

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-172**

**CORRESPONDENCE**

**REQUEST FOR CONSULTATION**

*Sharon 1/7/00*

Division/Office: Peter Cooney, Ph.D., HFD-160

FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee

DATE: January 7, 2000

IND NO.:

NDA NO.: 21-172

TYPE OF DOCUMENT :  
New NDA

DATE OF DOCUMENT:  
January 4, 2000

NAME OF DRUG:  
Biphasic Insulin Aspart 30

PRIORITY CONSIDERATION:

CLASSIFICATION OF DRUG:

DESIRED COMPLETION DATE:  
July 30, 2000

NAME OF FIRM: Novo Nordisk

**REASON FOR REQUEST**

**I. GENERAL**

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

**II. BIOMETRICS**

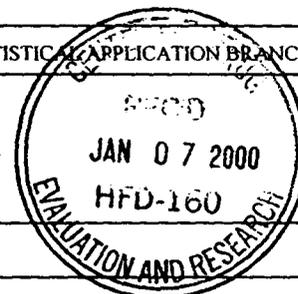
STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- TYPE A OR B NDA REVIEW  
 END OF PHASE II MEETING  
 CONTROLLED STUDIES  
 PROTOCOL REVIEW  
 OTHER:

*P. Stinauge  
1/10/00*

- CHEMISTRY REVIEW  
 PHARMACOLOGY  
 BIOPHARMACEUTICS  
 OTHER:



**III. BIOPHARMACEUTICS**

- DISSOLUTION  
 BIOAVAILABILITY STUDIES  
 PHASE IV STUDIES

*IS!*

- DEFICIENCY LETTER RESPONSE  
 PROTOCOL-BIOPHARMACEUTICS  
 IN-VIVO WAIVER REQUEST

**IV. DRUG EXPERIENCE**

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

**V. SCIENTIFIC INVESTIGATIONS**

CLINICAL

PRECLINICAL

**COMMENTS/SPECIAL INSTRUCTIONS:**

Peter, I am forwarding volumes M2.1 thru M2.4 of this new NDA 21-172 from Novo for Micro review. Could you please let me know who is going to review it? A filing meeting is scheduled on Jan 24 at 9 am in our c/r (14-56). When the review is completed, please return it to my attention. Thank you.

cc: Original NDA 21-172  
HFD-510/Div. Files

SIGNATURE OF REQUESTER:

*/S/*

*1-7-00*

METHOD OF DELIVERY (Check one):

MAIL

HAND

SIGNATURE OF RECEIVER:

SIGNATURE OF DELIVERER:

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>Date:</b> September 14, 2001
<p>Dr. Elizabeth Koller and I called Dr. Tan and asked for narratives for allergic type of reactions associated with the use of NovoLog Mix 70/30 or human insulin mix 70/30 in Studies 038 and 067.</p> <p style="text-align: center;"><b>APPEARS THIS WAY ON ORIGINAL</b></p> <p>----- <b>Name: Julie Rhee</b></p>	<p><b>NDA#: 21-172</b></p> <p><b>Telecon/Meeting initiated by:</b></p> <p style="padding-left: 40px;">FDA</p> <p><b>By: Telephone</b></p> <p><b>Product Name:</b> NovoLog Mix 70/30</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Elizabeth Tan, Ph.D. Regulatory Affairs</p> <p><b>Phone:</b> (609) 987-5940</p>

**APPEARS THIS WAY  
ON ORIGINAL**

---

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Julie Rhee

9/14/01 04:19:42 PM

CSO

**APPEARS THIS WAY  
ON ORIGINAL**



drug product. However, the sponsor has submitted their proposed name \_\_\_\_\_  
70/30" for the 3<sup>rd</sup> time. Again, we recommended "NovoLog Mix 70/30" as a trade name.  
Dr. Reit agreed to submit a new proposed tradename.



---

Julie Rhee  
Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/  
-----

Julie Rhee  
8/29/01 04:56:54 PM  
CSO

**APPEARS THIS WAY  
ON ORIGINAL**

<p><b>RECORD OF TELEPHONE CONVERSATION/MEETING</b></p>	<p><b>Date:</b> July 30, 2001</p>
<p>Re: 2/9/01 submission</p> <p>Background: The sponsor requested that the Agency re-evaluate their proposed tradename _____. The 2/9/01 submission was forwarded to OPDRA for a consult. On 7/27/01, OPDRA recommended that _____, 70/30" as a tradename. However, the DMEDP over-ruled the OPDRA's decision and recommended "NovoLog Mix 70/30".</p> <p style="text-align: center;">*****</p> <p>I called Dr. McElligott and conveyed the DMEDP's decision on the proposed tradename of "NovoLog Mix 70/30". She wanted to know why _____ was rejected by OPDRA. I stated that it is because _____ does not correctly reflect the ratio of "70/30".</p> <p>I asked Novo to submit their response asap. Dr. McElligott asked what would happen if they do not agree with our recommendation. I told her that if the name is not decided before the action date, then the action will have to be approvable at best because of labeling. She said she would discuss internally and will get back to me.</p> <p style="text-align: center;"><b>APPEARS THIS WAY ON ORIGINAL</b></p> <p>----- <b>Name: Julie Rhee</b></p>	<p><b>NDA#: 21-172</b></p> <p><b>Telecon/Meeting initiated by:</b></p> <p><input type="radio"/> FDA</p> <p><b>By: Telephone</b></p> <p><b>Product Name:</b> NovoLog Mix 70/30</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Mary Ann McElligott, Ph.D. Director Regulatory Affairs</p> <p><b>Phone:</b> (609) 987-5831</p>

---

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Julie Rhee

7/30/01 06:00:20 PM

CSO

**APPEARS THIS WAY  
ON ORIGINAL**

Note to the file

NDA 21-172  70/30 (insulin aspart 30)

Date: August 8, 2000

\*\*\*\*\*

After an industry meeting with Novo Nordisk for their other application, I informed Mr. Timothy Urschel, Director, Regulatory Affairs, that their proposed tradename of  70/30 is not acceptable since  is not the parent drug. The parent drug for  is NovoLog.

I also informed Mr. Urschel to take a look at Humalog mixture's nomenclature and asked him to come up with a new proposed tradename, e.g., NovoLog Mix 70/30. Mr. Urschel agreed to do so.

**APPEARS THIS WAY  
ON ORIGINAL**

---

Julie Rhee

cc:OrigNDA  
HFD-510DivFile

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

-----  
Julie Rhee  
2/13/01 06:37:28 PM  
CSO

**APPEARS THIS WAY  
ON ORIGINAL**

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>Date:</b> May 9, 2001
<p>I called Dr. McElligott and informed her that we will consider their 4/30/01 submission as a complete response to our 11/15/00 AE letter.</p> <p>I informed her that we will issue an acknowledgement letter.</p> <p style="text-align: center;"><b>APPEARS THIS WAY ON ORIGINAL</b></p> <p>----- <b>Name: Julie Rhee</b></p>	<p><b>NDA#:</b> 21-172</p> <p><b>Telecon/Meeting initiated by:</b></p> <p><input type="radio"/> FDA</p> <p><b>By:</b> Telephone</p> <p><b>Product Name:</b> NovoLog Mix 70/30</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Mary Ann McElligott, Ph.D. Director, Regulatory Affairs..</p> <p><b>Phone:</b> (609) 987-5831</p>

**APPEARS THIS WAY  
ON ORIGINAL**

---

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Julie Rhee  
5/9/01 06:36:28 PM  
CSO

APPEARS THIS WAY  
ON ORIGINAL



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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE:** April 25, 2001

<b>To:</b> Mary Ann McElligott	<b>From:</b> Julie Rhee
<b>Company:</b> Novo Nordisk Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
<b>Fax number:</b> (609) 987-3916	<b>Fax number:</b> (301) 443-9282
<b>Phone number:</b> (609) 987-5831	<b>Phone number:</b> (301) 827-6424
<b>Subject:</b> NDA 21-172 March 7, 2001, t-con minutes	

---

**Total no. of pages including cover:** 2

---

**Comments:**

---

---

**Document to be mailed:**       YES       NO

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.

APPEARS THIS WAY  
ON ORIGINAL

**MEMORANDUM OF TELECON**

DATE: March 7, 2001

APPLICATION NUMBER: NDA 21-172, NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)

BETWEEN:

Name:

Novo Nordisk, Princeton, NJ:

Michael Barbush, Assistant Director, Regulatory Affairs  
Won-Chin Huang, Director, Biostatistics  
Mary Ann McElligott, Senior Director, Regulatory Affairs  
Barry Reit, Vice President, Regulatory Affairs  
Olga Santiago, Medical Director  
John Whisnant, Vice President, Drug Development

Novo Nordisk, Denmark:

Dorrit Espersen, Regulatory Project Manager  
Alice Brinch Hansen, Clinical Positioning  
Hanne Henriksen, Regulatory Project Manager  
Anders Lindholm, International Clinical Project Manager  
Ulla Oddershede, Project Vice President  
Renee de Habanera y Palacios, Statistician  
Mark White, Medical Writer

Phone: (609) 987-5831  
Representing: Novo Nordisk Pharmaceuticals, Inc.

AND

Division of Metabolic and Endocrine Drug Products, HFD-510:  
Julie Rhee, Regulatory Project Manager  
Saul Malozowski, M.D., Medical Team Leader  
Elizabeth Koller, M.D., Medical Officer

SUBJECT: February 9, 2001, resubmission

BACKGROUND: The Agency had issued an approvable letter to the sponsor on November 15, 2000. A copy of the letter is attached to this t-con minutes. The sponsor responded to the action letter on February 9, 2001. However, the 2/9/01 submission lacked antibody data and, therefore, it could not be considered as a major amendment to re-start the review clock.

The Agency requested a tele-con to inform the sponsor that the Agency does not consider their 2/9/01 re-submission as a complete response and, therefore, the review clock would not be re-started until we receive the complete raw data including serial HgbA1c , insulin doses, and cross-reacting antibodies from their two-year study. The Agency requested that these data to be provided as Excel spreadsheet.

The sponsor agreed that the two-year study had not been completed when they made the submission on 2/9/01 but the study is now completed and they are in the process of validating the study. The sponsor agreed to submit the complete dataset on the study as Excel spreadsheet.

The sponsor also acknowledged that they understood the review clock would not be re-started until the Agency receive the complete and satisfactory dataset on the antibody .

---

Julie Rhee  
Regulatory Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

/s/

-----  
Julie Rhee

4/26/01 08:49:53 AM

CSO

APPEARS THIS WAY  
ON ORIGINAL

<p><b>RECORD OF TELEPHONE CONVERSATION/MEETING</b></p>	<p><b>Date:</b> April 25, 2001</p>
<p>Re: 4/10/01 submission</p> <p>I called Dr. McElligott and conveyed the following requests for additional information from Dr. Koller on their 4/10/01 submission:</p> <ol style="list-style-type: none"> <li>1. Identify each patient in Study 038D as either IDDM or NIDDM patient.</li> <li>2. Only 204 patients continued with the extension study, but we need all information from all 291 patients who were originally enrolled in the study.</li> <li>3. Clarify the matching number of weeks for visit #1, #2, etc. For example, visit #1 is occurred 2 weeks after the treatment and visit #2 is 4 weeks after the treatment, etc.</li> </ol> <p>Dr. McElligott stated that the above requests are different from the information requested during our March 7, 2001, telecon with them and asked to fax her a copy of the 3/7/01 telecon minutes. I agreed to do so and faxed a copy of the minutes when I got off the phone.</p> <p style="text-align: center;"><b>APPEARS THIS WAY ON ORIGINAL</b></p> <p>----- <b>Name: Julie Rhee</b></p>	<p><b>NDA#:</b> 21-172</p> <p><b>Telecon/Meeting initiated by:</b></p> <p><input type="radio"/> FDA</p> <p><b>By:</b> Telephone</p> <p><b>Product Name:</b> NovoLog Mix 70/30</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Mary Ann McElligott, Ph.D. Director, Regulatory Affairs</p> <p><b>Phone:</b> (609) 987-5831</p>

---

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Julie Rhee

4/26/01 09:50:14 AM

CSO

**APPEARS THIS WAY  
ON ORIGINAL**

## MEMORANDUM OF TELECON

DATE: March 7, 2001

APPLICATION NUMBER: NDA 21-172, NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)

BETWEEN:

Name:

Novo Nordisk, Princeton, NJ:

Michael Barbush, Assistant Director, Regulatory Affairs  
Won-Chin Huang, Director, Biostatistics  
Mary Ann McElligott, Senior Director, Regulatory Affairs  
Barry Reit, Vice President, Regulatory Affairs  
Olga Santiago, Medical Director  
John Whisnant, Vice President, Drug Development

Novo Nordisk, Denmark:

Dorrit Espersen, Regulatory Project Manager  
Alice Brinch Hansen, Clinical Positioning  
Hanne Henriksen, Regulatory Project Manager  
Anders Lindholm, International Clinical Project Manager  
Ulla Oddershede, Project Vice President  
Renee de Habanera y Palacios, Statistician  
Mark White, Medical Writer

Phone: (609) 987-5831

Representing: Novo Nordisk Pharmaceuticals, Inc.

AND

Division of Metabolic and Endocrine Drug Products, HFD-510:

Julie Rhee, Regulatory Project Manager  
Saul Malozowski, M.D., Medical Team Leader  
Elizabeth Koller, M.D., Medical Officer

SUBJECT: February 9, 2001, resubmission

BACKGROUND: The Agency had issued an approvable letter to the sponsor on November 15, 2000. A copy of the letter is attached to this t-con minutes. The sponsor responded to the action letter on February 9, 2001. However, the 2/9/01 submission lacked antibody data and, therefore, it could not be considered as a major amendment to re-start the review clock.

Page 2  
NDA 21-172  
3/7/01 t-con minutes

The Agency requested a tele-con to inform the sponsor that the Agency does not consider their 2/9/01 re-submission as a complete response and, therefore, the review clock would not be re-started until we receive the complete raw data including serial HgbA1c , insulin doses, and cross-reacting antibodies from their two-year study. The Agency requested that these data to be provided as Excel spreadsheet.

The sponsor agreed that the two-year study had not been completed when they made the submission on 2/9/01 but the study is now completed and they are in the process of validating the study. The sponsor agreed to submit the complete dataset on the study as Excel spreadsheet.

The sponsor also acknowledged that they understood the review clock would not be re-started until the Agency receive the complete and satisfactory dataset on the antibody .

---

Julie Rhee  
Regulatory Project Manager

**APPEARS THIS WAY  
ON ORIGINAL**

---

**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**

---

/s/

-----  
Julie Rhee  
4/17/01 02:24:14 PM  
CSO

APPEARS THIS WAY  
ON ORIGINAL

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

---

**FACSIMILE TRANSMITTAL SHEET**

---

**DATE: April 4, 2001**

<b>To:</b> Mary Ann McElligott, Ph.D.	<b>From:</b> Julie Rhee
<b>Company:</b> Novo Nordisk Pharmaceuticals, Inc.	Division of Division of Metabolic and Endocrine Drug Products
<b>Fax number:</b> (609) 987-3916	<b>Fax number:</b> (301) 443-9282
<b>Phone number:</b> (609) 987-5831	<b>Phone number:</b> (301) 827-6424
<b>Subject:</b> NDA 21-172 NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)	
<b>Total no. of pages including cover:</b> 2	

**Comments:**

Clinical requests on your 3/15/01 submission. The 3/15/01 submission is not considered as a complete response.

---

**Document to be mailed:**

---

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-6430. Thank you.**

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-172 NovoLogMix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)

Date of submissions: March 15 and 22, 2001

Clinical review comments

The submitted data sets are not that which we requested. There is one data set with serial insulin doses and another data set with lots of unnecessary demographic data, serial antibody data, and serial HgbA1c data. They include all of the antibodies- insulin specific, cross-reacting, and — when only the cross-reacting levels are needed. They do not appear to have included alkaline phosphatase data. These data sets cannot be easily merged and rotated.

Please provide the information in the following format:

Patient ID	Treatment	Weight			HgbA1c			Cross-reacting Antibodies			Alk Phos			Insulin Dose (Total)		
		V*1	V*2	etc	V*1	V*2	etc	V*1	V*2	etc	V*1	V*2	etc	V*1	V*2	etc
AAAA																
BBBB																
CCCC																
XXXX																
YYYY																
ZZZZ																

\* Visit

**APPEARS THIS WAY  
ON ORIGINAL**

/s/

-----  
Julie Rhee  
4/4/01 01:37:33 PM  
CSO

**APPEARS THIS WAY  
ON ORIGINAL**

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>Date:</b> February 13, 2001
<p>Re: 2/9/01 submission</p> <p>Background: The 2/9/01 submission is a response to our 11/15/00 approvable letter. The submission also included additional requests to (1) re-evaluate their proposed trade name _____ by OPDRA, and (2) include NovoLog Mix 70/30 FlexPen™. The sponsor stated that they believe the 2/9/01 is to be classified as a Class 1 resubmission.</p> <p>*****</p> <p>I called Dr. McElligott to inform her the following:</p> <ol style="list-style-type: none"> <li>1. The 2/9/01 submission is going to be classified as a Class 2 resubmission since the submission includes data that need to be reviewed. The UF due date for the re-submission is 8/12/01.</li> <li>2. OPDRA had previously turned down their proposed tradename of _____ 70/30 because _____ is not the parent drug for this insulin mixture. Dr. McElligott stated that they provided additional information for their rationale in the 2/9/01 submission. I agreed to forward a nomenclature consult to OPDRA.</li> <li>3. Addition of FlexPen should be submitted as a supplement once the NDA is approved. Dr. McElligott stated that it requires a very small information for an approval and since the re-submission is going to take 6 months for a review, she wanted the addition of FlexPen to be reviewed at this time. I informed her that since the addition of FlexPen was not one of the deficiencies listed in our 11/15/00 approvable letter, we're talking apples and oranges. She asked me to discuss it with Dr. Stephen Moore*. I agreed to do so.</li> </ol> <p>* After the t-con, I discussed it with Dr. Moore and he agreed the addition of FlexPen should be handled as a supplement.</p> <p>-----</p> <p><b>Name: Julie Rhee</b></p>	<p><b>NDA#:</b> 21-172</p> <p><b>Telecon/Meeting initiated by:</b></p> <p><input type="radio"/> FDA</p> <p><b>By:</b> Telephone</p> <p><b>Product Name:</b> NovoLog Mix 70/30</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Mary Ann McElligott, Ph.D. Senior Director Regulatory Affairs</p> <p><b>Phone:</b> (609) 987-5831</p>

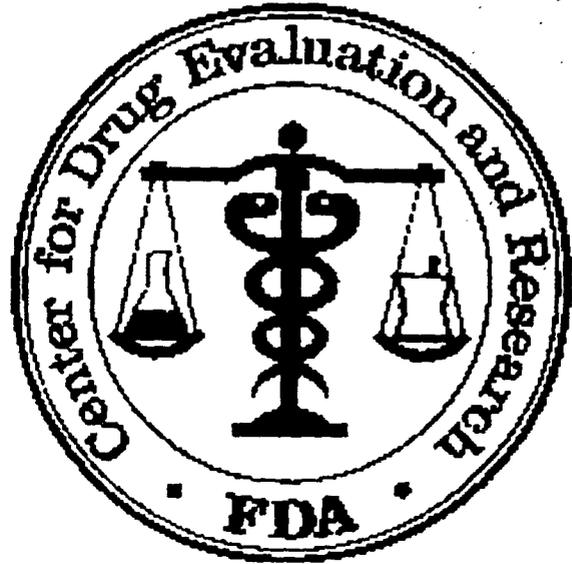
/s/

-----  
Julie Rhee  
2/14/01 12:57:39 PM  
CSO

APPEARS THIS WAY  
ON ORIGINAL

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

DATE: October 10, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 7

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 NovoLog Mix 70/30

Preliminary clinical review comments on the 12/17/99 submission.

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

NDA 21-172 NovoLog Mix 70/30

Date of submission: December 17, 1999

Clinical review comments

1. Additional studies to show the distinctiveness of NovoLog Mix 70/30 compared to other insulin products in the insulin aspart family must be done. If you do not intend to market \_\_\_\_\_ or if it is shown that NPH and \_\_\_\_\_ are essentially equivalent, NPH may be used as one of the comparators for NovoLog Mix 70/30. Please see comments from Biopharm that were faxed to you on September 28, 2000.
2. It may not be implied or stated that that X-14 70/30 has a more rapid onset of action than human insulin or human insulin mixtures. Its profile is likely to be similar to that of human insulin 50/50. A table comparing the PK-<sup>PD</sup> profiles of the insulin and analogue products would be helpful. Head-to-head comparisons would not be required. The product reference guide that was published in 1998 could be used as a template.
3. Even if distinctiveness of this insulin mixture is established, it cannot be inferred or stated that the insulin provides superior post-prandial glycemic control.
4. The methodology for determining the antibody levels in both the short-term and long-term studies should be delineated. How non-specific antibody binding is delineated from specific antibody binding and how total antibody levels are delineated from free antibody levels should be indicated.
5. Long-term safety data regarding the clinical significance of cross-reacting antibodies should be provided. Insulin dose and HgbA1c data should be included.

*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.*

Cleared for faxing by:

/S/

Elizabeth Kotler, M.D.  
Medical Officer

/S/

10/3/00

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

APPEARS THIS WAY  
ON ORIGINAL

# MESSAGE CONFIRMATION

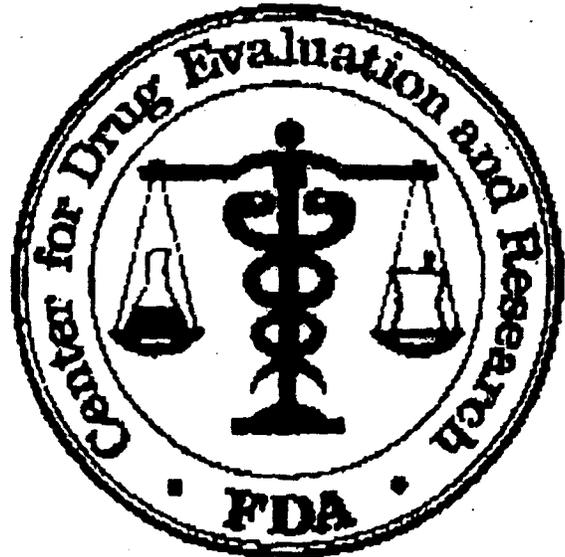
10/10/00 17:34  
ID=DMEDP-CDER-FDA

ID.	MODE	BOX	GROUP
11	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
10/10 17:33	00:4	609 987 3916	003/003	OK		0000

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

DATE: October 10, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Nove Nordisk

Pages (including this cover sheet): 7

FROM:

Name: Julie Rhee

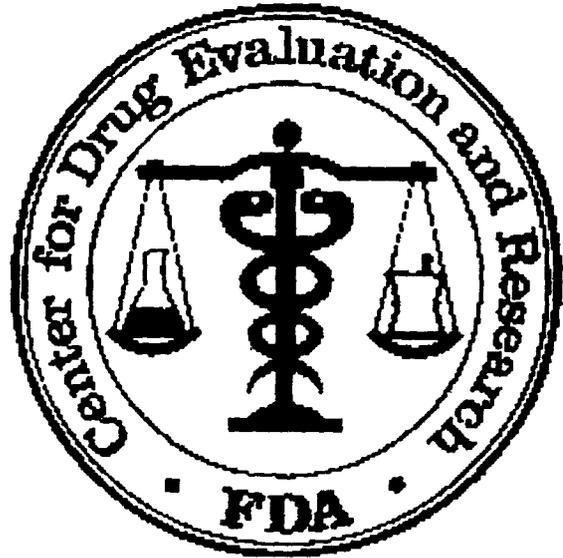
Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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

DATE: October 3, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 3

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 NovoLog Mix 70/30

Preliminary pharm/tox labeling comments. These are preliminary review comments. 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.

cc: Orig NDA  
HFD-510/Div File  
HFD-510/Coiler/Antonipillai

NDA 21-172 NovoLog Mix 70/30

Date of submission: December 17, 1999

Labeling comments for Pharm/Tox section of package insert

*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.*

*Additions are noted by double underline.*

*Deletions are noted by ~~strikethrough~~.*

**Carcinogenicity, Mutagenicity, Impairment of Fertility**

Standard 2-year carcinogenicity studies in animals have not been performed to evaluate the carcinogenic potential of ~~NovoLog~~ 70/30. In 52 week studies, ~~NovoLog~~ <sup>Sprague</sup> ~~Dawley~~ rats were dosed subcutaneously with ~~NovoLog~~ NovoLog, the rapid-acting component of NovoLog Mix 70/30, at 10, 50, and 200 U/kg/day (approximately 2, 8, and 32 times the ~~NovoLog~~ human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area, respectively). At a dose of 200 U/kg/day, NovoLog increased the incidence of mammary gland tumors in females when compared to untreated controls. The incidence of mammary tumors for NovoLog was not significantly different than for regular human insulin. The relevance of these findings to human is not known.

NovoLog was not genotoxic in the following ~~NovoLog~~ tests; Ames test, mouse lymphoma cell forward gene mutation test, human peripheral blood lymphocyte chromosome aberration test, in vivo micronucleus test in mice, and in ex vivo UDS test in rat liver hepatocytes. In fertility studies in male and female rats, NovoLog at subcutaneous doses up to 200 U/kg/day (approximately 32 times the ~~NovoLog~~ human subcutaneous dose, based on U/body surface area), had no direct adverse effects on male and female fertility, or on general reproductive performance of animals.

**Pregnancy: Teratogenic Effects: Pregnancy Category - C:**

~~NovoLog~~ teratology studies have been performed with NovoLog (the rapid-acting component of NovoLog Mix 70/30) and regular human insulin in rats and rabbits. In these studies, NovoLog was given to female rats before mating, during mating, and throughout pregnancy, and to rabbits during organogenesis.

The effects of NovoLog did not differ from those observed with subcutaneous regular human insulin. NovoLog, like human insulin, caused pre- and post-implantation losses and visceral/skeletal abnormalities in rats at a dose of 200 U/kg/day (approximately 32-times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area), and in rabbits at a dose of 10 U/kg/day (approximately three times the human subcutaneous dose of 1.0 U/kg/day, based on U/body surface area). The effects are probably secondary to maternal hypoglycemia at high doses. No significant effects were observed in rats at a dose of 50 U/kg/day and rabbits at a dose of 3 U/kg/day. These doses are approximately 8 times the human subcutaneous dose of 1.0 U/kg/day for rats and equal to the human subcutaneous dose of 1.0 U/kg/day for rabbits, based U/body surface area. There are no adequate and well-controlled studies NovoLog Mix 70/30 in pregnant women.

*Nursing mothers*-It is unknown whether 70/30 is excreted in human milk.

Cleared for faxing by:

/S/

Elizabeth Koller, M.D.  
Medical Officer, DMEDP

/S/

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

/S/

for J Antonipillai  
Indra Antonipillai, Ph.D.  
Pharmacologist, DMEDP  
10/3/00

/S/

10/2/00  
Jer El-Hage, Ph.D.  
Pharm/Tox Team Leader, DMEDP

/S/

10-3-00  
David G. Orloff, M.D.  
Director, DMEDP

# MESSAGE CONFIRMATION

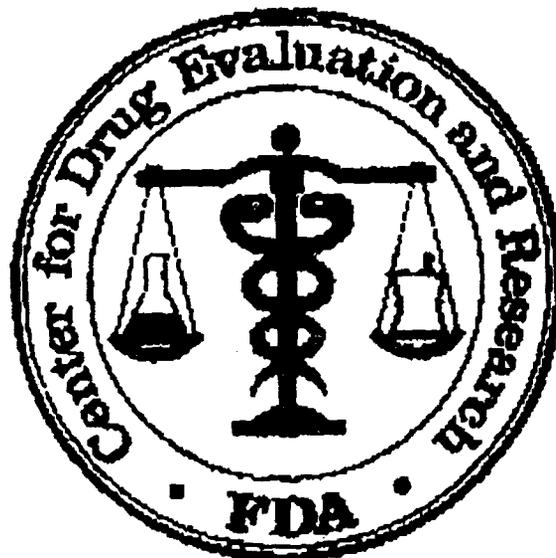
10/03/00 10:46  
ID=DMEDP-CDER-FDA

NO.	MODE	EXT.	GROUP
466	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
10/03 10:45	01:11	609 987 3916	003/003	OK		0000

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

DATE: October 3, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 7

FROM:

Name: Julie Rhee

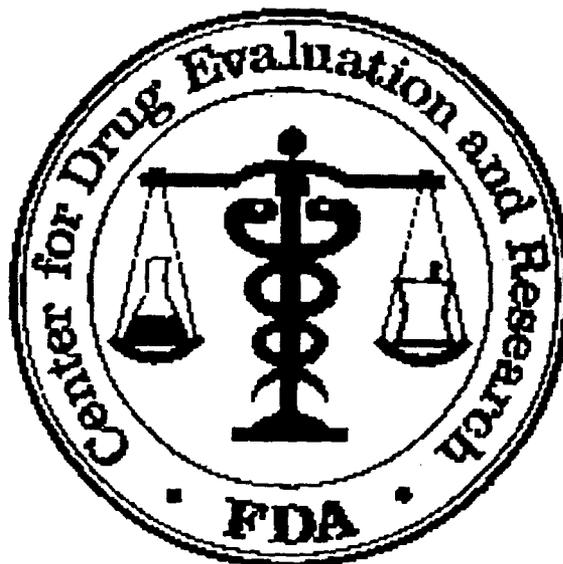
Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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

DATE: September 28, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 2

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 . ——— 70/30

Biopharm review comments on your 12/17/99 submission. These are preliminary review comments. 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.

cc: orig NDA  
HFD-510/Div File



# MESSAGE CONFIRMATION

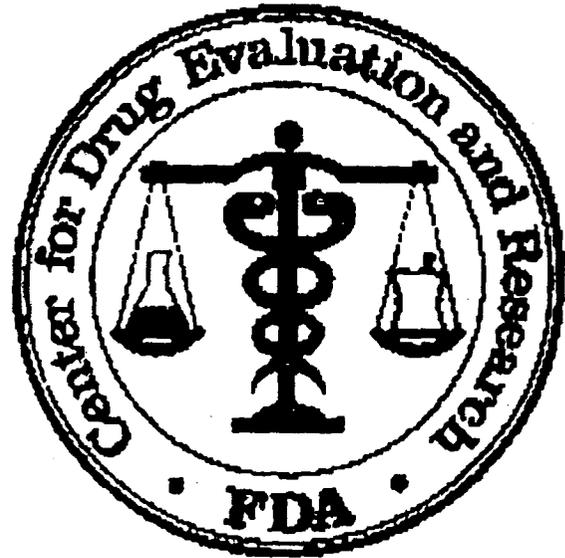
09/28/00 15:43  
ID=DMEDP-CDER-FDA

ID.	MODE	EXT	GROUP
450	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. CODE
09/28 15:43	00:37	609 987 3916	002/002	OK		0000

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

DATE: September 28, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

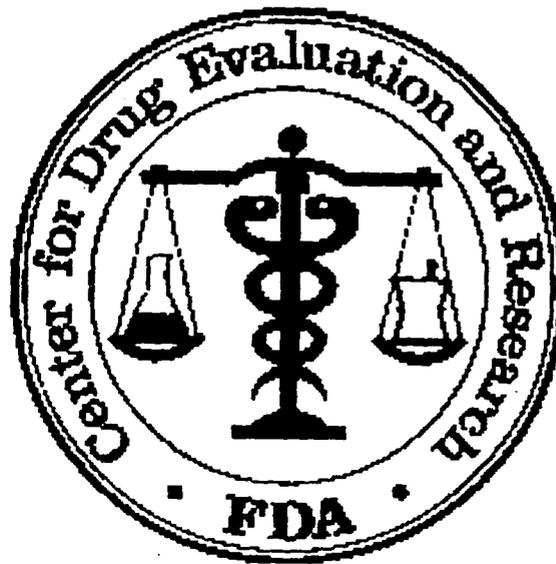
Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

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

DATE: September 27, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 — 70/30

CMC review comments on your 12/17/99 submission.

cc: Orig NDA  
HFD-510/Div File  
HFD-510/Commandari/Moore

NDA 21-172 NovoLog Mix 70/30 (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection)

Date of submission: December 17, 1999

CMC review comments

- c The package insert provides a temperature range (2-8°C) for storage of the product; however, other labeling indicates that the product should be stored           . This temperature range should be provided on all labeling.
- d Instructions for proper storage of the drug product should be included in the patient package insert.

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.

Cleared for faxing by:

/S/

9/27/00

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

# MESSAGE CONFIRMATION

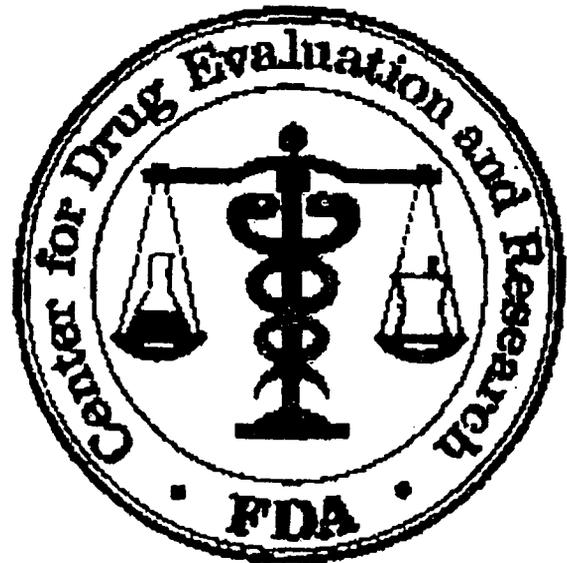
09/27/00 17:35  
ID=DMEDP-CDER-FDA

NO.	MODE	BOX	GROUP
445	TX		

DATE/TIME	TIME	DISTANT STATION ID	PAGES	RESULT	ERROR PAGES	S. COD
09/27 17:34	00:38	609 987 3916	002/002	OK		0000

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

DATE: September 27, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 2

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

MEMO TO THE FILE: T-COM 6/28/00  
NDA #21172 70/30 X-14 insulin mix ✓

Tim Urschel was called to confirm that no extension data were available for the X-14  
70/30 insulin mix NDA. Then Dr. Mc Elligott came in to ask questions about

/S/

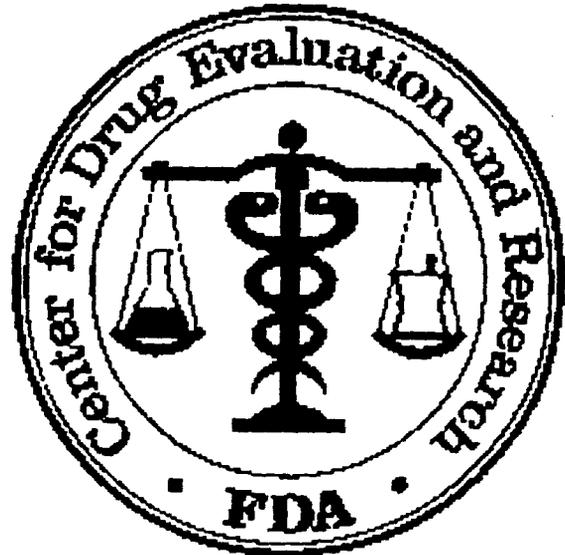
Elizabeth Koller, M.D.  
CC; HFD 510 DF/RheeJ/Koller

/S/

APPEARS THIS WAY  
ON ORIGINAL

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

DATE: May 8, 2000



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

Pages (including this cover sheet): 6

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 ————— 70/30

Additional clinical information request.

cc: only NDA  
HFD-510/D. J. F. I. e  
HFD-510/IC. I. I. e

STUDY 38				treatment	prior exposure to X14	completed	days in	weight	
patient ID	type diabetes	gender	age	randomized	actual (if yes, duration)	study	treatment arm	entry	3 mo endpoint
	1					yes			
	1					yes			
	1					yes			
	1					no			
	1					no			
	etc								
patient ID	2								
	2								
	2								
	2								
	2								
	2								

Also list hypoglycemic episodes requiring third party intervention. Include day duration of treatment after randomization, time of event, the  
 Also list episodes of hyperglycemia >350 mg/dl or DKA.

**APPEARS THIS WAY  
 ON ORIGINAL**

height                      HgbA1c                      Alkaline phos                      Insulin dose  
entry 3 mo endpoint entry 3 mo endpoint entry 3 mo endpoint; entry 3 mo endpoint

blood glucose level, the type of intervention required, and whether the patient was comatose.

**APPEARS THIS WAY  
ON ORIGINAL**

Cross-reacting antibodies entry	3 mo	endpoint	Mean Blood Glucose entry	# of measurments	3 mo	# of measurements	endpoint	# of measurements
------------------------------------	------	----------	-----------------------------	------------------	------	-------------------	----------	-------------------

APPEARS THIS WAY  
ON ORIGINAL

Fasting Glucose  
entry

# of measurments 3 mo # of measurements endpoint # of measurements

90 min post breakfast

# of measurments 3 mo # of measurements endpoint # of measurements

APPEARS THIS WAY  
ON ORIGINAL

Glucose before Lunch  
entry

# of measurements 3 mo # of measurements

endpoint

# of measurements  
entry

2 AM glucose

# of measurements

3 mo

# of measurements  
endpoint

# of measurements

APPEARS THIS WAY  
ON ORIGINAL

# BEST POSSIBLE COPY

## MESSAGE CONFIRMATION

05/08/00 10:27  
ID=FDA CDER DMEDP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
05/08	01'07"	609 987 3916	CALLING	06	OK 0000

05/08/00 10:25 FDA CDER DMEDP → 916099873916

NO.009 001

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

DATE: May 8, 2000

**APPEARS THIS WAY  
ON ORIGINAL**



TO:

Name: Mr. Timothy Urschel

FROM:

Name: Julie Rhee

# BEST POSSIBLE COPY

## MESSAGE CONFIRMATION

05/08/00 10:27  
ID=FDA CDER DMEDP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
05/08	01'07"	609 987 3916	CALLING	06	OK

05/08/00 10:25 FDA CDER DMEDP → 916099873916

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

DATE: May 8, 2000

APPEARS THIS WAY  
ON ORIGINAL



TO:

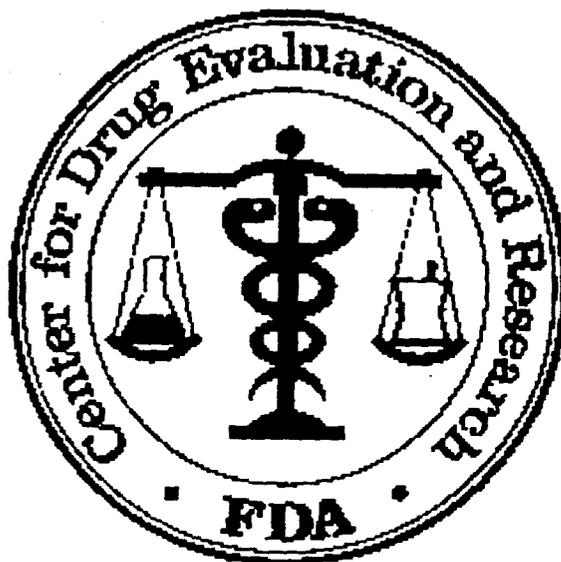
FROM:

Name: Julie Rhee

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

DATE: February 28, 2000

**APPEARS THIS WAY  
ON ORIGINAL**



TO:

Name: Mr. Timothy Urschel

Fax No: (609) 987-3916

Phone No.: (609) 987-5940

Location: Novo Nordisk

FROM:

Name: Julie Rhee

Fax No.: (301) 443-9282

Phone No.: (301) 827-6424

Location: FDA

Pages (including this cover sheet): 7

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination, copy, or other action based on the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone (301-827-6430) and return it to us at the above the above address by mail. Thank you

COMMENTS:

NDA 21-172 ——— 70/30

Please provide the information requested on a diskette. Thank you.

CC: NDA 21-172

HFD-510/Div File

HFD-510/Koiler

page 1

Investigator	Site	Diabetes Type	Completion of 12 week trial	Time of early DC	Reason for early DC	Completion of extension (wk 24)	Time of early DC	Reason for early DC	# insulin injections/d Baseline	12 wks	End study
--------------	------	---------------	-----------------------------	------------------	---------------------	---------------------------------	------------------	---------------------	------------------------------------	--------	-----------

A1  
P12  
P13

↓  
↓

DC=discontinued

Completion of 12 week study-->yes

Completion of extension-->yes or no with number of days in extension

Time of DC for 12 wk trial=#days p randomization

Time of DC for extension=#days p entry into extension trial

Fasting serum glucose=serum/plasma values assessed in a clinical lab. Please specify if a \_\_\_\_\_ was used.

Hypoglycemia=glucose <=36 mg/dl OR requiring third party assistance

Intervention=nature of intervention

APPEARS THIS WAY  
ON ORIGINAL WAY  
ORIGINAL

R5e 2

Total insulin dose/d					HgbA1c					Fasting serum glucose			
24 wks	End extension	Baseline	12 wks	End study	24 wks	End extension	Baseline	12 wks	End study	24 wks	End extension	Baseline	12 wks

APPEARS THIS WAY  
ON ORIGINAL

Appendix 1

End study 24 wks End extension

Fasting glucose-meter  
Baseline

12 wks End study 24 wks End extension

90 min p breakfast glucose-meter  
Baseline

12 wks End study 24 wks

APPEARS THIS WAY  
ON ORIGINAL

12 wks End extension

page 4

Glucose excursion-all meals-meter				Mean glucose profile-meter				X-reacting antibodies					
End extension	Baseline	12 wks	End study	24 wks	End extension	Baseline	12 wks	End study	24 wks	End extension	Baseline	12 wks	End study

APPEARS THIS WAY  
ON ORIGINAL

Episodes glucose > 400 mg/dl/DKA, GI upset			Alk phos								
24 wks	End extension	Baseline	12 wks	End study	24 wks	End extension	Baseline	12 wks	End study	24 wks	End extension

APPEARS THIS WAY  
ON ORIGINAL

Hypoglycemia during 12 week study  
# patients

# events # events requiring 3rd party intervention

intervention

Hypoglycemia-last 4 wks of 12  
# patients

# events # events requiring 3rd party intervention

intervention

APPEARS THIS WAY  
ON ORIGINAL

# MESSAGE CONFIRMATION

02/28/00 16:33  
ID=FDA CDER DMEDP

DATE	S,R-TIME	DISTANT STATION ID	MODE	PAGES	RESULT
02/28	01'17"	609 987 3916	CALLING	07	OK 0000

02/28/00 16:27 FDA CDER DMEDP → 916099873916

NO.132 001

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

DATE: February 28, 2000



TO:

Name: Mr. Timothy Urschel

FROM:

Name: Julie Rhee

**RECORD OF TELEPHONE  
CONVERSATION/MEETING**

**Date:**  
February 18, 2000

Re: 12/17/99 submission

I called Mr. Timothy Urschel but since he was not available, I conveyed the following messages to Ms. Kelly, his assistant:

1. Please submit the Human PK summary, individual study synopsis, and proposed package insert in MS Word format in diskettes.
2. I would like to schedule a t-con with clinician and biopharm reviewer on 2/28/00 between 11:00-11:30.

cc:Orig NDA  
HFD-510/DivFile  
HFD-870/Wei

**APPEARS THIS WAY  
ON ORIGINAL**

/S/

Name: Julie Rhee

**NDA#:** 21-172

**Telecon/Meeting  
initiated by:**

FDA

**By:** Telephone

**Product Name:**  
\_\_\_\_\_ 70/30

**Firm Name:**  
Novo Nordisk

**Name and Title of Person  
with whom conversation  
was held:**  
Ms. Maureen Kelly  
Regulatory Affairs

**Phone:**  
(609) 987-5940

**APPEARS THIS WAY  
ON ORIGINAL**