CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

CORRESPONDENCE

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: June 9, 2005

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Levemir carton/container label comments from DMEDP

Total no. of pages including cover: 3

Comments:

Document to be mailed: ☐ YES ☑ NO

NDA 21-536 Levemir (insulin detemir [rDNA origin] injection)

Date of submission: December 20, 2004

Comments on the carton/container labels (from DMEDP)

We have reviewed your submitted labeling for NDA 21-536 (submissions dated 5-DEC-2002, 20-DEC-2004, and 1-JUN, 2005) and have the following recommendations on the color branding on the cartons, vials, cartridges, and pens. These recommendations are designed to enhance label readability and product differentiation. Also, these recommendations are consistent with previously approved labeling for two of your other insulin products, namely, Novolog (NDA 20-986/S-019) and Novolog 70/30 (NDA 21-172/S-013) (see Agency's approval letter, dated 08-OCT-2004).

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/s/

Julie Rhee
6/9/05 11:38:31 AM

Rhee, H Julie

From: Rhee, H Julie

Sent: Tuesday, May 31, 2005 1:18 PM

To: 'ELTA@nnpi.com'

Subject: NDA 21-536 Insulin detemir labeling comments from DMETS

Hi Elizabeth,

Here're the labeling recommendations from DMETS. Please let me know when we could expect your response on carton/container labels.

Regards,
Julie

5/31/05

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: May 31, 2005

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Insulin detemir labeling comments (from DMETS)

Total no. of pages including cover: 7

Comments:

The attached is labeling recommendations from DMETS. Please let me know when you plan to submit your revised labeling. Thank you.

Document to be mailed: ☐ YES ☑ NO

2 Page(s) Withheld

____ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

I. Vial Carton Labeling (Trade and Sample)

J. Innolet Patient Information

1. How Should I take Levemir Section

   a. Revise the statement, "The effect of an injected insulin injected into your upper arm, abdomen...," to read, "...into your upper arm *or* abdomen (stomach area)..."

   b. Revise the statement, "Change (rotate) injection sites..." — — as well as injection sites within body areas.

2. Revise all references to hyperglycemia and hypoglycemia so that they are consistent [e.g. hypoglycemia (too low blood sugar) **or** — , but do not interchange both wordings] (e.g. page 3, "What are the possible side effects of Levemir," section).

3. Pages 7 through 11

   a. Currently, there is no name for this section. Label this section, "Levemir Innolet — for Use."

   b. Number the, "Preparing the Levemir Innolet," section as number 1, followed by "Setting the Dose," as number 2, "Giving the Injection," as number 3, and so on, in order to ensure that patients are informed that they need to prepare the Innolet before each injection.

   c. List instructions in a step-by-step format (e.g. "Preparing the Levemir Innolet" Section, letters a and b) rather than in paragraph form (e.g. letters c through e).

   For example: Levemir Innolet Instructions for Use

      1. Preparing the Levemir Innolet

         a. Pull off the cap
         b. Wipe the rubber membrane with an alcohol swab.
         c. Remove the protective tab from the disposable needle...

2. Setting the Dose

   d. Revise the labeling of the figures so that they correspond with the particular step in the instructions, (e.g. the figure currently labeled 1A, should be labeled 1C.) Additionally, place the figure so that it appears directly below the corresponding step of instruction.

   e. Revise any statements regarding to read "priming," so that is consistent with the information regarding the Innolet found on the NovoNordisk website. In addition, define "priming" in consumer-friendly terms on all labels and labeling.

K. Penfill Cartridge and Vial Patient Information

1. See comment J-1 and J-2.

2. How Should I Take Levemir Section

   The statement, : — ." does not appear in the package insert. If this statement is correct, include it in the package insert (see page 2).

3. Using the Levemir 3 mL PenFill cartridge Section See comment J-3-e.

4. After the first use of PenFill cartridge Section See comment J-3-e.

L. FlexPen Patient Information

See comments J-1, J-3-c, J-3-d, and J-3-e.

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/s/

Julie Rhee
5/31/05 01:07:12 PM

4/21/05

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 21, 2005

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: 21-536 Insulin detemir

Total no. of pages including cover: 3

Comments:

Attached is biopharm review comment on your January 24, 2005, submission.

Document to be mailed: ☐ YES ☑ NO

NDA 21-536 Insulin detemir

Date of submission: January 24, 2005

Biopharm review comments

The Agency recommends a bioequivalence study be conducted if the proposed excipient changes (replacing mannitol [redacted] in the commercial formulation takes place, where a euglycemic clamp study is preferred.

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/s/

Julie Rhee
4/21/05 02:36:26 PM

Rhee, H Julie

From: ELTA (Elizabeth Tan) [elta@novonordisk.com]
Sent: Friday, April 08, 2005 12:19 PM
To: Rhee, H Julie
Cc: brownj@cder.fda.gov
Subject: RE: NDA 21-536 Insulin detemir

Julie,

This message is to confirm that Novo Nordisk has opted to cancel the April 11 meeting. I left you a phone message at around 8:20 am this morning as I know you said you'd be out of the office today but can pick up phone messages from home.

We will be asking for clarifications regarding some of the FDA's comments or suggestions once we put together our questions next week.

Regards,
Elizabeth

-----Original Message-----
From: ELTA (Elizabeth Tan)
Sent: Thursday, April 07, 2005 11:21 AM
To: 'Rhee, H Julie'
Subject: RE: NDA 21-536 Insulin detemir

Julie,

I just left a phone message explaining that we'd like to give our answer, whether to cancel the meeting or not, tomorrow morning instead of today. Some of the team members in headquarters are off-site and are not able to look at the Agency's response today. I'll definitely get back to you tomorrow as early in the morning as possible.

Thanks again for providing the answers to our questions beforehand. It is very helpful.

Regards,
Elizabeth

-----Original Message-----
From: Rhee, H Julie [mailto:RHEEJ@cder.fda.gov]
Sent: Thursday, April 07, 2005 9:34 AM
To: ELTA (Elizabeth Tan)
Subject: NDA 21-536 Insulin detemir

Hi Elizabeth,

I am forwarding our internal minutes in preparation to the coming Monday (April 11) meeting.

If you do not have any other questions, you have an option to cancel the meeting. Please let me know.

Best Regards,
Julie

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/s/

Julie Rhee
4/18/05 02:13:16 PM

-----Original Message-----
From: Rhee, H Julie
Sent: Thursday, April 07, 2005 2:25 PM
To: Duffy, Eric P; Fraser, Blair; Moore, Stephen K; Brown, Janice
Subject: FW: NDA 21-536 Insulin detemir

fyi

-----Original Message-----
From: Rhee, H Julie
Sent: Thursday, April 07, 2005 9:34 AM
To: 'ELTA@nnpi.com'
Subject: NDA 21-536 Insulin detemir

Hi Elizabeth,

I am forwarding our internal minutes in preparation to the coming Monday (April 11) meeting.

If you do not have any other questions, you have an option to cancel the meeting. Please let me know.

Best Regards,
Julie

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 7, 2005

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Inc.	Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Insulin Detemir
Draft version of our internal meeting minutes

Total no. of pages including cover: 5

Comments:

You have the option of canceling the April 11, 2005, meeting (1:30-2:30 pm) if the following answers are clear to you. If you require further clarification, we will be prepared to clarify any questions you have regarding our response. However, be advised that any new information, data, or questions not contained in your March 10, 2005, meeting package and presented in response to these draft comments will not be considered for official comment at the scheduled tele-conference.

If the tele-conference is no longer necessary, please contact me as soon as possible so that the April 11, 2005, meeting can be cancelled.

Document to be mailed: ☐ YES ☑ NO

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4 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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/s/

Julie Rhee
6/10/05 03:53:22 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

2/4/05

Novo Nordisk Inc.
Attention: Bary Reit, Ph.D.
Vice President
Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin detemir (rDNA origin) injection.

We also refer to your January 21, 2005, correspondence, received January 24, 2005, requesting a meeting to discuss the comparability protocol for a newly constructed purification facility for insulin detemir drug substance.

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: April 11, 2005
Time: 1:30 – 2:30
Location: Parklawn Building 3rd floor conference room "B"
CDER participants (Tentative):
Eric Duffy, Ph.D., Director, Division of New Drug Chemistry II
Blair Fraser, Ph.D., Deputy Director, Division of New Drug Chemistry II
Stephen Moore, Ph.D., Chemistry Team Leader, DMEDP
Janice Brown, Chemist, DMEDP
Julie Rhee, Regulatory Project Manager, DMEDP

Please have all attendees bring photo identification and allow 15 to 30 minutes to complete security clearance. Please email me the name and title of your attendees at rheej@cder.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 at 827-6424; Kyle Boyd at 827-6432.

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. If the materials presented in the information package are inadequate to justify holding a meeting, or if we do not receive the package by March 11, 2005, we may cancel or reschedule the meeting.

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
2/4/05 02:37:31 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

1/12/05

Novo Nordisk Inc.
Attention: Barry Reit, M.D.
Vice President, Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

We acknowledge receipt on December 20, 2004, of your December 20, 2004, resubmission to your new drug application for Insulin detemir (rDNA origin) injection.

We consider this a complete, class 2 response to our October 2, 2003, action letter. Therefore, the user fee goal date is June 20, 2005.

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 submitted pediatric studies under NDA 21-878. Once the review of NDA 21-878 is complete, we will notify you whether you have fulfilled the pediatric study requirement for this application.

If you have any question, call Julie Rhee 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
1/12/05 02:08:20 PM

9/30/04

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: September 30, 2004

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals	Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 insulin detemir

Total no. of pages including cover: 3

Comments:

Clinical review comments on your June 22, 2004, submission.

Document to be mailed: ☐ YES ☑ NO

NDA 21-536 Insulin detemir

Date of submission: June 22, 2004

Clinical review comments

When the NDA is resubmitted, the revised label should make the following information clear:

1. In patients with type 2 diabetes, somewhat more insulin detemir is required relative to NPH than in patients with type 1 diabetes.

2. A "unit" of insulin detemir has one fourth the potency of an "international unit" of NPH.

3. Additional information about dosing recommendations for different ethnic groups should be revised when the trial 1439, which is currently ongoing, is completed.

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/s/

Julie Rhee
9/30/04 01:16:27 PM

8/20/04

Rhee, H Julie

From: Rhee, H Julie

Sent: Friday, August 20, 2004 10:47 AM

To: 'ELTA (Elizabeth Tan)'

Subject: FW: Questions on NDA Resubmission (NDA 21-536, Insulin Detemir)

Dear Elizabeth,

I am forwarding our response to your questions. Please let me know if you need any further clarification.

Best regards,
Julie

-----Original Message-----
From: ELTA (Elizabeth Tan) [mailto:elta@nnpi.com]
Sent: Friday, August 13, 2004 5:10 PM
To: Rhee, H Julie
Subject: Questions on NDA Resubmission (NDA 21-536, Insulin Detemir)
Importance: High

Hi Julie,

I left you a phone message yesterday and tried calling several times today. It appears definite now that we are going to be submitting our full response to the NDA approvable letter in December 2004 (week of December 20). In preparation for the resubmission, I wanted to ask for guidance regarding formatting and labeling. You will notice a number of our questions is due to the CTD format and the need to clarify your expectations. A prompt response would be much appreciated. It would be a tremendous help in guiding us on how to execute everything that needs to be done.

QUESTIONS

1) We plan to submit another safety update since the 120-Day update was in April 2003. Given this fact, would we still need to provide an updated Clinical Safety section (Module 2, Section 2.7.4)? We believe it's not necessary but wanted to check that the Agency is in agreement.

This is a content question. It would seem that you would be required to update 2.7.4 if your update changes what would be in 2.7.4. If it didn't, then you wouldn't have to.

2) We are submitting Phase 1 and Phase 3B clinical reports therefore we plan to amend the Module 2 sections of Clinical Pharmacology (2.7.2) and Clinical Efficacy (2.7.3). Instead of trying to insert the new information into the pertinent sections of the original NDA submission (December 5, 2002), we are opting to provide the Agency with new documents which contain only the new information instead. It would be along the line of how clinical protocol amendments are submitted. Do you agree to this proposal?

Again, this is a content issue. We do not require data previously submitted to be resubmitted.

3) Do you require us to update the Clinical Overview section (Module 2, Section 2.5)?

I would say yes if new information in the resubmission changed what should be in the clinical overview.

4) Since we are also addressing Quality questions in the NDA resubmission, are we required to update

the Quality Overall Summary (Module 2, Section 2.3)?

Again, I would say yes if new information in the resubmission changed what should be in the quality overall summary.

5) We plan to provide udpated Annotated Labeling Text in our pending submission. In the original NDA, the annotations included information on the module and volume where clinical reports, from which information were sourced, reside in the CTD. If we were to follow the same practice in the updated annotated label, this would cause confusion. Module 5 for the NDA resubmission is not the same Module 5 for the original NDA. This fact, however, would not be apparent in the annotations of the physician insert. One option we could think of is to identify information from clinical studies newly being submitted to the NDA by using a different code for the new Module 5. As example, the old studies would have "M5 [study #]/ Volume #: Page #" whereas the new studies would have something like "ResubM5 [study #]/ Volume #: Page #". Is this acceptable?

This seems acceptable.

6) The Agency is planning to issue a final rule on revised drug labeling format. Since our NDA resubmission is in December 2004, it would have an action date of mid-2005. Most likely, the final labeling format rule would have been issued at that time. Do you expect us to submit our updated labels (Physician and Patient Inserts) in the new format when we do our submission in December? If not, what happens if the final rule comes out during the review period of the NDA resubmission? Would we be expected to update our labels before labeling negotiations begin? If not, would we be expected to update the labels after NDA approval?

I do not know when the final rule will publish, but based on the proposed implementation schedule, if the application is pending when the rule becomes final, you would not have to revise labeling during the review cycle.

Regards,
Elizabeth

Elizabeth L. Tan, Ph.D.
Assistant Director
Regulatory Affairs & Quality Assurance

Novo Nordisk Pharmaceuticals, Inc.
100 College Road, West
Princeton, New Jersey 08540
USA
(609) 987-5940 (direct)
elta@novonordisk.com

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/s/

Julie Rhee
8/20/04 10:51:24 AM
CSO

Rhee, H Julie 8/20/04

From: Rhee, H Julie
Sent: Friday, August 20, 2004 2:53 PM
To: 'ELTA (Elizabeth Tan)'
Subject: NDA 21-536 Insulin detemir (6/22/04 submission)

Dear Elizabeth,

I have the following clinical review comment on your June 22, 2004, submission for NDA 21-536:

"Trial 1350 appears to establish that Detemir and NPH, each given twice daily, are equally effective in controlling type 2 diabetes."

Best regards,
Julie

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/s/

Julie Rhee
8/20/04 02:58:51 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

6/4/04

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for — (insulin detemir [rDNA origin] injection).

We also refer to your May 21, 2004, correspondence, received May 24, 2004, requesting a meeting to discuss the adequacy of Trial 1530 to establish non-inferiority of insulin detemir to NPH in patients with type 2 diabetes. We have considered your request and concluded that the meeting is unnecessary at this time. Please submit your intended meeting background material with your specific question(s) for our review, and we will respond in writing.

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

Sincerely,

{See appended electronic signature page}

David G. Orloff, M.D.
Director
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/

David Orloff
6/4/04 04:57:11 PM

Rhee, H Julie

From: Rhee, H Julie
Sent: Wednesday, December 17, 2003 12:57 PM
To: 'Tan, Elizabeth (ELTA)'
Subject: RE: Additional Questions for Race/Ethnicity Study (NDA 21-536, Insulin detemir)

HI Elizabeth,

Here's our response to your additional questions.

Have a very happy holiday season.

Julie

-----Original Message-----
From: Tan, Elizabeth (ELTA) [mailto:ELTA@nnpi.com]
Sent: Tuesday, December 16, 2003 3:00 PM
To: Rhee, H Julie
Subject: Additional Questions for Race/Ethnicity Study (NDA 21-536, Insulin detemir)

Julie,

Thank you for providing clarification regarding the e-mail on the required PK/PD study to investigate effect of race/ethnicity in patients on insulin detemir.

Novo Nordisk is in the process of planning the said study. As of this morning, two questions came up for which we need early FDA input because we are trying to finalize the protocol very soon.

(1) In preliminary discussions, the clinical investigators (California) for the clamp study are now suggesting that it may be easier to recruit Type 2 patients, especially for African Americans and Latinos. If it does turn out that our pre-approval clamp study is run in Type 2 patients, is it correct to assume that we will not be required to run a PK/PD study for race/ethnicity in Type 1 patients at all?

FDA's response: If no differences are found in patients with Type 2 diabetes, PK/PD study is not required for patients with Type 1 diabetes. However, if there is a difference, we may still want data in patients with Type 1 diabetes.

(2) At our December 9 meeting, we gave our commitment to address race/ethnicity in future Phase 3B/4 studies but did not discuss use of sites outside the US, e.g. sites in Mexico. Would you consider that Novo Nordisk would be meeting its commitment with race/ethnicity if a clinical trial were run in Mexico?

FDA's response: Studies done in Mexico could provide answers related to certain Hispanics, but would not address African Americans.

Thank you in advance,
Elizabeth

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/s/

Julie Rhee
12/19/03 01:51:07 PM

Rhee, H Julie

From: Rhee, H Julie

Sent: Tuesday, December 16, 2003 12:12 PM

To: 'Tan, Elizabeth (ELTA)'

Subject: RE: Titles of Novo Nordisk Participants at NDA 21-536 Meeting on December 9

Hi Elizabeth,

Thanks for the information.

Here's our clarification on your question:

"If the OAD study in DM2 shows non-inferior efficacy of detemir relative to marketed comparator and the clamp study in DM1 suggests no effect of race on PK/PD, then we feel there will be sufficient information to label the drug for safe and effective use in DM! and DM2. A clamp study in DM2 analogous to that in DM1 would therefore be acceptable in phase 4."

Hope this answers your question.

Thanks,

Julie

p.s. I think I said our additional comments on Q2 when I sent you the e-mail on Dec 10 but I should have said additional comments for Q3. Hope it didn't cause too much confusion.

-----Original Message-----
From: Tan, Elizabeth (ELTA) [mailto:ELTA@nnpi.com]
Sent: Tuesday, December 16, 2003 9:53 AM
To: Rhee, H Julie
Subject: Titles of Novo Nordisk Participants at NDA 21-536 Meeting on December 9

Hi Julie,

As promised, here are the remaining names with the titles that you requested.

Peter Bonne Eriksen - M.Sc.
Hanne Henriksen - M.Sc.
Silvia Garcia Codony - M.Sc.

Regards,
Elizabeth
P.S. I look forward to hearing the clarification on our PK/PD study (race/ethnicity) today.

Rhee, H Julie

From: Tan, Elizabeth (ELTA) [ELTA@nnpi.com]
Sent: Friday, December 12, 2003 6:24 PM
To: Rhee, H Julie
Subject: RE: NDA 21-536 Insulin detemir 12/9/03 meeting

Julie,

Thank you for the quick reply. Can I just clarify which study you are referrring to in the last sentence, "Therefore we advise that this study be implemented ASAP".

(1) Are you referring to the DM1 or the DM2 study? I'm interpreting it to be DM1.
(2) If you are referring to DM2, are you saying that if results with DM1 are inconclusive, you expect results from DM2 to still be part of our complete response to the approvable letter? If yes, please define what you'd consider inconclusive.

Thanks,
Elizabeth

-----Original Message-----
From: Rhee, H Julie [mailto:RHEEJ@cder.fda.gov]
Sent: Wednesday, December 10, 2003 1:27 PM
To: Tan, Elizabeth (ELTA)
Subject: NDA 21-536 Insulin detemir 12/9/03 meeting

Hi Elizabeth,

I am forwarding yesterday's meeting attendee's list as well as the following additional comments to Q2:

"A submission of the results of (1) a clamp study in DM1 patients to explore racial/ethnic differences in pharmacodynamic response to NPH and detemir and (2) study 1530 will be considered a complete response to the clinical deficiencies in the October 2, 2003, AE letter. However, the conduct and submission of an analogous clamp study in DM2 will ultimately be required, whether prior to or after approval (depending upon findings on review of the other data). Therefore, we advise that this study be implemented ASAP."

Thanks,

Julie

Encrypted message from "Rhee, H Julie" <RHEEJ@cder.fda.gov> was successfully received by NNPI.COM.

Rhee, H Julie

From: Rhee, H Julie

Sent: Wednesday, December 10, 2003 1:27 PM

To: 'Tan, Elizabeth (ELTA)'

Subject: NDA 21-536 Insulin detemir 12/9/03 meeting

Hi Elizabeth,

I am forwarding yesterday's meeting attendee's list as well as the following additional comments to Q2:

"A submission of the results of (1) a clamp study in DM1 patients to explore racial/ethnic differences in pharmacodynamic response to NPH and detemir and (2) study 1530 will be considered a complete response to the clinical deficiencies in the October 2, 2003, AE letter. However, the conduct and submission of an analogous clamp study in DM2 will ultimately be required, whether prior to or after approval (depending upon findings on review of the other data). Therefore, we advise that this study be implemented ASAP."

Thanks,

Julie

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: July 30, 2003

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Insulin detemir

Total no. of pages including cover: 2

Comments:

Please provide the additional information requested by a Biopharm reviewer. Please let me know when I could expect the submission. Thank you.

Document to be mailed: ☐ YES ☑ NO

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

NDA 21-536 Insulin detemir

Date of submission: December 5, 2002

Request from Biopharm

Please provide the supporting evidences (either your own studies or publications) for the following statement in the NDA (page 24 of 100, Summary of Clinical Pharmacology):

"Despite the limited number of subjects in Trial 1223, the results are consistent with the previously published findings. The rate of absorption of human soluble insulin has been shown to be slower for subjects with type 2 diabetes compared with subjects with type 1 diabetes.[7] One explanation for delayed absorption in subjects with type 2 diabetes may be related to a higher total dose due to greater body weight."

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/s/

Julie Rhee
7/30/03 01:36:34 PM
CSO

Rhee, H Julie

From: Wei, Xiaoxiong

Sent: Tuesday, July 29, 2003 3:26 PM

To: Rhee, H Julie

Subject: question for insulin detemir

Hi Julie,

We would like to ask the sponsor to provide the supporting evidences (their own studies or publications) for their statements.

In the Study 1223, absorption of insulin detemir and NPH in subjects with type 2 diabetes is slower than subjects with type 1 diabetes. The sponsor indicates that their current study results are consistent with the literature that the rate of absorption of human soluble insulin has been shown to be slower for subjects with type 2 diabetes compared with patients with type I diabetes. Please provide these publications or the study reports.

Thanks!

Jim

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/s/

Julie Rhee
7/30/03 03:14:52 PM
CSO

Rhee, H Julie

From: Misbin, Robert I
Sent: Wednesday, April 02, 2003 11:33 AM
To: Rhee, H Julie
Cc: Orloff, David G
Subject: Detemir

Julie

I have the following questions for NovoNordisk regarding the Detemir NDA. Please foreword these to them.

1 In trial 1221, are the insulin and Detemir levels free or bound with respect to endogenous antibodies? Please provide background therapy for patients with type 2 diabetes and a time course of the mean change in C peptide. What is the basis of the Detemir assay?Please provide evidence that what is being measured is biologically active?

2 Trial 1337 - Please provide mean metformin doses at initial visit, baseline and endpoint. Please provide mean FPG and HbA1c at initial visit and baseline.

3 Please provide methodology for the antibody measurements. What is meant by cross-reacting antibodies?

thanks

bob

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/s/

Julie Rhee
4/2/03 02:40:54 PM
CSO

Rhee, H Julie

From: Wei, Xiaoxiong
Sent: Wednesday, March 26, 2003 8:48 AM
To: Rhee, H Julie
Subject: more info needed for analytical assay for detemir

Hi, Julie:

Would you please forward these questions to the sponsor. I need more information about monoclonal antibodies recognizing the acylation site of insulin detemir.

1) What is the composition of recognition site in insulin detemir by monoclonal antibodies? In other words, where does the binding site of detemir exactly locate?

2) Is the fatty acid chain a required component for the recognition by the monoclonal antibody?

3) Does the monoclonal antibody recognize the insulin detemir molecules without fatty acid chain? Does the monoclonal antibody recognize fatty acid alone?

4) Does the monoclonal antibody recognize regular insulin (cross-reaction) ?

Thanks,

Jim

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/s/

Julie Rhee
4/2/03 02:11:02 PM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

12/19/03

Novo Nordisk Pharmaceuticals Inc.
Attention: Barry Reit, Ph.D.
Vice Presidnent
Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540-7810

Dear Dr. Reit:

Please refer to the meeting between representatives of your firm and FDA on December 9, 2003. The purpose of the meeting was to discuss issues in the October 2, 2003, approvable letter.

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, 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

Enclosure: December 9, 2003, meeting minutes

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 22, 2003

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Insulin detemir

Total no. of pages including cover: 2

Comments:

Additional request from Biopharm.

Document to be mailed: ☐ YES ☑ NO

NDA 21-536 Insulin detemir

Date of submission: December 5, 2002

Additional request from Biopharm

Please let us know where in the submission the following information can be found:

1. Have you determined if insulin antibodies in patients with previous exposure would interfere with ELISA method?

2. Have you precipitated insulin antibodies before assay?

3. Have you compared ELISA assay between naïve patients and treated patients?

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

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/s/

Julie Rhee
4/22/03 05:37:33 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 2, 2003

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424
Subject: NDA 21-536 insulin detemir	
Total no. of pages including cover: 2	

Comments:

Attached is CDRH review comments. Please let me know when we could expect your response.

Thank you.

Document to be mailed: ☐ YES ☑ NO

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

NDA 21-536 Insulin detemir

Date of submission: December 5, 2002

Review comments from CDRH

1. A statement, comparable to that required in a device premarket notification, indicating how the FlexPen is similar to and/or different from the NovoPen3/NovoPen Junior. This statement should compare the design, features, operating mechanism, and final assembly procedures between the FlexPen and the NovoPen 3/ NovoPen Junior. Where appropriate, the statement should be supported by data. A similar statement should be provided for the InnoLet and the Innovo which are different devices from the FlexPen and the NovoPen 3/NovoPen Junior.

2. A discussion about what modifications to the dose setting mechanism of the FlexPen and InnoLet to administer insulin detemir by volumes rather than in units. This discussion should include an evaluation of the effects of these modifications on device performance and dose accuracy testing.

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

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/s/

Julie Rhee
4/3/03 02:14:25 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: April 2, 2003

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 insulin detemir

Total no. of pages including cover: 2

Comments:

Additional clinical information request. Please let me know when we could expect your response.

Thank you.

Document to be mailed: ☐ YES ☑ NO

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

NDA 21-536 Insulin detemir

Date of submission: December 5, 2002

Additional clinical information request

1. In trial 1221, are the insulin and Detemir levels free or bound with respect to endogenous antibodies? Please provide background therapy for patients with type 2 diabetes and a time course of the mean change in C peptide. What is the basis of the Detemir assay? Please provide evidence that what is being measured is biologically active?

2. Trial 1337 - Please provide mean metformin doses at initial visit, baseline and endpoint. Please provide mean FPG and HbA1c at initial visit and baseline.

3. Please provide methodology for the antibody measurements. What is meant by cross-reacting antibodies?

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

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/s/

Julie Rhee
4/2/03 03:15:09 PM
CSO

Rhee, H Julie

From: Rhee, H Julie
Sent: Wednesday, April 02, 2003 3:27 PM
To: 'elta@nnpi.com'
Subject: 4/2/03 fax clarification

Hi Elizabeth,

I just faxed you an additional information request for clinical and wanted to clarify item #2. Please add the following statement after
item #2: "These data should be prepared by subset-metformin alone, metformin plus TZD, and metformin combo without TZD."

Thanks,

Julie

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/s/

Julie Rhee
4/2/03 03:23:55 PM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE II

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2003

To: Elizabeth Tan, Ph.D.	**From:** Julie Rhee
Company: Novo Nordisk Pharmaceuticals Inc.	Division of Division of Metabolic and Endocrine Drug Products
Fax number: (609) 987-3916	**Fax number:** (301) 443-9282
Phone number: (609) 987-5940	**Phone number:** (301) 827-6424

Subject: NDA 21-536 Insulin detemir

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES ☑ NO

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

NDA 21-536 Insulin detemir

Date of submission: December 5, 2002

Additional Information Request from Biopharm

Please provide additional information on the following questions concerning monoclonal antibodies recognizing the acylation site of insulin detemir:

1. What is the composition of recognition site in insulin detemir by monoclonal antibodies? In other words, where does the binding site of detemir exactly locate?

2. Is the fatty acid chain a required component for the recognition by the monoclonal antibody?

3. Does the monoclonal antibody recognize the insulin detemir molecules without fatty acid chain? Does the monoclonal antibody recognize fatty acid alone?

4. Does the monoclonal antibody recognize regular insulin (cross-reaction)?

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/s/

Julie Rhee
3/26/03 11:52:15 AM
CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW ISSUES IDENTIFIED

NDA 21-536

2/3/03

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs & Quality Assurance
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

Please refer to your December 5, 2002, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for insulin detemir (rDNA origin) injection.

We also refer to your submissions dated January 15 and 24, 2003.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is filed under section 505(b) of the Act on February 3, 2003, in accordance with 21 CFR 314.101(a).

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

1. The efficacy results in Type 1 patients are potentially confounded by the increased use of bolus doses of insulin in insulin detemir treated patients compared to the control (NPH). The Division's concern is the purported demonstration of non-inferiority for insulin detemir may be the result of bias induced by a mean 6 to 18% relative increase in bolus insulin. This issue will be reviewed thoroughly from both clinical and statistical perspectives.

2. The Type 2 efficacy results are, on face, not encouraging. Only one of the three trials demonstrated non-inferiority of insulin detemir to NPH. The efficacy for the single positive trial is potentially confounded by a mean 12% greater use of bolus doses of insulin in the insulin detemir treatment group compared to NPH.

3. Exposure of black patients to insulin detemir is small, only about 1% of the total patient population.

4. You have requested a categorical exclusion from submitting an environmental assessment for the drug product, insulin detemir. However, your request did not include a statement, as required under 21 CFR 25.15(d), "that to the applicant's knowledge, no extraordinary circumstances exist." Please submit the statement.

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.

We do not expect a response to this letter, and we may not review any such response during the current review cycle. However, we request that you submit the following information to the electronic document room:

i. Individual and summary human pharmacokinetic data, and
ii. Individual human pharmacokinetic study synopsis.

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/

Kati Johnson
2/3/03 03:24:55 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-536

12/11/02

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. Reit:

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:	Levemir™ (insulin detemir [rDNA origin] injection)
Review Priority Classification:	Standard (S)
Date of Application:	December 5, 2002
Date of Receipt:	December 5, 2002
Our Reference Number:	NDA 21-536

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 February 3, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 5, 2003.

Under 21 CFR 314.102(c), you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

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: Fishers Document Room, 8B-45
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
12/11/02 02:04:11 PM