and medical terminology.[4] The association between educational attainment and health literacy skills is poor.[1] It is difficult to identify people with low general or health literacy because they come from all walks of life. Patients with low literacy are often ashamed of the condition and are quite successful at hiding the limitation.

1. The submitted patient labeling with instructions for use have a Flesch-Kincaid Reading Level of 11.1 (approximating an 11th grade reading level) and a Flesch Reading Ease of 44.3%. These PPIs along with Novo Nordisk Pharmaceutical's other Novolog product PPIs fail to address the health literacy needs for the majority of diabetic adults in the U.S. For optimal comprehension across a broad patient population, patient materials should be written at a 5th to 8th grade reading level and have a reading ease of at least 60% (60% corresponds to an 8th grade reading level).

    - Revise all NovoLog-product PPIs and Instructions for use to meet the comprehension needs of the majority of patients with diabetes.
        - We recommend a question and answer format, such as that used for Medication Guides (see 21 CFR § 208). This format is voluntary for PPIs, but has research to support its effectiveness as a risk communication tool.
        - Use simple, short sentences to enhance readability. Avoid the use of technical terms or define them in patient-friendly terms.
        - Use cognitive accessibility principles such as "chunking" for comprehensibility. Chunking allows people to access and retrieve information more readily. (The chunking principle involves classifying items into groups to avoid information overload.)
        - Use enhanced visuals in the instructions for use and write instruction steps using short, clear steps.
        - Demonstrate good principles of type-size and design by using at least a 10-point font, serif type, and not using all upper case letters in the text.
        - Demonstrate good principles of page layout and design by left justifying margins, using ample white space throughout the document and using good contrast between ink and paper colors.
        - Keep information on diabetes brief. Patient information leaflets (PPIs) are to enhance appropriate use of medications and provide important risk information. Description of an underlying medical condition should be brief or placed in a separate sheet and provided as a separate educational material for the patient.

2. We suggest consideration for insulin class language to include in product-specific patient labeling to ensure consistency and comprehension across the Class.

Please let us know if you have any questions.

[1] Chew, LD. The impact of low health literacy on diabetes outcomes, *Diabetes Voice* 2004; 49: 30-32

[2] Williams MV, Baker DW, Parker RM, Nurss JR. Relationship of functional health literacy to patients' knowledge of their chronic disease. A study of patients with hypertension and diabetes. *Arch Intern Med* 1998; 158: 166-72

[3] Schillinger D, Grumback K, Piette J, Wang F, Osmond D, Daher C, Palacios J, Sullivan GD, Bindman AB. Association of health literacy with diabetes outcomes, *JAMA* 2002; 288: 475-82

[4] The National Academy of Sciences. Health Literacy: A Prescription to End Confusion, 2004

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/s/

Jeanine Best
2/17/2006 02:56:54 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
2/17/2006 04:08:43 PM
DRUG SAFETY OFFICE REVIEWER

MEMORANDUM

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

DATE: February 2, 2006

TO: David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology Products
(HFD-510)

FROM: Michael F. Skelly, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDAs 21-809 and 21-810, NovoLog Mixes 30/70 and 50/50, Insulin Aspart Protamine Suspension and Soluble, Sponsored by Novo Nordisk Pharmaceuticals, Inc.

At the request of DMEP, the Division of Scientific Investigations audited the clinical-pharmacodynamic and analytical portions of the following bioequivalence study. HFD-510 requested and cancelled audit of the same study in 2000 and 2001 during its review of NDA 21-172.

Protocol #BIAsp1086: ""A Randomized, Four Period Crossover Trial in Healthy Subjects Investigating the Pharmacodynamics and Pharmacokinetics of Biphasic Insulin Aspart 30, Biphasic Insulin Aspart 50, Biphasic Insulin Aspart 70 and Soluble Insulin Aspart"

The primary measures evaluated in this study were the plasma pharmacokinetics of [Asp^{B28}]-insulin (IAsp) and the pharmacodynamics of the glucose infusion rate (GIR) profile from the euglycemic clamp technique. This memorandum discusses the IAsp analyses conducted at
A separate memorandum will discuss the audit of the clinical-pharmacodynamic portion of the study.

b(4)

Following inspections at Novo Nordisk (October 24-26, 2005) and
(October 27-31, 2005), both in

[redacted] Form 483 was issued at each site. The objectionable observations and our evaluations are as follows: b(4)

NOVO NORDISK A/S:

1. **Failure to submit a bioanalytical study report.**
2. **Failure to submit to the Agency (FDA) the individual subject insulin concentration values. The derived AUC values were submitted.**
3. **Failure to document and maintain records of the receipt of insulin analytical data (IAsp concentrations in plasma) from [redacted]**

[redacted] is a contract research organization that analyzed the study samples for the sponsor Novo Nordisk. The sponsor reported only derived pharmacokinetic parameters (e.g., AUC); they did not submit the original IAsp concentration values, the source data, generated by [redacted] to the Agency in its NDA. Furthermore, Novo Nordisk was unable to retrieve records of the original IAsp concentration data received from [redacted] b(4) Thus, it was not possible to verify Novo Nordisk's pharmacokinetic calculations since the authenticity of the source data were not known.

In their response dated November 22, 2005, Novo Nordisk failed to explain why their original NDA submissions on June 22, 2005 lacked a bioanalytical report or why the report was created only in October 2005, just prior to the start of the DSI inspection, given that study BIASP-1086 was conducted in 1999. While Novo Nordisk claimed that emails documenting the data transfer from [redacted] were subsequently retrieved from their facility in [redacted] b(4) (responsible for data management for study BIASP-1086), these records were not provided; instead, they provided a summary memo of the transfer dated November 2, 2005.

Conclusion: It was not possible to verify the authenticity of the source data of IAsp concentrations from which the PK data were derived.

[redacted]: b(4)

4. **Failure to write and retain a Final Study Report. A brief bioanalytical report dated 13 October 2005 was complied after the announcement of the impending FDA inspection.**

5. **Failure to maintain a specific record to document the transmission of concentration data for the entire study.**

There is a gap in the audit trail between [redacted] generation of IAsp concentration results and reporting of them to the sponsor. In their response dated November 25, 2005, [redacted] claimed that their contract with the sponsor did not include a final report. b(4)

6. **Failure to reject assay runs based on "partly approved" QC results in runs #101, 102, 113, 123, 129, 130, 134, 135, 139, 141, and 158. The following subjects' data should have been excluded: #15, 17, 18, 20, 21, 22, 24, 26, 27, and 28.**

The cited runs should have been rejected when more than 50% of the QC samples at a single concentration failed the acceptance criterion. Instead, the firm attempted to salvage subject concentrations bracketed by only two acceptable QC concentration levels.

7. **Failure to retain source data in the preparation of QC samples. Also, the stock solutions for preparing the QC samples were prepared approximately 1.5 years prior to the start of study analyses.**
8. **Expired QC solutions were used in the study.**
9. **Failure to maintain the source data in calculating the QC acceptance limits (originally target value ± 2.8 x SD; later SD was replaced with 1.75 plus 0.0629 x target value).**

The QC samples used for run acceptance provide no information about the accuracy of the IAsp assays because their true concentrations at the time of preparation and use are not known. In their response to the Form 483 [redacted] claimed that they prepared the QCs according to their SOP without further documentation and that the sponsor instructed them to use the expired reference solution. [redacted] also stated that the sponsor proposed the specification for calculating run acceptance limits. Because there were no records of how the formulae to calculate the QC acceptance limits were derived, there is no assurance that these limits were established without bias. b(4)

10. **The record documenting the 20 Sept 1999 receipt of supplies (antibody-coated microtiter plates, biotinylated second antibody, and IAsp calibrators), from Novo Nordisk contained calibrator concentration**

data which were added to the document after it was signed, by someone other than the signatory, on an unknown date.

11. Failure to label the calibrators with expiration date and storage temperature.

The accuracy of the IAsp assays was not demonstrated because source records were insufficient to establish the concentrations of the calibrators. Furthermore, there is no assurance that the calibrators were stored within the durations and conditions of demonstrated stability. In response to the Form 483, ——— stated that they received the calibrators from the sponsor without the required handling information. b(4)

12. Failure to maintain an SOP specifying criteria for repeat analysis used in the study.

13. Failure to maintain criteria for repeating samples based on "unexpected values."

In the absence of written criteria, it is not possible to assure that decisions to repeat analyses were unbiased.

14. Failure to maintain adequate and accurate sample records. For example:

A. Record systems fail to document storage of study subject samples from receipt until assay.

B. Record systems fail to document removal and return of test samples to and from the frozen storage areas. The person who removed or returned the samples and the date and time of the events were not recorded.

It was not demonstrated that study samples were stored and handled under conditions of known stability to maintain their integrity.

15. The compliance certification in the Bioanalytical Report dated 13 Oct 2005 is inaccurate and misleading in that the firm is not in compliance "with internationally-accepted principles of Good Laboratory Practice." For example, the firm failed to write a final report in a timely manner; no expiration dates were listed for the calibration standards, etc.

The false claim of GLP compliance should not confer credibility on the results.

Conclusions:

DSI recommends that the analytical data from the pharmacokinetic portion of Study BIAsp1086 be **NOT** accepted for review. The accuracy of the reported concentrations of IAsp was not demonstrated because ——— b(4)

- Failed to retain source data to establish the actual concentrations of the calibrators used to calculate IAsp levels in study samples and the QCs used to monitor assay performance. (items 10-11, 7-8 above)
- Failed to reject data from runs with unacceptable QC performance. (item 6 above)
- Failed to document that subject samples were stored under conditions adequate to maintain their integrity prior to analysis. (item 14 above)

Furthermore, the sponsor did not submit a final bioanalytical study report to the Agency. ——— failed to write a final report for the sponsor; it was only prepared after the FDA inspection was announced. Additionally, neither ——— nor Novo Nordisk provided records to document the transfer of the IAsp results. Thus, it is not possible to verify whether the IAsp data were reported accurately and without bias. In conclusion, the authenticity of the source data is not known. b(4)

After you have reviewed this transmittal memo, please append it to the original NDA submissions.

Michael F. Skelly, Ph.D.
Pharmacologist

Final Classification:
OAI - Novo Nordisk, Copenhagen, Denmark
OAI - [redacted]

b(4)

Recommendation: Pharmacokinetic data from study BIAsp1086 are unacceptable for review.

cc:
HFA-224
HFD-45/RF
HFD-48/Himaya
HFD-48/CF
HFD-510/NDAs 21-809, 21-810, and 21-172/Rhee
HFD-870/Wei
HFD-870/Ahn
HFR-NE340/Kewley
HFD-SE240/Shambaugh
Drafted: MFS 11/8/05
Edit: JAO 11/28/05
Edit: CTV 12/19/05
Revise: JAO 12/20/05
Edit: CTV 2/2/06
DSI: 5341, 5646; O:\BE\EIRCover\21809nov.IASa.doc
FACTS: [redacted]

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/s/

Amalia Himaya
2/2/2006 04:57:07 PM
CSO

Paper copy signed by Dr. Viswanathan on 2/2/06 and available upon request.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ONDC

FACSIMILE TRANSMITTAL SHEET

DATE: January 30, 2006

To: Elizabeth D'Amato	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolism and Endocrinology Products
Fax number: 609-987-3916	**Fax number:** (301) 796-9718
Phone number: 609-919-7789	**Phone number:** (301) 796-1280

Subject: NDA 21-809 NovoLog Mix 30/70
NDA 21-810 NovoLog Mix 50/50

Total no. of pages including cover: 4

Comments:

ODS review comments for NDA 21-809 NovoLog Mix 30/70 and NDA 21-810 NovoLog Mix 50/50. Please let me know when we could expect your response. Thank you.

Document to be mailed: ☐ **YES** ☑ **NO**

Appears This Way
On Original

NDA 21-809 NovoLog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin])
NDA 21-810 NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

Date of submission: June 22, 2005

Review comments (from DMETS)

GENERAL COMMENTS:

1. Include the route of administration on all labels and labeling where space permits and revise the statement to indicate subcutaneous use for Prefilled syringe and Penfill cartridge labeling.

2. DMETS recommends that the statement, "New Product Strength" appears on product labels and labeling for a period of time not to exceed six months.

CONTAINER, PENFILL (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample):

1. Relocate the declaration of net quantity of contents to appear as a distinct item on the carton labeling and increase its prominence.

2. Revise the expressions of strength on the principal display panel to read:

300 units per 3 mL
100 units/mL (U-100)

CARTON, PENFILL (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample):

1. Relocate the declaration of net quantity of contents, "5 cartridges per package", to appear as a distinct item on carton labeling.

2. Revise the labeling statement, ' ——— _ , to read "300 units per 3 mL" and increase its prominence. b(4)

3. Increase the prominence of the secondary expression of strength, "100 units/mL (U-100)".

CARTON, FLEXPEN (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, 5 X 3 mL Retail and 1 X 3 mL Sample):

1. Relocate the declaration of net quantity of contents, "5 X 3 mL Prefilled Insulin syringes" or "1 X 3 mL Prefilled Insulin syringes", to appear as a distinct item on carton labeling.

2. Revise the expressions of strength to read as follows and increase its prominence.

300 units per 3 mL
100 units/mL (U-100)

CONTAINER, FLEXPEN (NovoLog® Mix 30/70 and NovoLog® Mix 50/50, Retail and Sample):

1. Relocate the declaration of strength to appear beneath the statement of identity, increase its prominence, and revise as follows:

300 units per 3 mL
100 units/mL (U-100)

PATIENT INFORMATION:

DMETS recommends that Patient Information should include reference to and education about other strengths of NovoLog Mix, that there exists a NovoLog which is not a mix, and request that the patient be sure about the product that their physician intends for them to use.

COLOR BRANDING:

We are unable to provide comments on color branding at this time.

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/s/

Julie Rhee
1/30/2006 02:47:29 PM

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On Original

MEMORANDUM

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

DATE: January 18, 2006

TO: David G. Orloff, M.D.
Director
Division of Metabolism and Endocrinology Products
(HFD-510)

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D.
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering NDAs 21-809 and 21-810, NovoLog Mixes 30/70 and 50/50, Insulin Aspart Protamine Suspension and Soluble, Sponsored by Novo Nordisk Pharmaceuticals, Inc.

At the request of DMEP, the Division of Scientific Investigations audited the clinical-pharmacodynamic and analytical portions of the following bioequivalence study. This report is limited to the audit of the clinical-pharmacodynamic portion of the study. DSI's audit of the analytical portion of the study will be reported separately.

Protocol #BIAsp1086: "A Randomized, Four Period Crossover Trial in Healthy Subjects Investigating the Pharmacodynamics and Pharmacokinetics of Biphasic Insulin Aspart 30, Biphasic Insulin Aspart 50, Biphasic Insulin Aspart 70 and Soluble Insulin Aspart"

The primary objective of this study was to assess the glucose infusion rate (GIR) profiles between 0 to 2 hrs of the biphasic insulin aspart (i.e. BIAsp 30, BIAsp 50 and BIAsp 70) and soluble insulin aspart (IAsp) products using the euglycaemic clamp technique. In this technique, blood glucose (BG) is clamped at a preset level and any BG lowering effect of insulin is countered by infusion of glucose to maintain the target BG level. The GIRs measured using this technique is a reflection of the blood

glucose lowering effect of insulin, and thus allows for quantification of the pharmacodynamic properties of the insulin products. The euglycaemic clamp experiments for the study were conducted at Profil GmbH, Neuss, Germany.

Following the inspection at Profil GmbH (November 14-18, 2005), Form 483 was issued. The inspection found significant problems with documentation and analysis of blood glucose concentrations. Our evaluation of the significant findings and the firm's response (Attachment 1) is as follows:

Documentation Problems

a. Treatment administered to the study subjects cannot be assured to have followed the randomization code. (Form 483, Item 1)

Profil stated that duplicate peel-off labels of the treatments administered to the subjects were affixed in the original CRFs' "Drug label forms". However, the original drug label forms were not available for review during the audit. The firm stated that the forms were returned to the sponsor. The duplicate drug label forms and the drug infusions forms retained by the firm do not indicate the treatments. Also, Profil failed to retain the sealed randomization code. Profil returned the code to the sponsor. In the absence of the Drug label forms and the sealed codes, the treatments administered to the subjects cannot be confirmed.

b. Lack of records of the lots and expiry dates of human insulin and glucose solutions. (Form 483, Item 5a)

The specifications (i.e. concentration, lot number, expiry date) of the human insulin and glucose solutions used for infusion cannot be verified, as Profil failed to retain records to identify these reagents.

c. Failure to properly record source data in that the data includes cross-out and 'White out' entries without the research assistant's initials and date. (Form 483, Item 6)

Entries in clamp source forms and BG logs were overwritten or crossed out without the date and initials of the staff making the changes.

Findings Related to Blood Glucose Analysis

d. Discrepancies in acceptance of glucose clamp data. (Form 483, Item 3)

During the inspection, Profil stated that the Biostator's BG analyzer was susceptible to drift. Therefore, the external BG measurements were used as the reliable BG measurements. Due to the drift, the site had to routinely adjust the Biostator's BG measurement to match the external BG concentrations. The external BG concentrations were not reported to the Agency and were collected during the inspection (Attachment 2). As the quality of glucose clamp is judged by the deviation from target BG concentrations (90 mg/dL) and since the external BG was the reliable measurement, DSI reviewed the external BG data. DSI's review of external BG concentrations (Figures 1-4: BG of representative subjects) revealed that BG was not clamped at 90 mg/dL for many subjects, especially during the first two hours which is the relevant time period for the primary efficacy end point (GIR_{0-2hr}). Also, DSI's comparison of the external and Biostator BG concentrations revealed that Biostator BG concentrations did not mimic the external BG concentrations for some subjects (Figures 1-4). As GIR is based on the Biostator BG measurement, the reliability of GIR_{0-2hr} measurements cannot be verified.

Profil's response to support the quality of clamp was acceptable is misleading in that mean and standard error of BG concentrations reported in the response were derived from Biostator BG concentrations (not the external BG concentrations) and were based on data from the whole study. In contrast, when DSI estimated the mean and standard error for representative subjects using the external BG concentrations, the subjects had significant imprecision[1] (see table below).

Subject	Visit	BG Imprecision (%CV) for 0-2 hrs
4	4	8.4%
6	4	13.1%
8	3	8.9%
10	4	9.5%
10	5	13.6%
11	4	13.5%
12	4	8.1%

[1] **"Usually a CV of the blood glucose concentration of <5% is considered to be criterion for a successful glucose clamp of sufficient quality"** - L. Heinemann & J.H. Anderson Jr., Diabetes Technology & Therapeutics, 6(5), 698-718, 2004.

Also, the inspection revealed that in some euglycaemic clamp experiments, the Biostator was frequently on "hold" status due to problems with Biostator's BG sensor and other Biostator problems (Attachment 3: Raw data collected during the inspection).

e. The precision and accuracy of the external glucose analyzer was not validated for the entire calibration range. (Form 483, Item 4)

The firm did not conduct a study to demonstrate the linearity, precision and accuracy of the Glucose analyzer over the entire range. Instead the firm did a daily two point calibration with a single quality control (QC) sample. It is not known if the calibration solution and QC samples used were in the same matrix as the study samples (see Item 5b). Also, the accuracy of the QC checks cannot be assured as the nominal concentration of the QC used was not recorded. Profil only recorded the acceptable range (82.8-112 mg/dL). Also, between 4/13/99 and 1/8/00, the instrument calibration logs did not record the QC concentrations of the daily checks and the acceptance range of the QC used; the log only indicated if the QCs passed.

f. Lack of records for the lots and specification of the calibration and control solutions used for daily checks of the external glucose analyzer. (Form 483, Item 5b)

Profil did not have the specifications of the calibration solution and QCs used for the study. It is not known if the reagents were in the same matrix as the study samples.

g. Failure to retain source records (i.e. printouts) for the external blood glucose (BG) concentration measurements. (Form 483,Item 2)

During the inspection, the firm maintained that they did not retain the external BG analyzers' printouts of the BG concentrations and that concentrations were transcribed to the clamp source forms. Profil's written response stated that printers were not available for the external BG analyzers contradicts their response during the inspection.

h. Lack of written procedures for conducting eugylcaemic clamp experiments at the time of the study (Form 483, Item 8).

In their response, Profil concurred with the finding but maintained that the study was conducted as per the current procedures. Due to problems in documentation (Findings a, b, c, f and g) and lack of procedures for conducting euglycaemic clamp at time of the study, DSI cannot assure the conduct of the study.

Other Findings

i. Failure to retain reserve samples of the study drugs. (Form 483, Item 7)

Contrary to Profil's response, this study assess the relative bioavailability using a pharmacodynamic end point and thus requires retention of reserve samples as per 21 CFR 320.38 (Retention of Bioavailability Samples).

Conclusions

The Division of Scientific Investigations (DSI) recommends that the glucose clamp data for Study BIAsp1086 be **not** accepted for review due to the following significant findings:

1) Dosing of subjects cannot be assured to have followed the randomization code (Finding a).
2) The accuracy of the GIRs during the time period (0 to 2 hrs) relevant for the primary end-point ($AUC_{GIR,0-2hrs}$) cannot be assured (Findings d to h).
3) The concentrations, lot numbers and expiry dates of the glucose and insulin solutions are not known (Finding b).

The inspection results of the analytical portion of Study BIAsp1086 will be discussed in a separate report.

Following your review, please attavch this transmittal memo to the original NDA submission.

Sriram Subramaniam, Ph.D.

DSI Final Classification:
VAI - Profil GmbH, Neuss, Germany.

Attachment 1 - Profil's 12/1/04 response to the Form 483
Attachment 2 - Profil's external BG measurements for Study BIAsp1086
Attachment 3 - CD of glucose clamp data files for Study BIAsp1086 and Profil's 11/18/05 description of the data files.

Note:
Due to the number of pages involved Attachments 2 and 3 will be forwarded only to the HFD-870 reviewer. Additional copies will be available upon request.

cc:
HFA-224
HFD-45/RF
HFD-48/Subramaniam(2)/Himaya/CF
HFD-510/Rhee/NDA 21-809/NDA 21-810
HFD-870/Ahn/Wei
Draft: SS 1/18/06
Edit: MKY 1/19/06
DSI:5646; O:\BE\EIRCOVER\21809nov.ins.doc

FIGURE 1

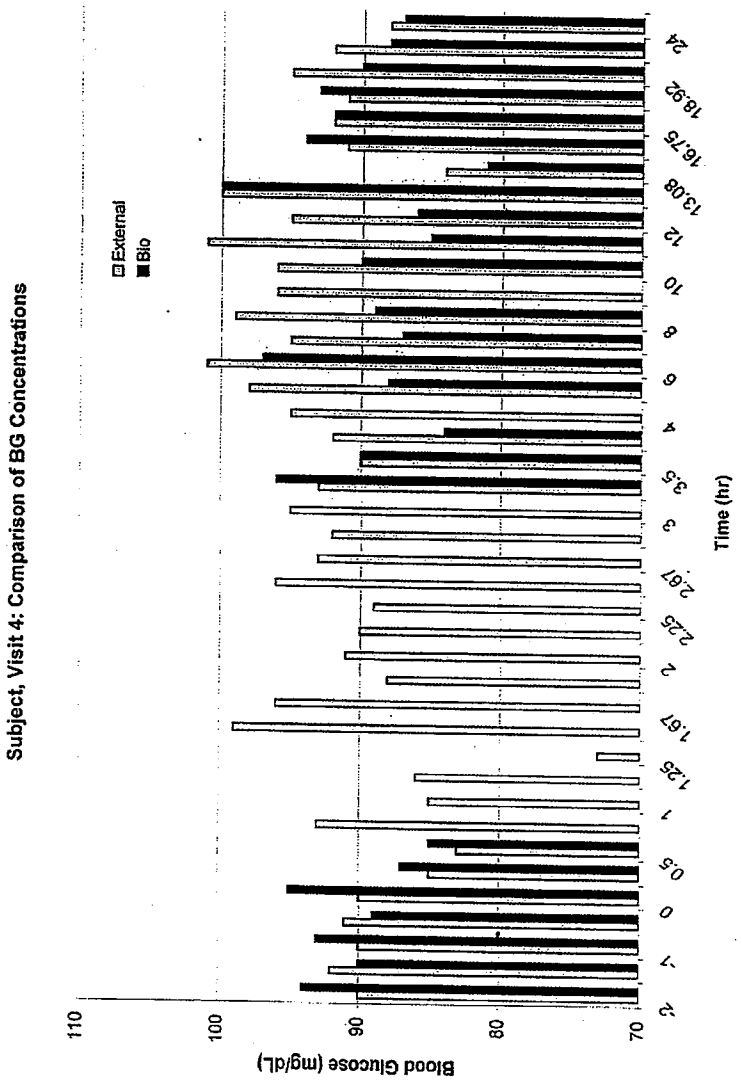

Subject, Visit 4: Comparison of BG Concentrations
External
Bio
Blood Glucose (mg/dL)
110
100
90
80
70
Time (hr)
-2
-1
0
0.5
1
1.25
1.67
2
2.25
2.67
3
3.5
4
6
8
10
12
13.08
16.75
18.92
24

FIGURE 2

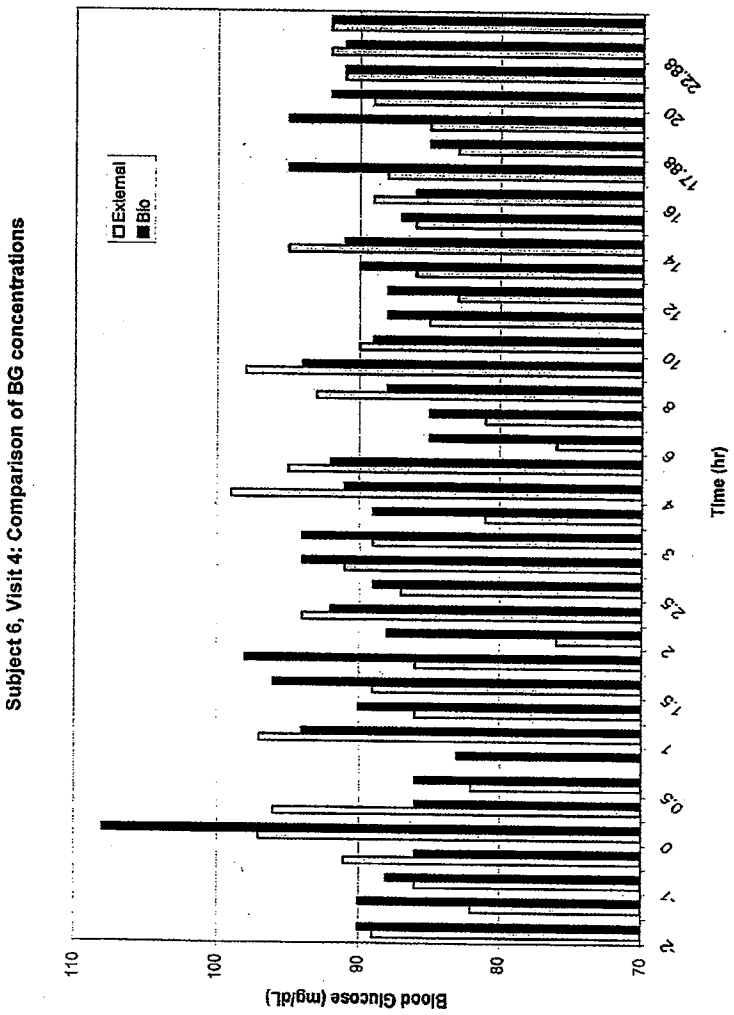

Subject 6, Visit 4: Comparison of BG concentrations
External
Bio
Blood Glucose (mg/dL)
110
100
90
80
70
Time (hr)
-2
-1
0
0.5
1
1.5
2
2.5
3
4
6
8
10
12
14
16
17.88
20
22.88

FIGURE 3

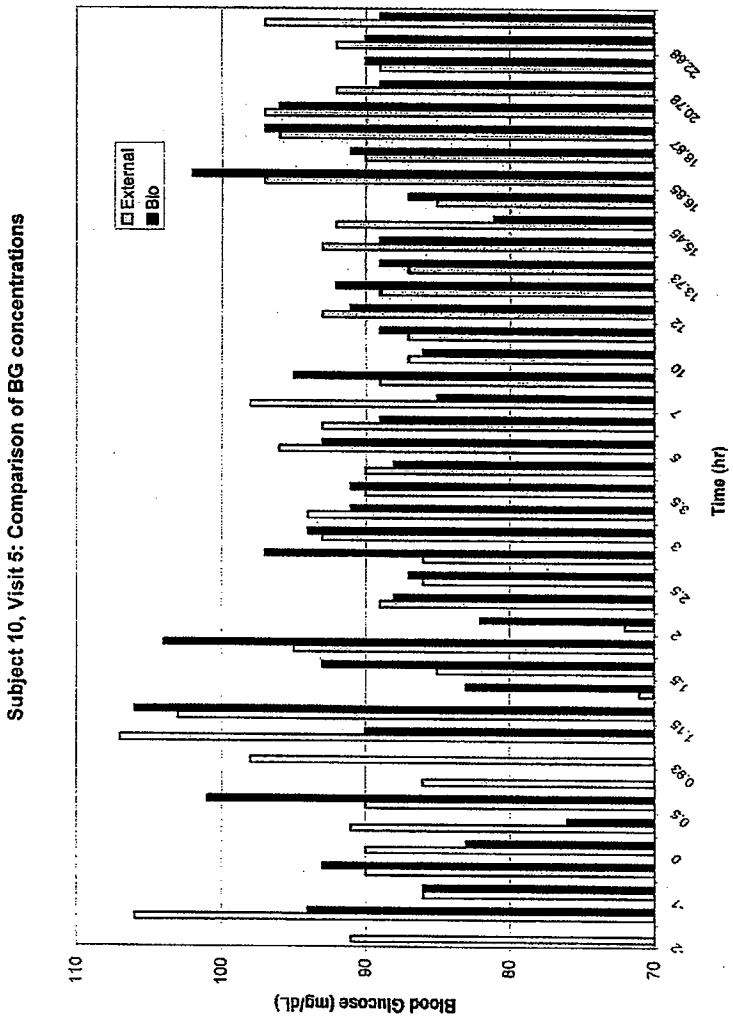
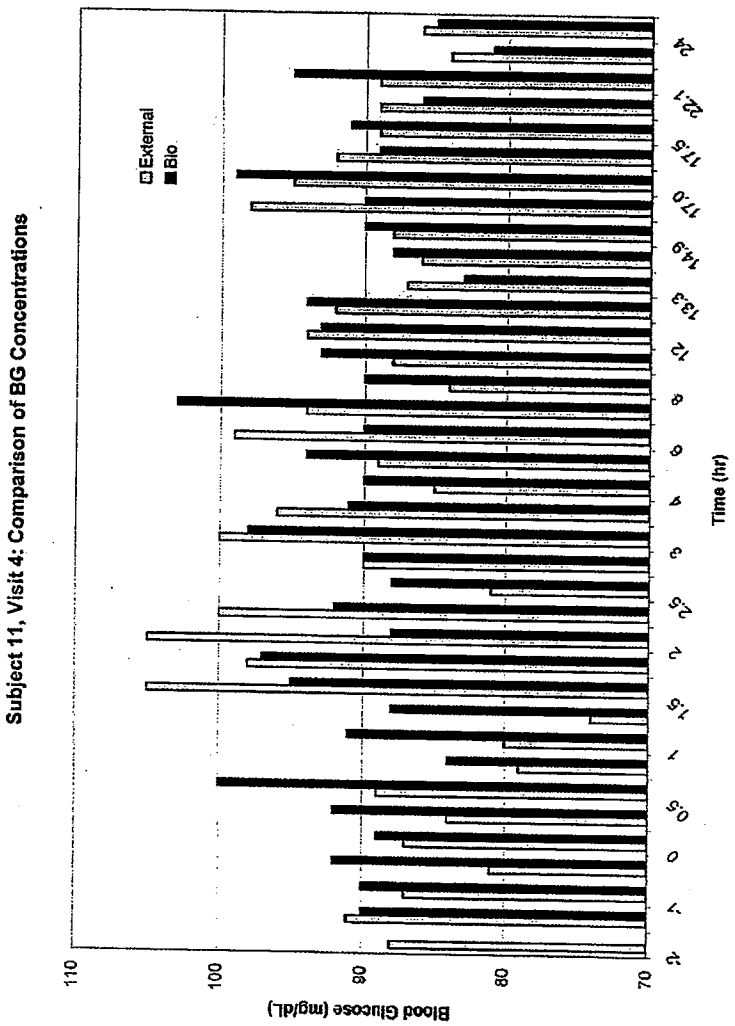

Subject 10, Visit 5: Comparison of BG concentrations
External
Bio
Blood Glucose (mg/dL)
110
100
90
80
70
Time (hr)
-.2
-.1
0
0.5
0.83
1.15
1.5
2
2.5
3
3.5
5
7
10
12
13.73
15.45
16.65
18.67
20.78
22.88

FIGURE 4


Subject 11, Visit 4: Comparison of BG Concentrations
External
Bio
Blood Glucose (mg/dL)
110
100
90
80
70
Time (hr)
-2
-1
0
0.5
1
1.5
2
2.5
3
4
6
8
12
13.3
14.9
17.0
17.5
22.1
24

5 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Amalia Himaya
2/2/2006 05:03:01 PM
CSO
Paper copy signed by Dr. Viswanathan on 2/2/06 and available upon request.

MEMORANDUM

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

DATE: August 29, 2005

TO: Associate Director
International Operations Drug Group
Division of Emergency and Investigational Operations
(HFC-130)

FROM: C.T. Viswanathan, Ph.D. CTV 9/6/05
Associate Director (Bioequivalence)
Division of Scientific Investigations (HFD-48)

SUBJECT: FY 2005, **High Priority CDER User Fee NDA,** Pre-approval Data Validation Inspection, Bioresearch Monitoring, Human Drugs, CP 7348.001

RE: NDA 21-809 and 21-810
DRUG: NovoLog Mix 30/70 and 50/50 (Insulin Aspart protamine suspension and soluble)
SPONSOR: Novo Nordisk Pharmaceuticals, Inc.

This memo requests that you arrange inspections of the clinical and analytical portions of the following bioequivalence study. **Due to user fee deadlines, the inspections must be completed by March 3, 2006.**

Study: **#BIAsp1086:** "A Randomized, Four Period Crossover Trial in Healthy Subjects Investigating the Pharmacodynamics and Pharmacokinetics of Biphasic Insulin Aspart 30, Biphasic Insulin Aspart 50, Biphasic Insulin Aspart 70 and Soluble Insulin Aspart"

Clinical Site: Profil GmbH Institut für Stoffwechselforschung
Stresemannallee 6
D-41460 Neuss, Germany
TEL: 011-49-2131-411
FAX: 011-49-2131-409

Clinical Investigator: Tim Heise, M.D.

Sponsor Contact: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
TEL: 609-987-5831
FAX: 609-987-3916

Background: NovoLog Mix 30/70, aka Biphasic Insulin Aspart 70, is a formulation of [Asp^{B28}]-insulin (IAsp), in which 70% of IAsp is soluble for relatively rapid release from the injection site, and 30% of IAsp is complexed with protamine in crystalline suspension for prolonger release. Other mixes are named similarly. The mixes are designed for biphasic release of the two fractions from the injection site.

The primary measures evaluated in this study were the pharmacodynamics of the glucose infusion rate (GIR) profile from the euglycemic clamp technique and the plasma pharmacokinetics of IAsp.

Please check the batch numbers of all test and the reference drug formulations used in the study with the descriptions in documents submitted to the Agency. Reserve samples of both the test and reference drug formulations should be collected and mailed to the Division of Drug Analysis, St. Louis, MO, for screening. (Note: Protect from freezing or temperatures above 30°C. Refrigerate if possible.)

Please have the records of all study subjects audited. The subject records in the NDA submissions should be compared to the original documents at the firm. In addition to the standard investigation involving the source documents, case report forms, adverse events, concomitant medications, number of evaluable subjects, drug accountability, etc., the files of communication between the clinical site and the sponsor should be examined for their content.

Please confirm the presence of 100% of the signed and dated consent forms, and comment on this informed consent check in your EIR.

Analytical Site: Novo Nordisk A/S
Symbion Science Park, Novo 3
Fruebjergvej 3
DK-2100 Copenhagen, Denmark
TEL: 011 45 39179981

Analytical Investigator: _____ b(4)

Instrumentation: IAsp-specific two-site ELISA

All pertinent items related to the analytical method should be examined and the sponsor's data should be audited. The analytical data in the NDA submissions should be compared with the original documents at the firm. The method validation and the actual assay

of plasma samples, as well as the variability between and within runs, Q.C., stability, the number of repeat assays of subject plasma samples, and the reason for such repetitions, if any, should be examined. The SOPs for the various procedures need to be scrutinized. In addition to the standard investigation involving source documents, the files of communication between the analytical site and the sponsor should be examined for their content.

Following identification of the investigator, background material will be forwarded directly. **A member of the Bioequivalence Team from the Division of Scientific Investigations staff may participate in the inspections.**

Headquarters Contact Person: Michael F. Skelly, Ph.D.
(301) 594-2043

cc:
HFA-224
HFD-45/RF
HFD-48/Skelly(2)/Himaya/CF
HFD-510/Rhee/NDA 21-809/NDA 21-810
HFD-870/Ahn/Wei
Draft: MFS 8/29/05
DSI:5646; O:\BE\assigns\bio21809.doc

FACTS

b(4)

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/s/

Julie Rhee
11/16/2005 11:01:25 AM
CSO

We have requested an international inspection because:

__X__ There is a lack of domestic data that solely supports approval;

_____ Other (please explain):

Goal Date for Completion:

We request that the inspections be conducted and the Inspection Summary Results be provided by March 3, 2006. We intend to issue an action letter on this application by March 31, 2006.

Should you require any additional information, please contact Julie Rhee at 301-827-6424.

Note: These 2 NDAs are cross-referenced. NDA 21-810 (NovoLog Mix 50/50) is the main submission, which stands alone. Most of information in NDA 21-809 (NovoLog Mix 30/70) is cross-referenced to NDA21-810.

Concurrence:
Jim Wei, Ph.D, Biopharm Reviewer
Hae-Young Ahn, Ph.D., Biopharm Team Leader

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/s/

David Orloff
8/22/2005 04:44:38 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-809
NDA 21-810

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your June 22, 2005, new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following products:

NDA 21-809	NovoLog Mix 30/70 (30% insulin aspart protamine suspension and 70% insulin aspart injection, [rDNA origin])
NDA 21-810	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

We have completed our filing review and have determined that your applications are sufficiently complete to permit a substantive review. Therefore, these applications will be filed under section 505(b) of the Act on August 21, 2005, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issue:

A total of four formulations were studied during the development program. Formulation 1 was used in a pivotal clinical trial, and Formulation 4 is the planned to-be-marketed formulation.

b(4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above request for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

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

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee
8/11/05 04:20:41 PM
Signed for Kati Johnson

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-809
21-810

Supplement #

Efficacy Supplement Type SE-

Trade Name: NovoLog Mix 30/70 (NDA 21-809) and NovoLog Mix 50/50 (NDA 21-810)
Established Name: 30% insulin aspart protamine suspension and 30% insulin aspart injection, [rDNA origin]
50% insulin asprt protamine suspension and 50% insulin aspart injection, [rDNA origin]
Strengths: 100 Units/mL (U-100)

Applicant: Novo Nordisk, Inc.
Agent for Applicant: N/A

Date of Application: June 22, 2005
Date of Receipt: June 22, 2005
Date clock started after UN: n/a
Date of Filing Meeting: August 3, 2005
Filing Date: August 21, 2005
Action Goal Date (optional): March 31, 2006 User Fee Goal Date: April 22, 2006

Indication(s) requested: Treatment of patients with diabetes mellitus for the control of hyperglycemia

Type of Original NDA: (b)(1) ☒ (b)(2) ☐
OR
Type of Supplement: (b)(1) ☐ (b)(2) ☐

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.

(2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

☐ NDA is a (b)(1) application OR ☐ NDA is a (b)(2) application

Therapeutic Classification: S ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 3
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES ☒ NO ☐

User Fee Status: Paid ☒ Exempt (orphan, government) ☐
Waived (e.g., small business, public health) ☐

NOTE: *If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient*

population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES ☐ NO ☒
  If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES ☐ NO ☒

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES ☐ NO ☐

  If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES ☐ NO ☒
  If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐

- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐

- Was form 356h included with an authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
  If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A ☒ YES ☐ NO ☐
  If an electronic NDA, all forms and certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? N/A ☒ YES ☐ NO ☐

- Is it an electronic CTD (eCTD)? N/A ☐ YES ☐ NO ☒
  If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

  Additional comments:

- Patent information submitted on form FDA 3542a? YES ☒ NO ☐

- Exclusivity requested? YES, _____ Years NO ☒
  NOTE: *An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*

- Correctly worded Debarment Certification included with authorized signature? YES ☒ NO ☐
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: *Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*

- Financial Disclosure forms included with authorized signature? YES ☒ NO ☐
  (Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
  NOTE: *Financial disclosure is required for bioequivalence studies that are the basis for approval.*

- Field Copy Certification (that it is a true copy of the CMC technical section)? Y ☒ NO ☐

- PDUFA and Action Goal dates correct in COMIS? YES ☒ NO ☐
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.

- List referenced IND numbers: _____ b(4)
  I 65,182 for NDA 21-810 (NovoLog Mix 50/50)

- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO ☒
  If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES ☒ NO ☐
  If no, request in 74-day letter.

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
  YES ☒ NO ☐

- Risk Management Plan consulted to ODS/IO? N/A ☒ YES ☐ NO ☐

- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y ☒ NO ☐

- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A ☐ YES ☒ NO ☐

- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
  N/A ☒ YES ☐ NO ☐

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A ☒ YES ☐ NO ☐

- Has DOTCDP been notified of the OTC switch application? N/A ☐ YES ☐ NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A X
  ☐ YES ☐ NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? ☒ YES ☐ NO
  If no, did applicant submit a complete environmental assessment? ☐ YES ☐ NO
  If EA submitted, consulted to Florian Zielinski (HFD-357)? ☐ YES ☐ NO
- Establishment Evaluation Request (EER) submitted to DMPQ? ☐ YES ☒ NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? ☒ YES ☐ NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 3, 2005

BACKGROUND:

Since NDAs 21-809 and 21-810 are cross-referenced, a combined filing check list is prepared.

NDA 21-810 NovoLog Mix 50/50 is the main submission which stands alone. Most of the information in NDA 21-809 is cross-referenced to NDA 21-810.

These NDAs are submitted as paper NDAs but followed Common Technical Document format.

These products are not available in vial presentation. They are going to be available in 3 mL PenFill cartridge and 3 mL FlexPen only.

ATTENDEES:

David Orloff, M.D., Director, DMEDP
Hae Young Ahn, Ph.D, Biopharm Team Leader
Jim Wei, Ph.D., Biopharm Reviewer
Todd Sahlroot, Ph.D., Statistical Team Leader
Steve Moore, Ph.D., Chemistry Team Leader
Xavier Ysern, Ph.D., Chemist
Janet Barletta, Ph.D., Micro Reviewer
Julie Rhee, Project Manager

ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer
Medical:	Joanna Zawadzki
Secondary Medical:	N/A
Statistical:	Lee Pian
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Xavier Ysern
Environmental Assessment (if needed):	
Biopharmaceutical:	Jim Wei
Microbiology, sterility:	Janet Barletta
Microbiology, clinical (for antimicrobial products only):	
DSI:	Vish
Regulatory Project Management:	Julie Rhee
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☒ NO ☐

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☒ NO ☐

ELECTRONIC SUBMISSION:

Draft labeling, CRTs (case report tabulations), and CRFs (case report forms) are submitted electronically.

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

☐ The application is unsuitable for filing. Explain why:

☒ The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.

- ☐ No filing issues have been identified.
- ☒ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1.☐ If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.

2.☐ If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.

3.☒ Convey document filing issues/no filing issues to applicant by Day 74.

- During the filing meeting, it was decided that stat review is not needed. However, if there're any statistical questions, Dr. Lee Pian would be the contact person.
- Draft review to team leader is due on March 1, 2006.
- Final review needs to be signed-off by team leader in DFS by March 15, 2006.
- Action goal date is March 31, 2006.
- Action package is due to the Division Director on March 24, 2006.

Julie Rhee
Regulatory Project Manager, HFD-

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/s/

Julie Rhee
8/5/05 02:16:59 PM
CSO

ATTACHMENT

MEMO OF FILING MEETING

DATE: August 3, 2005

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ASSIGNED REVIEWERS (including those not present at filing meeting) :

Discipline	Reviewer
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Secondary Medical:	N/A
Statistical:	Lee Pian
Pharmacology:	N/A
Statistical Pharmacology:	N/A
Chemistry:	Xavier Ysern
Environmental Assessment (if needed):	
Biopharmaceutical:	Jim Wei
Microbiology, sterility:	Janet Barletta
Microbiology, clinical (for antimicrobial products only):	
DSI:	Vish
Regulatory Project Management:	Julie Rhee
Other Consults:	

Per reviewers, are all parts in English or English translation? YES ☒ NO ☐
If no, explain:

CLINICAL FILE ☒ REFUSE TO FILE ☐

- Clinical site inspection needed? YES ☐ NO ☒
- Advisory Committee Meeting needed? YES, date if known _____ NO ☒
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? N/A ☒ YES ☐ NO ☐

CLINICAL MICROBIOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☒ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☒ REFUSE TO FILE ☐

- Biopharm. inspection needed? YES ☒ NO ☐

PHARMACOLOGY N/A ☒ FILE ☐ REFUSE TO FILE ☐

- GLP inspection needed? YES ☐ NO ☐

CHEMISTRY FILE ☒ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☒ NO ☐
- Microbiology YES ☒ NO ☐

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Julie Rhee
Regulatory Project Manager, HFD-

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/s/

Julie Rhee
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CSO

AC 6.27.05

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-810

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])
Review Priority Classification:	Standard (S)
Date of Application:	June 22, 2005
Date of Receipt:	June 22, 2005
Our Reference Number:	NDA 21-810

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on August 21, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 22, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

U.S. Postal Service/Courier/Overnight Mail:
Food and Drug Administration:
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room, 8B45
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-6424.

Sincerely,

{See appended electronic signature page}

Julie Rhee
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Julie Rhee
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