

<b>RECORD OF TELEPHONE CONVERSATION/MEETING</b>	<b>Date:</b> January 19, 2000
<p>I called Mr. Urschel to convey the following requests from Dr. Koller:</p> <ol style="list-style-type: none"> <li>Vol 37, pg 179, Trial ID: ANA/DCD/038/D,UK, subject numer: 411, subject initials _____</li> </ol> <p>I mentioned that on this volume/page, the Case Report Form Accountability states "For this patient the following (series of) case report form pages have not been completed; page No. 48 through page No. 58"</p> <p>I asked Mr. Urschel for a clarification, i.e., why it was not completed.</p> <ol style="list-style-type: none"> <li>I informed Mr. Urschel that we need data on (1) antibodies, (2) HgbA1c, and (3) dose from extension study.</li> </ol> <p>Mr. Urschel responded that he will check with his clinical people and will get back to me.</p> <p>cc:)OrigNDA HFD-510/DivFile HFD-510/Koller</p> <p style="text-align: center;"><b>APPEARS THIS WAY ON ORIGINAL</b></p> <p><u>  /  S  /  </u> Name: Julie Rhee</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> _____. 70/30 injection (biphasic insulin aspart 30)</p> <p><b>Firm Name:</b> Novo Nordisk</p> <p><b>Name and Title of Person with whom conversation was held:</b> Mr. Tim Urschel Asst. Director Regulatory Affairs</p> <p><b>Phone:</b> (609) 987-5940</p>

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

S .itivity: COMPANY CONFIDENTIAL

Date: 24-Jan-2000 11:07am EST  
From: Pardhasarad Komanduri  
KOMANDURIP  
Dept: HFD-510 PKLN 14B18  
Tel No: 301-827-6420 FAX 301-443-928

TO: Julie Rhee

( RHEEJ )

CC: Stephen Moore

( MOOREST )

Subject: NDA 21-172

The sponsor has submitted all the required CMC information for \_\_\_\_\_  
70/30 to review the application. There are no CMC concerns to consider  
as filing issues.

Pardha

APPEARS THIS WAY  
ON ORIGINAL

## MEMORANDUM OF MEETING MINUTES

**Meeting Date:** January 24, 2000  
**Time:** 9:00 – 9:30 am  
**Location:** PKLN Room 14-56  
**Application:** NDA 21-172 ——— 70/30  
**Sponsor:** Novo Nordisk  
**Type of Meeting:** Filing

**Attendees:**

Saul Malozowski, M.D., Medical Team Leader, DMEDP  
Elizabeth Koller, M.D., Medical Officer, DMEDP  
Ronald Steigerwalt, Ph.D., Pharmacology Team Leader, DMEDP  
Indra Antonipillai, Ph.D., Pharmacology Reviewer, DMEDP  
Todd Sahlroot, Ph.D., Statistical Team Leader, DOB II  
Lee Pian, Ph.D., Statistical Reviewer, DOB II  
Hae-Young Ahn, Ph.D., Biopharm Team Leader, DOP II  
Jim Wei, Ph.D., Biopharm Reviewer, DOP II  
Julie Rhee, Project Manager, DMEDP

**Background:**

NDA 21-172 Insulin Aspart Mix 70/30 was submitted December 17, 1999 (received December 22, 1999). The filing date is February 20, 2000. The primary goal date (UF<sub>10</sub>) is October 22 and secondary goal date (UF<sub>12</sub>) is December 22, 2000. Currently, the original Insulin Aspart NDA (NDA 20-986) is not approved and is pending for action.

**Discussion Points:**

Clinical:

1. The NDA submission consisted of one clinical study and PK studies. The PK studies compare 70/30 human insulin and 70/30 insulin aspart mixes. The submission did not include data to distinguish the 70/30 mix from other insulins in the insulin aspart family. The NDA is also missing composites long-term antibody, dose, glucose control data as well as long-term data on alkaline phosphatase level.
  2. Since these data are missing, Dr. Malozowski is going to discuss with Dr. Jenkins whether or not we should file the NDA.\*
  3. The most important site for inspection will be the site with the comparative PK data.
  4. Registration to market this drug product will be based on the review of safety and PK data. The sponsor has had discussions with the Division regarding the PK-PD studies that need to be done to show distinctiveness from other insulins or insulin mixes since the 1980's.
- Dr. Malozowski informed me that he discussed with Dr. Jenkins whether or not this NDA should be filed and it was decided that the NDA is fileable.

Pharm/Tox:

The NDA is fileable.

CMC:

Neither Drs. Moore nor Komanduri attended the meeting. An e-mail from Dr. Komanduri is attached to this minutes.

Biometrics:

1. Statistical review may not be necessary since the NDA is mainly PK studies with one small clinical study.
2. Clinician needs to decide whether or not this NDA warrants a statistical review. DOB II is amenable to doing the review on a consult basis as needed.

Biopharm:

1. The NDA is fileable
2. The NDA includes four PK studies (3 Phase 1 studies and 1 Phase 2 study).
3. Assay validation was included in the NDA.

Microbiology:

The NDA is fileable.

.....  
Addendum:

On February 7, Dr. Koller informed me that after she had a more time to review the submission, it appeared that the submission has a limited PK-PD data. Dr. Koller told me that she is checking with Dr. Ahn whether or not this NDA should be filed. A copy of Dr. Koller's 2/7/00 e-mail to Dr. Malozowski is attached.

On February 16, 2000, Drs. Jenkins, Malozowskis, Koller, and I met to discuss further whether or not this NDA should be filed. It was decided that the NDA would be filed. However, we should let the sponsor know that there would be a problem with a labeling and arrange a tele-con with the sponsor to suggest conducting additional PK studies. A tele-con with the sponsor is scheduled on 2/28/00 between 11:00-11:30. The sponsor should be informed that the data generated from the PK studies might not be reviewed at this review cycle.

Conclusion:

1. The NDA is filed with the following timelines:

Final review with team leader's concurrence:	9/21/00
Action package to Division Director:	10/5/00
UF10 due date:	10/22/00

2. Dr. Koller will decide on DSI inspection sites.

cc: Original NDA

HFD-510/Div. Files

HFD-510/Koller/Steigerwaltr/Antonipillai/Moore/Komanduri

HFD-715/Sahlroot/Pian

HFD-870/Ahn/Wei

Drafted by: JRhee 2/22/00 c:/nda 21172/filing meeting minutes

Initialed by: Steigerwalt 2-22-00/Malozowskis 2-22-00/Antonipillai 2-23-00/Koller 2-23-00

final: JRhee 2-25-00

MEETING MINUTES

**APPEARS THIS WAY  
ON ORIGINAL**

**OFFICES OF DRUG EVALUATION**  
**ORIGINAL NDA/ANDA EFFICACY SUPPLEMENT**  
**ACTION PACKAGE CHECKLIST**

<b>NDA:</b>	21-172 (IND <del>IND</del> )
<b>Drug:</b>	NovoLog Mix 70/30
<b>Applicant:</b>	Novo Nordisk Pharmaceutical
<b>Chem/Ther/other Types:</b>	4S
<b>CSO/PM:</b>	Julie Rhee
<b>Phone:</b>	827-6424
<b>HFD-</b>	510
<b>USER FEE GOAL DATE:</b>	UF <sub>6</sub> : November 1, 2001
<b>CHECKLIST COMPLETE:</b>	

Arrange package in the following order (include a completed copy of this CHECKLIST):

1. ACTION LETTER with supervisory signatures	AP	x	AE		NA	
Are there any Phase 4 commitments?			Yes		No	x
2. Have all disciplines completed their reviews?			Yes	x	No	
3. LABELING (package insert and carton and container labels). Note: If final or revised draft, include copy of previous version with ODEs comments and state where in action package the Division's review is located. If RX-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.	Draft		x			
	Revised Draft					
	Final					
4. PATENT INFORMATION	Yes	x	No			
5. EXCLUSIVITY CHECKLIST	Yes	x	No			
6. PEDIATRIC PAGE (all NDAs)	Yes	x	No			
7. DEBARMENT CERTIFICATION (copy of applicant's certification for all NDAs submitted on or after June 1, 1992).	Yes	x	No			
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES. Note: If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status. If no audits were requested, include a memo explaining why.	Yes	x	No			
9. REVIEWS & MEMORANDA						
a. DIVISION DIRECTOR'S MEMO	Yes	x	No			
b. GROUP LEADER'S MEMO	Yes		No			
c. MEDICAL REVIEW	Yes		No			
d. SAFETY UPDATE REVIEW	Yes		No			
e. STATISTICAL REVIEW	Yes	x	No			
f. BIOPHARMACEUTICS REVIEW	Yes	x	No			
g. PHARMACOLOGY REVIEW (Include pertinent IND reviews)	Yes	x	No			
1) Statistical Review of Carcinogenicity Study(ies)	Yes		No			x
2) CAC Report/Minutes	Yes		No			x
h. CHEMISTRY REVIEW	Yes	x	No			
1) Labeling and Nomenclature Committee Review Memo	Yes	x	No			
2) Date EER completed						
3) EER Results (attach signed form or CIRT's printout) (Acceptable: 3/13/00)	OK	x	No			
4) FUR needed	Yes		No			x
5) FUR requested	Yes		No			x

6) Have the methods been validated?	Yes		No	x
7) Environmental Assessment Review	Yes		No	x
8) FONSI	Yes	x	No	
i. MICROBIOLOGY REVIEW	Yes	x	No	
1) What is the status of the monograph?				
10. CORRESPONDENCE, TELECONS, and FAXes	Yes	x	No	
11. MINUTES OF MEETINGS	Yes	x	No	
a. Date of End-of-Phase 2 Meeting:				
b. Date of pre-NDA Meeting:				
12. ADVISORY COMMITTEE MEETING				
a. Meeting Conducted	Yes		No	x
b. Minutes	Yes		No	x
c. Info Alert	Yes		No	x
d. Transcript	Yes		No	x
13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS	Yes		No	x
14. If AP letter, has ADVERTISING MATERIAL been reviewed?	Yes		No	x
a. If no and this is an AP with draft labeling letter, has advertising material already been requested?	Yes, documentation attached			x
	No, included in AP letter			
15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)	Yes		No	x
16. INTEGRATED SUMMARY OF SAFETY (from NDA)	Yes		No	x

revision: 5/14/96; edited LR: 5/29/96;  
designed for web: Hardeman 7/17/98

**APPEARS THIS WAY  
ON ORIGINAL**

1.1

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** 3/13/00

**DUE DATE:** 5/13/00

**OPDRA CONSULT #:** 00-0084

**TO:**

**John Jenkins, M.D.**  
**Acting Director, Division of Metabolic and Endocrine Drug Products**  
**HFD-510**

**THROUGH:**

**Julie Rhee**  
**Project Manager**  
**HFD-510**

**PRODUCT NAME:**

\_\_\_\_\_ **70/30**  
(70% protamine crystallized insulin  
aspart, 30% soluble insulin aspart)  
**NDA #: 21-172**

**MANUFACTURER:** Novo Nordisk

**SAFETY EVALUATOR:** Peter Tam, R.Ph.

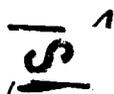
**OPDRA RECOMMENDATION:**

OPDRA does not recommend the use of the proprietary name, \_\_\_\_\_ **70/30**.

**APPEARS THIS WAY  
ON ORIGINAL**

  
**Jerry Phillips, R.Ph.**  
**Associate Director for Medication Error Prevention**  
**Office of Post-Marketing Drug Risk Assessment**  
**Phone: (301) 827-3242**  
**Fax: (301) 827-5189**

5/24/00

 - 5/24/00  
**Peter Honig, M.D.**  
**Director**  
**Office of Post-Marketing Drug Risk**  
**Assessment**  
**Center for Drug Evaluation and**  
**Research**  
**Food and Drug Administration**

Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: 5/9/00  
NDA#: 21-172  
NAME OF DRUG: \_\_\_\_\_ 70/30  
(70% protamine crystallized insulin aspart, 30% soluble insulin aspart suspension  
(rDNA origin))  
NDA HOLDER: Novo Nordisk

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) on March 13, 2000, to review the proposed proprietary drug name, \_\_\_\_\_ 70/30 in regard to potential name confusion with existing proprietary/generic drug names.

PRODUCT INFORMATION

\_\_\_\_\_ 70/30 injection (rDNA origin) is a human insulin analogue suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. It is a parenteral blood glucose-lowering agent with a rapid onset and an intermediate duration of action.

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart reduces the molecule's tendency to form hexamers as observed with regular human insulin. The soluble phase of \_\_\_\_\_ 70/30 is therefore more rapidly absorbed after subcutaneous injection compared to regular human insulin. The protamine crystallized phase has an activity profile that is very similar to that of Novolin 70/30. The insulin aspart in the soluble phase of \_\_\_\_\_ 70/30 is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin 70/30. The maximum serum insulin concentration is, on average, 1.5 times higher with \_\_\_\_\_ 70/30 than with biphasic human insulin 70/30. The time to maximum concentration is, on average, half of that for biphasic human insulin 70/30.

When \_\_\_\_\_ 70/30 is injected subcutaneously, the onset of action will occur within 10-20 minutes of injection. The maximum effect is exerted between 1 and 4 hours after injection. The duration of action is up to 24 hours. It is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia. The total daily individual insulin requirement is usually between 0.5-1 units/kg/day. Due to its fast onset of action, \_\_\_\_\_ 70-30 should generally be given immediately before a meal.

\_\_\_\_\_ 70/30 will be available in 10 mL (each mL containing 100 units) vial, 3 mL PenFill cartridges and syringe.

## II. RISK ASSESSMENT:

The medication error staff of OPDRA conducted a search of several standard published drug product reference texts<sup>1,2,3</sup> as well as several FDA databases<sup>4</sup> for existing drug names which sound alike or look alike to \_\_\_\_\_ to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted<sup>5</sup>. An expert panel discussion was conducted to review all findings from the searches. In addition, OPDRA conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

### A. EXPERT PANEL DISCUSSION

The expert panel consists of members of OPDRA's medication error Safety Evaluator Staff and a representative from the Division of Drug Marketing, Advertising and Communications (DDMAC).

1. The expert panel expressed some concerns with the existing approved product, Novolin 70/30 and a few other similar insulin products such as Humalog \_\_\_\_\_, Humalog \_\_\_\_\_ Humalin 50/50, Humalin 70/30 and Nuromax.

**BEST POSSIBLE COPY**

Novolin 70/30	70% NPH insulin and 30% regular insulin (rDNA) for subcutaneous use	Similar usual dose but onset of action-20-40 minutes, duration up to 24 hrs. Peak serum reached in 60-120 minutes.	
---------------	---	--	--

<sup>1</sup> MICROMEDEX Healthcare Intranet Series, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Emergindex, Reprodisk, Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc).

<sup>2</sup> American Drug Index, online version, Facts and Comparisons, St. Louis, MO.

<sup>3</sup> Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.

<sup>4</sup> Drug Product Reference File [DPR], the Established Evaluation System [EES], the AMF Decision Support System [DSS], the Labeling and Nomenclature Committee [LNC] database of Proprietary name consultation requests, and the electronic online version of the FDA Orange Book.

<sup>5</sup> WWW location <http://www.uspto.gov/tmdb/index.html>.

**BEST POSSIBLE COPY**

Product Name	Package (units) Generic	Usual Dose	Observation
Humalog Mix 75/25	75% insulin lispro protamine suspension, 25% insulin lispro injection (rDNA origin)	Similar usual dose Onset of action- 15-25 minutes, duration up to 24hrs. Peak serum reached 30-240 minutes	
Humalog Mix 50/50	50% lispro protamine suspension, 50% insulin lispro injection (rDNA origin)	Onset of action- 10-25 minutes, duration up to 24 hrs. Peak serum reached 45-120 minutes	
Humalin 50/50	50% NPH insulin and 50% Regular insulin (rDNA)	Onset of action- 15-30 minutes, duration up to 24 hrs. Peak serum reached in 120 minutes.	
Humalin 70/30	70% NPH insulin and 30% regular insulin (rDNA)	Similar to Novolin 70/30	
Nuromax	Injection, doxacurium, neuromuscular blocker	0.05mg/kg for induction and intubation, IV	*SA

\*SA = Sound-alike

According to the expert panel, the proposed name, \_\_\_\_\_ 70/30, could be easily mistaken for Novolin 70/30 since both formulations is a mixture of two different forms of insulin. \_\_\_\_\_ 70/30 has a faster onset of action and a little shorter duration. Other Humalin and Humalog products whose glucose lowering properties are similar are from a different manufacturer. Nuromax would not pose a safety risk since it is mostly used in Operation Room/Anesthesia areas and there is no overlapping dose intervals and route of administration. Since \_\_\_\_\_ 70/30 is a new formulation being added to a product line with the similar root name (e.g. Novolin N, Novolin R, Novolin 70/30, etc.), confusion may occur between existing product and a new product. Previous experience with medication errors have demonstrated that a lack of familiarity with a product added to an existing product line such as this can result in confusion when a prescription for the new product is received and possibly dispensed. In addition, the term \_\_\_\_\_ is instructional in tone. When followed by a number, this combination may cause the user to wonder if adjustments needed to be made in terms of dose or dosing methods.

**B. PRESCRIPTION ANALYSIS STUDIES**

**1. Methodology:**

These studies were conducted by OPDRA and involved 94 health professionals comprised of pharmacists, physicians, and nurses within FDA to determine the degree of confusion of \_\_\_\_\_ 70/30 with other drug names due to the similarity in handwriting and verbal pronunciation of the name. Inpatient and outpatient prescriptions were written, each consisting of (known/unknown) drug products and a prescription for \_\_\_\_\_ (see below). These prescriptions were scanned into a computer and were then delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

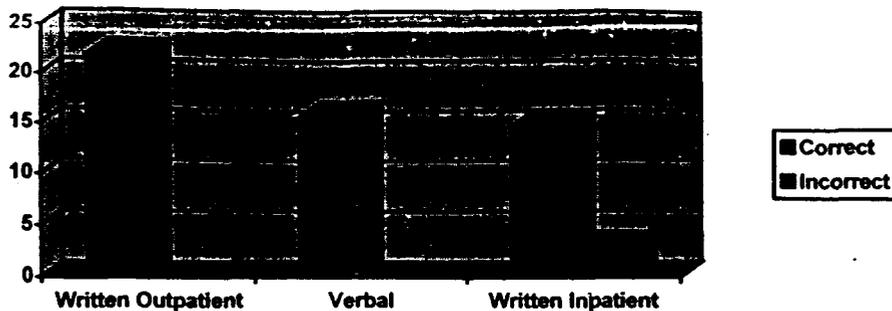
<b>HANDWRITTEN PRESCRIPTION</b>	<b>VERBAL PRESCRIPTION</b>
<b>Outpatient RX:</b> _____ 70/30 #1 Sig: As directed	_____ 70/30 #1 Sig: As directed
<b>Inpatient RX:</b> Increase _____ 70/30 to 10 units before meals	

**2. Results:**

The results are summarized in Table I.

Table I

<u>Study</u>	<u># of Participants</u>	<u># of Responses (%)</u>	<u>Correctly Interpreted</u>	<u>Incorrectly Interpreted</u>
Written Outpatient	31	22 (71%)	22	0
Verbal	32	16 (50%)	16	0
Written Inpatient	31	18(58%)	15	3
<b>Total</b>	<b>94</b>	<b>56 (60%)</b>	<b>53 (95%)</b>	<b>3 (5%)</b>



Ninety-five percent of the participants responded with the correct name, [redacted]. The incorrect written responses are as follows in Table II.

Table II

Written Inpatient	<u>Incorrectly Interpreted</u>
	[redacted]
	[redacted]

\* One verbal respondent kept thinking Novolin 70/30 but answering correctly with the name, [redacted] 70/30.

C. SAFETY EVALUATOR RISK ASSESSMENT

Results of the verbal and written analysis studies show 3 (5%) participants interpreted the proprietary name, [redacted] 70/30, incorrectly. However, the incorrect interpretation did not involve any marketed products. We did not uncover any overlapping existing approved drug product names in our studies. However, a negative finding in a small sample size does not rule out the possibilities of confusion between Novolin 70/30 and [redacted] 70/30, a new product with [redacted].

We conducted prescription studies in an attempt to simulate the prescription ordering process. In this case, there was a confirmation that [redacted] 70/30 could be mistaken with Novolin 70/30. One verbal participant responded that while he interpreted the proposed name [redacted] 70/30 correctly, he kept thinking about the existing approved product Novolin 70/30.

Furthermore, [redacted] onset of action is twice as fast as Novolin 70/30 (10-20 vs 20-40 minutes). A search in AERS found that there were five reports of drug maladministration involving Novolin 70/30 resulting in hyperglycemia. Four hyperglycemia cases were due to not receiving the correct amount of insulin. The other one is due to failure of the insulin-delivery device for the correct amount of insulin. One report resulted in hypoglycemia and hospitalization because the insulin was accidentally injected into the vein. Hence, a prescription for Novolin 70/30 misinterpreted as [redacted] 70/30 could result serious patient outcome because of its rapid onset and shorter duration of action. In addition, we also have concerns about the term [redacted] since it is instructional in tone, and when followed by a number, this combination may cause confusion as to whether dosing adjustment is required.

For these reasons, we object to the use of the name, [redacted] 70/30, for this product. However, OPDRA did approve previously names with the term [redacted] such as Humalog Mix 50/50 and Humalog Mix 75/25 since these products is not directly linked [redacted].

### III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the packaging and the labeling of \_\_\_\_\_ 70/30, OPDRA has attempted to focus on safety issues relating to possible medication errors. Many of the items discussed in this consult involves issues normally reviewed by the chemist and the medical officer.

#### CARTON LABELING (cartridge and vial)

1. We recommend to change the term, \_\_\_\_\_ to For Subcutaneous Use Only.

2. We recommend adding the following to the labeling for 10 ml vial.

“Avoid vigorously shaking \_\_\_\_\_”

3. We recommend adding the following to the labeling for 3 ml cartridge.

“Roll the cartridge between your palms 10 times

4. We recommend deleting \_\_\_\_\_, the Spanish phrase, since this is an English Labeling and might cause confusion. Spanish phrase should be in Spanish labeling.

#### CONTAINER LABELS (cartridge and vial)

See comments under CARTON LABELING

#### PACKAGING INSERT

Under Dosage and Administration, \_\_\_\_\_ Often times, \_\_\_\_\_ lead to medication errors. OPDRA recommends deleting this \_\_\_\_\_

### IV. RECOMMENDATIONS:

- 1) OPDRA does not recommend the use of the proprietary name, \_\_\_\_\_70/30.
- 2) OPDRA recommends the above labeling revisions which might lead to safe use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Peter Tam, RPh. at 301-827-3241.

JS 5/23/00

\_\_\_\_\_  
Peter Tam, RPh.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

JS 5/24/00

\_\_\_\_\_  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

**APPEARS THIS WAY  
ON ORIGINAL**

CC:

NDA – 21-172

Office Files

HFD-510; Julie Rhee, Project Manager, DMEDP

HFD-510; John Jenkins, Acting Division Director, DMEDP

HFD-042; Patricia Staub, Regulatory Review Officer, DDMAC (Electronic Only)

HFD-440; Lanh Green, Safety Evaluator, DDRE II, OPDRA

HFD-400; Jerry Phillips, Associate Director, OPDRA

HFD-400; Peter Honig, Director, OPDRA (Electronic Only)

HFD-002; Murray Lumpkin, Deputy Center Director for Review Management (Electronic Only)

**APPEARS THIS WAY  
ON ORIGINAL**

**RECORD OF TELEPHONE  
CONVERSATION/MEETING**

**Date:**  
July 30, 2001

Re: 2/9/01 submission

Background: The sponsor requested that the Agency re-evaluate their proposed tradename \_\_\_\_\_ The /9/01 submission was forwarded to OPDRA for a consult. In 7/27/01, OPDRA recommended that \_\_\_\_\_ 70/30" as tradename. However, the DMEDP over-ruled the PDRA's decision and recommended "NovoLog Mix 70/30".

\*\*\*\*\*

Called Dr. McElligott and conveyed the DMEDP's decision the proposed tradename of "NovoLog Mix 70/30". She stated to know why \_\_\_\_\_ was rejected by OPDRA. I stated that it is because \_\_\_\_\_ does not correctly reflect the ratio of "70/30".

Requested Novo to submit their response asap. Dr. McElligott stated 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 available at best because of labeling. She said she would discuss internally and will get back to me.

**APPEARS THIS WAY  
ON ORIGINAL**

-----  
Julie Rhee

**NDA#: 21-172**

**Telecon/Meeting  
initiated by:**

FDA

**By: Telephone**

**Product Name:**  
NovoLog Mix 70/30

**Firm Name:**  
Novo Nordisk

**Name and Title of Person  
with whom conversation  
was held:**  
Mary Ann McElligott, Ph.D.  
Director  
Regulatory Affairs

**Phone:**  
(609) 987-5831

**BEST POSSIBLE COPY**

**CONSULTATION RESPONSE**  
**Office of Post-Marketing Drug Risk Assessment**  
**(OPDRA; HFD-400)**

**DATE RECEIVED:** 03/13/01

**DUE DATE:** 07/27/01

**OPDRA CONSULT #:** 00-0084

**TO:**

David Orloff, M.D.  
Director, Division of Metabolic and Endocrine Drug Products  
HFD-510

**THROUGH:**

Julie Rhee  
Project Manager  
HFD-510

**PRODUCT NAME:** \_\_\_\_\_ 70/30 (70% crystallized  
insulin aspart, 30% soluble insulin aspart)

**MANUFACTURER:** Novo Nordisk

**NDA:** 21-172

**SAFETY EVALUATOR:** David Diwa, Pharm.D.

**SUMMARY:** In response to a consult from the Division of Metabolic and Endocrine Drug Products (HFD-510), OPDRA has performed a resubmission review of the proposed proprietary name \_\_\_\_\_

**OPDRA RECOMMENDATION:**

Upon review of information submitted by the sponsor, OPDRA does not recommend the use of the proprietary name \_\_\_\_\_ However, we recommend the use of the name, \_\_\_\_\_ 70/30.

/s/

/s/

\_\_\_\_\_  
Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment  
Phone: (301) 827-3242  
Fax: (301) 480-8173

\_\_\_\_\_  
Martin Himmel, MD  
Deputy Director  
Office of Post-Marketing Drug Risk Assessment  
Center for Drug Evaluation and Research  
Food and Drug Administration

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Division/Office): Sammie Beam, HFD-400			FROM: HFD-510 (Division of Metabolic and Endocrine Drug Products) Julie Rhee		
September 19, 2000	IND NO.:	NDA NO.: 21-172	TYPE OF DOCUMENT : Correspondence	DATE OF DOCUMENT: September 14, 2000	
NAME OF DRUG: NovoLog Mix 70/30 (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection)		PRIORITY CONSIDERATION:	CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: September 29, 2000	
NAME OF FIRM: Novo Nordisk					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>II. BIOMETRICS</b>					
STATISTICAL EVALUATION BRANCH			STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER:			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER:		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG EXPERIENCE</b>					
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> PRECLINICAL		
<b>COMMENTS/SPECIAL INSTRUCTIONS:</b> This submission provides for a new proposed tradename--NovoLog Mix 70/30 (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection). Please review whether or not the new proposed tradename is acceptable. The action goal date is Oct 6, 2000. Thank you.					
cc: Original NDA 21-172 HFD-510/Div. Files					
SIGNATURE OF REQUESTER: 			METHOD OF DELIVERY (Check one): <input type="checkbox"/> MAIL <input checked="" type="checkbox"/> HAND		
SIGNATURE OF RECEIVER:			SIGNATURE OF DELIVERER:		

**Rhee, H Julie**

---

**From:** MTHO@nnpi.com  
**Sent:** Thursday, November 01, 2001 9:41 PM  
**To:** rheej@cder.fda.gov  
**Cc:** ELTA@nnpi.com; MHOD@nnpi.com  
**Subject:** Confirmation of receipt of approval letter

Dear Julie,

As requested, this is to confirm receipt of your 3 page fax, which contained the approval letter for NovoLog Mix 70/30.

Many thanks for your efforts.

Regards,

Michelle

**APPEARS THIS WAY  
ON ORIGINAL**

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Security:** COMPANY CONFIDENTIAL

**Date:** 26-Sep-2000 03:02pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**TO:** See Below

**Subject:** FWD: Trademark consultation for NDA 21-172 (OPDRA 00-0254)

fyi

**Distribution:**

<b>TO:</b> Saul Malozowski	( MALOZOWSKIS )
<b>TO:</b> Elizabeth Koller	( KOLLERE )
<b>TO:</b> Stephen Moore	( MOOREST )
<b>TO:</b> Pardhasarad Komanduri	( KOMANDURIP )
<b>TO:</b> Jeri El Hage	( ELHAGEJ )
<b>TO:</b> Indra Antonipillai	( ANTONIPILLAI )
<b>TO:</b> Todd Sahlroot	( SAHLROOTT )
<b>TO:</b> Lee Pian	( PIAN )
<b>TO:</b> Hae Young Ahn	( AHNH )
<b>TO:</b> He Sun	( SUNH )
<b>CC:</b> David Orloff	( ORLOFFD )
<b>CC:</b> Enid Galliers	( GALLIERS )

**APPEARS THIS WAY  
ON ORIGINAL**

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Date:** 26-Sep-2000 02:03pm  
**From:** Sammie Beam  
BEAMS  
**Dept:** HFD-400 PKLN  
**Tel No:** 301-827-3161 FAX

15-13

301-480-8173

**Subject:** Trademark consultation for NDA 21-172 (OPDRA 00-0254)

Hello Julie,

The name **NovoLog Mix 70/30** (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection) for NDA 21-172 was reviewed by OPDRA in the Expert Panel group on Monday, September 25, 2000. The name was found in line with the current naming of insulin products and therefore acceptable.

Please consider this a final review. You may contact me at 827-3161 if you have any questions.

Thank you,  
Sammie Beam  
Project Manager  
Medication Errors/OPDRA

APPEARS THIS WAY  
ON ORIGINAL

*Noted  
ISI 27 Sep 00*

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Date:** 18-Jul-2000 02:52pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**Subject:** FWD: NDA 21-172 - - - 70/30 Nomenclature

**Please let me know of your thought on the Novo's proposed tradename.  
Dr. Jenkins wanted me to check with the group before he makes a  
decision.**

**Thanks,**

**Julie**

**APPEARS THIS WAY  
ON ORIGINAL**

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Date:** 17-Jul-2000 04:41pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**Subject:** NDA 21-172-\_\_\_\_\_ 70/30 Nomenclature

Dr. Jenkins,

Novo's proposed tradename for NovoLog 70/30 mixture is \_\_\_\_\_ 70/30".  
OPDRA does not recommend the use of \_\_\_\_\_ 70/30" because of the  
following reasons:

- (1) \_\_\_\_\_ 70/30 could be mistaken with Novolin 70/30,
- (2) drug maladministration due to a faster onset of action than Novolin  
70/30, and
- (3) the term \_\_\_\_\_ is instructional in tone and when followed by a  
number, it may cause confusion as to whether dosing adjustment is  
required.

The tradename for Humalog mixtures is Humalog Mix 75/25 and Humalog Mix  
50/50.

I would like to get your input on whether or not the Novo's proposed  
name is acceptable. If not, would you like me to call the sponsor and  
ask them to come up with an alternate tradename?

Thanks,

Julie

**APPEARS THIS WAY  
ON ORIGINAL**

## Electronic Mail Message

**Date:** 9/26/00 2:03:00 PM  
**From:** Sammie Beam ( BEAMS )  
**To:** Julie Rhee ( RHEEJ )  
**Cc:** Jerry Phillips ( PHILLIPSJ )  
**Subject:** Trademark consultation for NDA 21-172 (OPDRA 00-0254)

Hello Julie,

The name NovoLog Mix 70/30 (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection) for NDA 21-172 was reviewed by OPDRA in the Expert Panel group on Monday, September 25, 2000. The name was found in line with the current naming of insulin products and therefore acceptable. Please consider this a final review. You may contact me at 827-3161 if you have any questions.

Thank you,  
Sammie Beam  
Project Manager  
Medication Errors/OPDRA

CC: Orig NDA 21-172  
HFD-510/Div File  
HFD-510/Koller/Komanduri/Antonipillai

**APPEARS THIS WAY  
ON ORIGINAL**

**Office of Post-Marketing Drug Risk Assessment  
HFD-400; Rm. 15B03  
Center for Drug Evaluation and Research**

**PROPRIETARY NAME REVIEW**

**DATE OF REVIEW:** 6/11/01

**NDA#:** 21-172

**NAME OF DRUG:**                      70/30  
(70% protamine crystallized insulin aspart, 30% soluble insulin aspart suspension (rDNA origin))

**NDA HOLDER:** Novo Nordisk

**I. INTRODUCTION:**

This consult is written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510) on February 21, 2001 to review a request by the sponsor to reconsider the proprietary name                      70/30. The consult pertains to OPDRA's recommendation on the proposed proprietary name,                      70/30. We objected to the name and subsequently found the name NovoLog Mix 70/30 acceptable. However, the sponsor is now requesting a reconsideration of the name                     .

There are common elements in the proprietary names of insulin product line that aids practitioners in recognizing the drug class. In the US, the suffixes "lin", "log" (Novolin, Humalin, Humalog) and the name Iletin are unique to insulin products.

Table 1a.

Preparation	Brand	Onset (hrs)	Peak (hrs)	Duration (hrs)	Route
Insulin aspart Protamine suspension/ Soluble Insulin aspart	<b>NovoLog Mix 70/30</b>	0.2-0.3	1-4	24	SC

Table 1b (Novo Nordisk Insulin Products in the US)\*

Preparation	Brand	Onset (hrs)	Peak (hrs)	Duration (hrs)	Route
Insulin analogue	<b>NovoLog</b>	<0.20	0.67-0.8	3-5	SC
Regular insulin injection (R)	<b>Novolin R</b>	0.5	2.5-5	8	SC,IM,IV
	<b>Velosulin BR</b>	0.5	1-3	8	
Insulin Isophane suspension (NPH)/ Regular insulin (R)	<b>Novolin 70/30</b>	0.5	2-12	24	SC
Insulin Isophane suspension (NPH)	<b>Novolin N</b>	1.5	4-12	24	SC
Insulin zinc suspension (L)	<b>Novolin L</b>	2.5	7-15	22	SC

Table 2 (Eli Lilly Insulin Products)\*

Preparation	Brand	Onset (hrs)	Peak (hrs)	Duration (hrs)	Route
Insulin Analogue	Humalog	<0.25	1	3.5-4.5	SC
	Novolog				
Insulin Lispro Protamine/ Insulin Lispro	Humalog Mix 75/25	≤0.25	0.5-1.5	24	SC
Regular insulin injection (R)	Humulin R	0.5	2-4	6-8	SC,IM,IV
	Iletin II Regular				
Insulin Isophane suspension (NPH)/Regular insulin (R)	Humulin 70/30	0.5	2-12	24	SC
	Humulin 50/50	0.5	3-5	24	SC
Insulin Isophane suspension (NPH)	Humulin N	1-2	6-12	18-24	SC
	Iletin II NPH	1-2	6-12	18-26	SC
Insulin zinc suspension (L)	Humulin L	1-3	6-12	18-24	SC
	Iletin II Lente	1-3	6-12	18-26	SC
Insulin Extended zinc suspension (L)	Humulin U	4-6	8-20	24-48	SC

## PRODUCT INFORMATION

70/30 injection (rDNA origin) is a human insulin analogue suspension containing 70% insulin aspart protamine crystals and 30% soluble insulin aspart. It is a parenteral blood glucose-lowering agent with a rapid onset and an intermediate duration of action.

A single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart reduces the molecule's tendency to form hexamers as observed with regular human insulin. The soluble phase of 70/30 is therefore more rapidly absorbed after subcutaneous injection compared to regular human insulin. The crystallized protamine phase has an activity profile that is very similar to that of Novolin 70/30. Insulin aspart in the soluble phase of 70/30 is absorbed more rapidly from the subcutaneous layer than the soluble insulin component of biphasic human insulin 70/30. The maximum serum insulin concentration is, on average, 1.5 times higher with 70/30 than with biphasic human insulin 70/30. The time to maximum concentration is, on average, half of that for biphasic human insulin 70/30.

70/30 has a 10-20 minutes onset of action and reaches maximum effect between 1 and 4 hours after subcutaneous injection. The duration of action is up to 24 hours. The product is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia. The usual dose is between 0.5-1 units/kg/day. 70/30 should be administered immediately following a meal due to its fast onset of action. The product will be available in a 10 mL (each mL containing 100 units) vial, 3 mL PenFill cartridges and syringe.

## II. THE SPONSOR'S RATIONAL FOR REQUESTING A RECONSIDERATION OF THE PROPRIETARY NAME

The applicant is concerned about the use of the proprietary name NovoLog Mix 30 and believes that the product should be differentiated from NovoLog. The applicant prefers the name for the following reasons:

- i. NovoLog Mix 30 should be differentiated from NovoLog for several reasons as each product has its own distinctive use. While patients on NovoLog require intensive therapy, those on NovoLog Mix 30 administer insulin twice daily, often in significantly larger doses. The applicant is therefore concerned about the risk of prescription error confusing the two brands.

Diversity of activity and use in related lines of insulin is not unique to NovoLog Mix 70/30 and NovoLog. Novolin products have diverse onset of action ranging from 0.5 to 2.5 hours and duration of action ranging from 6 to 24 hours (see table 1). The name \_\_\_\_\_ appears to have similar potential for look-alike name confusion with *Novolin* and *Novolog* when compared to reports of product confusion between *Humalog Mix*, *Humulin* and *Humalog*. Moreover, the prefix \_\_\_\_\_ is used across different lines of insulin and pharmacologic drug classes.

\_\_\_\_\_ is the proprietary name for \_\_\_\_\_ while *Novolin* and *Novolog* are used for lines of insulin products. This creates a greater potential for look-alike and sound-alike product name confusion.

- ii. The suffixes for insulin mix ratio products are designated as soluble/intermediate outside the US. Since \_\_\_\_\_ is a global brand name, there is a risk that US patients going abroad will receive an inverse ratio of "high mix" analogs, which will have the same name abroad as the "low mix" product in the US. \_\_\_\_\_ is the global brand name for this product outside the US. Since insulin mix ratio suffixes outside the US are given as soluble/intermediate, "high mix" outside the US will have the same name as the "low mix" in the US. Therefore, US diabetic patients going abroad have a large risk of receiving the incorrect product.

We acknowledge the applicant's concern regarding the potential risk for US diabetic patients receiving incorrect insulin products abroad. However, we have no data to support this observation.

- iii. In view of errors involving Eli Lilly's *Humalog* and *Humalog Mix* in the United Kingdom and Australia (both English speaking countries), similar incidents could occur in the US with the use of *Novolog* and *Novolog Mix*.

We are also concerned about the potential risk of confusion between *Novolog* and *Novolog Mix* in the US. However, we agree with the UK's Medicines Control Agency (MCA) that practitioner awareness, labeling differentiation and the use of distinguishing symbols are key to effectively minimizing this problem.

In addition, the use of a prefix other than \_\_\_\_\_ will more likely minimize the risk of errors due look-alike/sound-alike product name confusion. Our search of AERS did not identify any reports of mix-ups between two of the applicant's regular insulin injection products *Novolin R* and *Velosulin BR*. These products bear different prefixes but can be identified as insulin products by the traditional "lin" suffix. Moreover, *Velosulin* was approved (July 19, 1999) in the same year that *Humalog Mix 50/50* and *Humalog Mix 75/25* were approved (22 December 1999), yet *Velosulin* has not generated mix-ups with other insulin products as compared with *Humalog Mix* insulin.

- iv. There were recent stories criticizing the impact of physician hand writing on physician prescription dispensing. There were also reports of FDA warning letters pertaining to dispensing errors involving Glaxo Wellcome's anti-epileptic drug *Lamictal* and Novartis'

antifungal Lamisil. Since name confusion generated from these different molecular entities used for very different conditions was due to name similarities, the potential for confusion increases given that the names in question are insulin products. Similar errors could occur due to similarities in name between NovoLog and NovoLog Mix, which would place patients at risk for hypoglycemic events.

As with all drug products, we emphasize labeling highlights to differentiate insulin drug products and minimize the risk of mix-ups. The risk of product mix-ups is heightened in the diabetic patient population due to failing eyesight at some stages of the disease process. The use of color differentiation to draw attention to error prone aspects, typographical name differentiation and distinguishing symbols are key to assisting end users in selecting the right product.

### III. RISK ASSESSMENT.

We identified 8 reports that could be attributed to sound-alike and look-alike mix-ups between Humalog and Humalog Mix in the AERS database. The search was performed using the MedDRA preferred term drug maladministration. Most of the errors resulted in significant harm requiring hospitalization. In addition, reporter's comments indicated that difficulties were encountered in distinguishing between Humalog and Humalog Mix due to similar labeling and packaging. A case summary listing is provided below.

Confidential, should be noted for FIO purposes.

The prefix Novo is applied across different therapeutic drug classes, while the name \_\_\_\_\_ lacks the "70/30" label indicating the composition of the two constituent products. Furthermore, "70/30" is a designation usually associated with mixed insulin analogues. It is also likely that the \_\_\_\_\_ after \_\_\_\_\_ could be misinterpreted as \_\_\_\_\_. This is an unusual label for a US mixed analogue insulin, \_\_\_\_\_ indicates only the ratio of one constituent.

The name \_\_\_\_\_ 70/30 not only contains all elements of the proposed name \_\_\_\_\_ but also retains a feature of the standard nomenclature for US mixed analogue insulin.

### III. RECOMMENDATIONS:

- 1.) OPDRA does not recommend the use of the proposed name \_\_\_\_\_.
- 2.) We recommend the use of the proprietary name, \_\_\_\_\_ 70/30.

We are willing reconsider a name that addresses our safety concerns and recommendation.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have any questions or need clarifications, please contact David Diwa at 301-827-0892.

---

David Diwa, Pharm.D.  
Safety Evaluator  
Office of Post-Marketing Drug Risk Assessment

Concur:

---

Jerry Phillips, RPh  
Associate Director for Medication Error Prevention  
Office of Post-Marketing Drug Risk Assessment

**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/

-----  
David Diwa  
7/20/01 10:43:18 AM  
PHARMACIST

Jerry Phillips  
7/20/01 11:21:50 AM  
DIRECTOR

Martin Himmel  
7/23/01 10:01:01 AM  
MEDICAL OFFICER

**APPEARS THIS WAY  
ON ORIGINAL**

## Electronic Mail Message

Date: 9/26/00 2:03:00 PM  
From: Sammie Beam ( BEAMS )  
To: Julie Rhee ( RHEEJ )  
Cc: Jerry Phillips ( PHILLIPSJ )  
Subject: Trademark consultation for NDA 21-172 (OPDRA 00-0254)

Hello Julie,

The name **NovoLog Mix 70/30** (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection) for NDA 21-172 was reviewed by OPDRA in the Expert Panel group on Monday, September 25, 2000. The name was found in line with the current naming of insulin products and therefore acceptable. Please consider this a final review. You may contact me at 827-3161 if you have any questions.

Thank you,  
Sammie Beam  
Project Manager  
Medication Errors/OPDRA

CC: Orig NDA 21-172  
HFD-510/Div File  
HFD-510/Koller/Komanduri/Antonipillai

APPEARS THIS WAY  
ON ORIGINAL

# Electronic Mail Message

Date: 9/14/00 4:26:00 PM  
From: Julie Rhee ( RHEEJ )  
To: Stephen Moore ( MOOREST )  
Cc: Pardhasarad Komanduri ( KOMANDURIP )  
Subject: NDA 21-172 nomenclature

Steve,

I just spoke with MaryAnn McElligott and informed her that their new proposed tradename (NovoLog Mix — is not acceptable since it does not identify the mixture. She said that was a typo and it should have been NovoLog Mix 70/30. I also informed her that the established name (biphasic insulin aspart 30) on form 356h is not USAN name and asked her to use "70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection".

I asked her to submit a correct proposed tradename and established name to the NDA file. She agreed to do so.

Julie

CC: Orig NDA 21-172  
HFD-510/Div File

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.

/S/

Julie Rhee

cc:OrigNDA  
HFD-510DivFile

APPEARS THIS WAY  
ON ORIGINAL

Entered by Elizabeth Koller  
**Electronic Mail Message**

NDA # 21.17  
DF

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 18-Jul-2000 04:04pm  
**From:** Stephen Moore  
MOOREST  
**Dept:** HFD-510 PKLN 14B19  
**Tel No:** 301-827-6430 FAX 301-443-9282

**TO:** See Below  
**Subject:** Re: FWD: NDA 21-172 ----- 70/30 Nomenclature

Julie,

I think we should inform the company that OPDRA has an objection to the tradename. The company should propose a new name.

Stephen

> Please let me know of your thought on the Novo's proposed tradename.  
> Dr. Jenkins wanted me to check with the group before he makes a  
> decision.  
>  
> Thanks,  
>  
> Julie

**Distribution:**

TO: Julie Rhee	( RHEEJ )
TO: Saul Malozowski	( MALOZOWSKIS )
TO: Elizabeth Koller	( KOLLERE )
TO: Stephen Moore	( MOOREST )
TO: Ardhasarad Komanduri	( KOMANDURIP )
TO: Geigerwaltr	
TO: Indra Antonipillai	( ANTONIPILLAI )
TO: Todd Sahlroot	( SAHLROOTT )
TO: Lee Pian	( PIAN )
TO: Hae Young Ahn	( AHNH )
TO: He Sun	( SUNH )

┌

/S/

/S/

└

Forwarded by Elizabeth Koller  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 18-Jul-2000 02:52pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**TO:** See Below  
**Subject:** FWD: NDA 21-172 ----- 70/30 Nomenclature

**Please let me know of your thought on the Novo's proposed tradename.  
Dr. Jenkins wanted me to check with the group before he makes a  
decision.**

**Thanks,**

**Julie**

**Distribution:**

<b>TO:</b> Saul Malozowski	( MALOZOWSKIS )
<b>TO:</b> Elizabeth Koller	( KOLLERE )
<b>TO:</b> Stephen Moore	( MOOREST )
<b>TO:</b> Pardhasarad Komanduri	( KOMANDURIP )
<b>TO:</b> steigerwaltr	
<b>TO:</b> Indra Antonipillai	( ANTONIPILLAI )
<b>TO:</b> Todd Sahlroot	( SAHLROOTT )
<b>TO:</b> Lee Pian	( PIAN )
<b>TO:</b> Hae Young Ahn	( AHNH )
<b>TO:</b> He Sun	( SUNH )

**APPEARS THIS WAY  
ON ORIGINAL**

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Date:** 17-Jul-2000 04:41pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**Subject:** NDA 21-172 \_\_\_\_\_ 70/30 Nomenclature

Dr. Jenkins,

Novo's proposed tradename for NovoLog 70/30 mixture is \_\_\_\_\_ 70/30".  
OPDRA does not recommend the use of \_\_\_\_\_ 70/30" because of the  
following reasons:

- (1) \_\_\_\_\_ 70/30 could be mistaken with Novolin 70/30,
- (2) drug maladministration due to a faster onset of action than Novolin  
70/30, and
- (3) the term \_\_\_\_\_ is instructional in tone and when followed by a  
number, it may cause confusion as to whether dosing adjustment is  
required.

The tradename for Humalog mixtures is Humalog Mix 75/25 and Humalog Mix  
50/50.

I would like to get your input on whether or not the Novo's proposed  
name is acceptable. If not, would you like me to call the sponsor and  
ask them to come up with an alternate tradename?

Thanks,

Julie

APPEARS THIS WAY  
ON ORIGINAL

Printed by Elizabeth Koller  
**Electronic Mail Message**

**Sensitivity:** COMPANY CONFIDENTIAL

**Date:** 18-Jul-2000 02:52pm  
**From:** Julie Rhee  
RHEEJ  
**Dept:** HFD-510 PKLN 14B04  
**Tel No:** 301-827-6424 FAX 301-443-9282

**TO:** See Below  
**Subject:** FWD: NDA 21-172 70/30 Nomenclature

**Please let me know of your thought on the Novo's proposed tradename.  
Dr. Jenkins wanted me to check with the group before he makes a  
decision.**

**Thanks,**

**Julie**

**Distribution:**

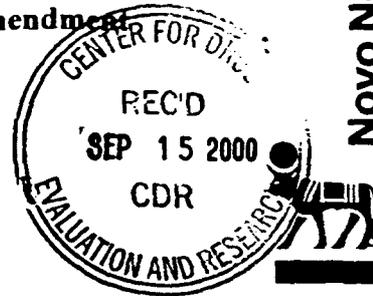
<b>TO:</b> Saul Malozowski	( MALOZOWSKIS )
<b>TO:</b> Elizabeth Koller	( KOLLERE )
<b>TO:</b> Stephen Moore	( MOOREST )
<b>TO:</b> Pardhasarad Komanduri	( KOMANDURIP )
<b>TO:</b> steigerwaltr	
<b>TO:</b> Indra Antonipillai	( ANTONIPILLAI )
<b>TO:</b> Todd Sahlroot	( SAHLROOTT )
<b>TO:</b> Lee Pian	( PIAN )
<b>TO:</b> Hae Young Ahn	( AHNH )
<b>TO:</b> He Sun	( SUNH )

**APPEARS THIS WAY  
ON ORIGINAL**

NDA Minor Amendment

14 September 2000

Dr. John K. Jenkins, M.D., F.C.C.P.  
Acting Director Division of Metabolic and  
Endocrine Drug Products (HFD-510)  
Parklawn Bldg., 14B-04  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



Novo Nordisk  
Pharmaceuticals, Inc.  
100 College Road West  
Princeton, NJ 08540  
Tel. 609-987-5800

**RE: NDA 21-172**  
**NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart protamine [rDNA origin]**  
**suspension and 30% insulin aspart [rDNA origin] injection)**  
**NDA Minor Amendment**

Dear Dr. Jenkins,

Reference is made to NDA 21-172 for Biphasic Insulin Aspart 30 submitted December 17, 1999, and to a conversation with Ms. Julie Rhee on August 8, 2000 and September 14, 2000 regarding the tradename. After conferring with Ms. Rhee, we hereby agree with the alternative tradename NovoLog<sup>®</sup> Mix 70/30 for this product. Please note that from this point on, we will utilize the following nomenclature: (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection).

This submission is made in duplicate. If you have any questions concerning the contents of this submission, please contact Timothy Urschel, Asst. Director, Regulatory Affairs at (609) 987-5940.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

*Maime Elliptik for Barry Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

cc: Julie Rhee (desk copy)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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

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

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

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT  
Novo Nordisk Pharmaceuticals, Inc.

DATE OF SUBMISSION  
September 14, 2000

TELEPHONE NO. (Include Area Code)  
(609) 987-5822

FACSIMILE (FAX) Number (Include Area Code)  
(609) 987-3916

APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code,  
and U.S. License number if previously issued):

100 College Road West  
Princeton, New Jersey 08540

AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State,  
ZIP Code, telephone & FAX number) IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-172

ESTABLISHED NAME (e.g., Proper name, USP/USAN name)  
(70% insulin aspart protamine [rDNA origin] suspension and  
30% insulin aspart [rDNA origin] injection)

PROPRIETARY NAME (trade name) IF ANY  
NovoLog® Mix 70/30

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)

CODE NAME (if any)

DOSAGE FORM:

Sterile parenteral suspension

STRENGTHS:

100 U/ml

ROUTE OF ADMINISTRATION:

s.c. injection

(PROPOSED) INDICATION(S) FOR USE:

Treatment of diabetes mellitus

APPLICATION INFORMATION

APPLICATION TYPE  
(check one)

NEW DRUG APPLICATION (21 CFR 314.50)

ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE

505 (b) (1)

505 (b) (2)

507

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

TYPE OF SUBMISSION  
(check one)

ORIGINAL APPLICATION

AMENDMENT TO A PENDING APPLICATION

RESUBMISSION

PRESUBMISSION

ANNUAL REPORT

ESTABLISHMENT DESCRIPTION SUPPLEMENT

SUPAC SUPPLEMENT

EFFICACY SUPPLEMENT  LABELING SUPPLEMENT

CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT  OTHER

REASON FOR SUBMISSION: Requested Information

PROPOSED MARKETING STATUS (check one)

PRESCRIPTION PRODUCT (Rx)

OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1

THIS APPLICATION IS  PAPER

PAPER AND ELECTRONIC

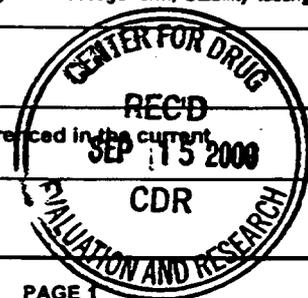
ELECTRONIC

ESTABLISHMENT INFORMATION

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

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

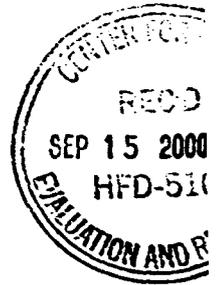
IND — NDA's 19-938, 20-986 Cross reference to NDA 20-986 for DMF Nos. & Letters of Authorization



DUPLICATE

~~NOV CORRECT~~  
NDA Minor Amendment C

Novo Nordisk



Novo Nordisk  
Pharmaceuticals, Inc.  
100 College Road West  
Princeton, NJ 08540  
Tel. 609-987-5800

14 September 2000

Dr. John K. Jenkins, M.D., F.C.C.P.  
Acting Director Division of Metabolic and  
Endocrine Drug Products (HFD-510)  
Parklawn Bldg., 14B-04  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

**RE: NDA 21-172  
NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart protamine [rDNA origin]  
suspension and 30% insulin aspart [rDNA origin] injection)  
NDA Minor Amendment**

Dear Dr. Jenkins,

Reference is made to NDA 21-172 for Biphasic Insulin Aspart 30 submitted December 17, 1999, and to a conversation with Ms. Julie Rhee on August 8, 2000 and September 14, 2000 regarding the tradename. After conferring with Ms. Rhee, we hereby agree with the alternative tradename NovoLog<sup>®</sup> Mix 70/30 for this product. Please note that from this point on, we will utilize the following nomenclature: (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection).

This submission is made in duplicate. If you have any questions concerning the contents of this submission, please contact Timothy Urschel, Asst. Director, Regulatory Affairs at (609) 987-5940.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

*M. M. Ellipt for Barry Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

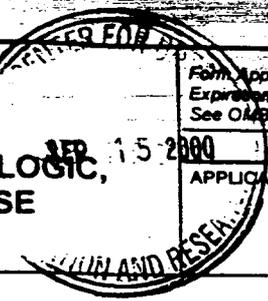
cc: Julie Rhee (desk copy)

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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

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

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



FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Novo Nordisk Pharmaceuticals, Inc.		DATE OF SUBMISSION September 14, 2000
TELEPHONE NO. (Include Area Code) (609) 987-5822	FACSIMILE (FAX) Number (Include Area Code) (609) 987-3916	
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):  100 College Road West Princeton, New Jersey 08540		AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-172		
ESTABLISHED NAME (e.g., Proper name, USP/USAN name) (70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] injection)	PROPRIETARY NAME (trade name) IF ANY NovoLog® Mix 70/30	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)	
DOSAGE FORM: Sterile parenteral suspension	STRENGTHS: 100 U/ml	ROUTE OF ADMINISTRATION: s.c. injection
(PROPOSED) INDICATION(S) FOR USE: Treatment of diabetes mellitus		

**APPLICATION INFORMATION**

APPLICATION TYPE (check one)			
<input checked="" type="checkbox"/> NEW DRUG APPLICATION (21 CFR 314.50)	<input type="checkbox"/> ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)	<input type="checkbox"/> BIOLOGICS LICENSE APPLICATION (21 CFR part 601)	
IF AN NDA, IDENTIFY THE APPROPRIATE TYPE <input type="checkbox"/> 505 (b) (1) <input type="checkbox"/> 505 (b) (2) <input type="checkbox"/> 507			
IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION Name of Drug _____ Holder of Approved Application _____			
TYPE OF SUBMISSION (check one)			
<input type="checkbox"/> ORIGINAL APPLICATION	<input checked="" type="checkbox"/> AMENDMENT TO A PENDING APPLICATION	<input type="checkbox"/> RESUBMISSION	
<input type="checkbox"/> PRESUBMISSION	<input type="checkbox"/> ANNUAL REPORT	<input type="checkbox"/> ESTABLISHMENT DESCRIPTION SUPPLEMENT	<input type="checkbox"/> SUPAC SUPPLEMENT
<input type="checkbox"/> EFFICACY SUPPLEMENT	<input type="checkbox"/> LABELING SUPPLEMENT	<input type="checkbox"/> CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT	<input type="checkbox"/> OTHER

REASON FOR SUBMISSION: Requested Information

PROPOSED MARKETING STATUS (check one)	<input checked="" type="checkbox"/> PRESCRIPTION PRODUCT (Rx)	<input type="checkbox"/> OVER THE COUNTER PRODUCT (OTC)
NUMBER OF VOLUMES SUBMITTED <u>1</u>	THIS APPLICATION IS <input checked="" type="checkbox"/> PAPER <input type="checkbox"/> PAPER AND ELECTRONIC <input type="checkbox"/> ELECTRONIC	

**ESTABLISHMENT INFORMATION**

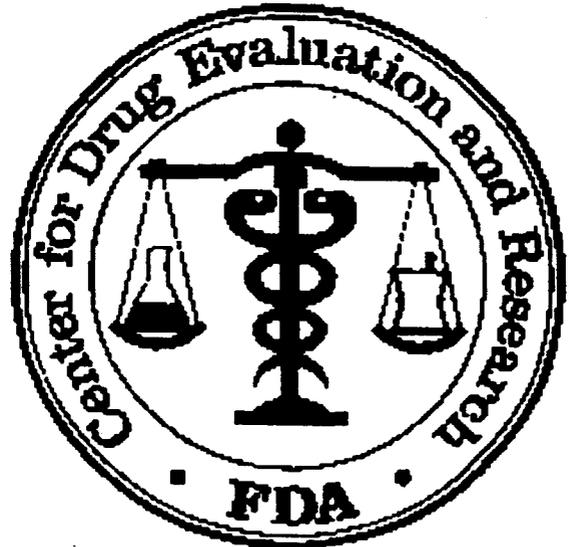
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage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

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

IND — NDA's 19-938, 20-986 Cross reference to NDA 20-986 for DMF Nos. & Letters of Authorization

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

DATE: July 26, 2000



TO:

Name: Mike Skelly

Fax No: 594-1204

Phone No.: 827-5457

Location: HFD-45

Pages (including this cover sheet): 8

FROM:

Name: Julie Rhee

Fax No.: 443-0072

Phone No.: 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

May 12, 2000 submission cover letter and interim analysis report (synopsis).

ORIGINAL

~~CONFIDENTIAL~~

BM

NDA Minor Amendment

Novo Nordisk



Novo Nordisk  
Pharmaceuticals, Inc.

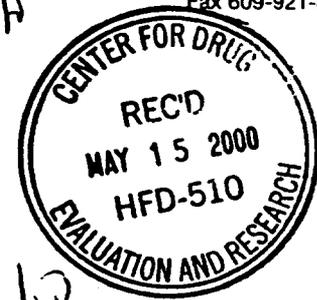
Suite 200  
100 Overlook Center  
Princeton, NJ 08540-7810  
Tel. 609-987-5800  
Fax 609-921-8082

12 May, 2000

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

RE: NDA 21-172  
Request for information  
Biphasic Insulin Aspart 30

*If you believe that the  
Amendment proposed will  
provide correct information to the  
FDA  
ISJ 5/15/00*



Dear Dr. Jenkins,

Reference is made to NDA 21-172 dated December 17, 1999, and our teleconference with the Division on February 28, 2000. Reference is also made to the NDA amendment submitted on April 7, 2000 detailing our plans to submit study 1086 to address Dr. Koller's request for submission of pharmacokinetic data comparing Insulin Aspart (Iasp) versus Biphasic Insulin Aspart 30 (BIAsp 30).

Enclosed is the complete report containing all final data, including safety, to support the pharmacokinetic and pharmacodynamic difference between BIAsp 30 and Iasp. These two arms (Iasp and BIAsp 30) of this four arm study are complete, and all data collected for these two arms has been analyzed for the generation of this report. The enclosed report for study BIAsp 1086 is entitled, "An interim analysis investigating the pharmacodynamics and pharmacokinetics of biphasic insulin aspart 30 compared to soluble insulin aspart in healthy subjects." This interim report presents final analyses inclusive of the primary and secondary objectives of the study with respect to Iasp and BIAsp 30. The remaining two arms, BIAsp 50 and BIAsp 70 that remain ongoing are and are not pertinent to this NDA.

The report demonstrates that; (a) the time action profiles of BIAsp 30 in healthy subjects were significantly different to that observed with soluble Iasp, both with regard to the

*we reviewed  
ok copy  
6/7/00*

Biphasic Insulin Aspart 30  
Request for Information  
May 12, 2000

rapid-acting and the intermediate-acting component, (b) the glucose lowering activity with BIAsp 30 was lower during the first 4 hours after injection and higher from 4 to 24 hours compared to soluble Iasp, and (c) the pharmacokinetic results were consistent with the pharmacodynamic observations. No safety issues were raised by this trial.

This submission is made in duplicate. If you have any questions concerning the contents of this submission, please contact Timothy Urschel, Asst. Director, Regulatory Affairs at (609) 987-5940.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

*M. McElroy for Barry Reit*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

Enclosures

REVIEWS COMPLETED	
CSCO ACTION:	
<input type="checkbox"/> RETURN	<input checked="" type="checkbox"/> FINAL
<input type="checkbox"/> MEMO	
/S/	7-18-00
INITIALS	DATE

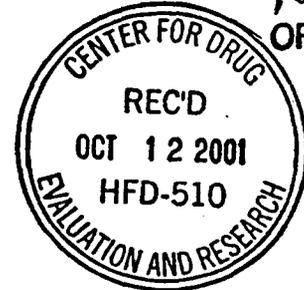
APPEARS THIS WAY  
ON ORIGINAL

Safety Update



October 12, 2001

David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine  
Drug Products, HFD-510, Room No. 14B19  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857



N000 SU  
ORIG AMENDM

RE: NDA 21-172

NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection)  
Safety Update Report

Dear Dr. Orloff:

Reference is made to NDA 21-172 for NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection) that was originally submitted on December 17, 1999 and to the NDA resubmission that was accepted for filing on April 30, 2001

This safety update includes all accumulated safety information completed on or before September 1, 2001. For ongoing trials and trials not finalized as of September 1, 2001, information has been included on serious adverse events (SAEs) occurring on or before September 1, 2001. However for the ongoing ANA/067 extension trial, all adverse event data until September 1, 2001 are presented, since this trial accounts for a major part of the subject years of exposure in the NovoLog Mix 70/30 development program.

The information presented in the safety update is consistent with the draft package insert submitted with the NDA. Therefore, there are no safety issues that would require updating of the originally submitted labeling at this time.

If you have any questions regarding this submission, please contact Elizabeth Tan, PhD, Asst. Director, Regulatory Affairs at (609) 987-5940.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

*Ina McElroy for B. Reit.*

Barry Reit, Ph.D.  
Vice President, Regulatory Affairs

Enclosure

NDA #21172 Insulin Analogue Mix  
SU and also important biopharm and clinical (alk phos) data  
Letter date: 8/29/00 Received: 8/30/00  
Received by physician: 9/7/00  
Biopharm data previously sent as a FAX 9/5/00  
Sponsor: Novo

Comment: The biopharm data really constitute a major amendment. This is under discussion. See e-mail.

Comment: The alk phos data came too late—although this data should have been immediately procurable. By indirect methods, the reviewer determined the reference range for alk phos and determined the number of alk phos elevations site by site. See NDA review.

Comment: There was an additional death in a 68 yo M treated with an X-14 compound. The cause of death was lung cancer.

Comment: There were several reports of hospitalization for gastroenteritis and abdominal pain. The data were insufficient for the reviewer to conclude that these were not episodes of DKA.

Comment: There was a report of injection site reactions attributed to protamine during a work-up. The nature of the evaluation was not provided.

/S/

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

for sub /S/ J 9/8/00

APPEARS THIS WAY  
ON ORIGINAL

GENERAL CORRESPONDENCE



August 30, 2001

David G. Orloff, M.D.  
Director, Division of Metabolic and Endocrine  
Drug Products, HFD-510, Room No. 14B19  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research  
Food and Drug Administration  
5600 Fishers Lane  
Rockville, MD 20857

Re: NDA 21-172

**NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and  
30% insulin aspart [rDNA origin] injection)  
Re: Tradename**

Dear Dr. Orloff:

Reference is made to NDA 21-172 for NovoLog<sup>®</sup> Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection) that was originally submitted on December 17, 1999, and to the NDA resubmission that was accepted for filing on April 30, 2001. Reference is also made to an August 14, 2001 written request from Novo Nordisk for reconsideration of the proposed tradename.

At an August 28, 2001 teleconference between the FDA (Dr. D. Orloff and Ms. J. Rhee) and NNPI (Dr. B. Reit), Novo Nordisk was advised that the proposal for reconsideration of the tradename,            70/30, was not approved.

We acknowledge the FDA's decision and hereby accept the previously suggested name of NovoLog Mix 70/30. With the closure on this matter, we request that efforts proceed with the timely review of the NDA.

If you have any question, please contact Elizabeth Tan, Ph.D., Assistant Director, Regulatory Affairs at (609) 987-5940.

Sincerely,  
NOVO NORDISK PHARMACEUTICALS, INC.

A handwritten signature in black ink, appearing to be "Barry Reit", written over the typed name.

Barry Reit, PhD.  
Vice President, Regulatory Affairs

Novo Nordisk  
Pharmaceuticals, Inc.  
100 College Road West  
Princeton, NJ 08540  
609-987-5800 phone  
www.novonordisk-us.com

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
FOOD AND DRUG ADMINISTRATION

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

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

Form Approved: OMB No. 0910-0338  
Expiration Date: March 31, 2003  
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

**APPLICANT INFORMATION**

NAME OF APPLICANT Novo Nordisk Pharmaceuticals, Inc.	DATE OF SUBMISSION 8/30/01
TELEPHONE NO. (Include Area Code) 609-987-5822	FACSIMILE (FAX) Number (Include Area Code) 609-987-3916
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued): 100 College Road West Princeton, NJ 08540	AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE

**PRODUCT DESCRIPTION**

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) 21-172

ESTABLISHED NAME (e.g., Proper name, USP/USAN name) (70% insulin aspart (rDNA origin) protamine suspension and 30% insulin aspart (rDNA origin) injection).	PROPRIETARY NAME (trade name) IF ANY NovoLog Mix 70/30	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (if any)	CODE NAME (if any)	
DOSAGE FORM Parenteral	STRENGTHS: 100 Units/ml	ROUTE OF ADMINISTRATION: Subcutaneous

(PROPOSED) INDICATION(S) FOR USE: Treatment of Diabetes Mellitus

**APPLICATION INFORMATION**

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

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

IF AN ANDA, or 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION  
Name of Drug Holder of Approved Application

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

IF A SUBMISSION OR PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: \_\_\_\_\_

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY  CBE  CBE-30  Prior Approval (PA)

REASON FOR SUBMISSION Tradename

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

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS  PAPER  PAPER AND ELECTRONIC  ELECTRONIC

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

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

This application contains the following items: (Check all that apply)

- 1. Index
- 2. Labeling (check one)  Draft Labeling  Final Printed Labeling
- 3. Summary (21 CFR 314.50(c))
- 4. Chemistry section
  - A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
  - B. Samples (21 CFR 314.50(e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
  - C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
- 5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
- 6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
- 7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
- 8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
- 9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
- 10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
- 11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
- 12. Case report forms (e.g., 21 CFR 314.50(f)(2); 21 CFR 601.2)
- 13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
- 14. A patent certification with respect to any patent which claims the drug (21 U.S.C.355(b)(2) or (j)(2)(A))
- 15. Establishment description (21 CFR Part 600, if applicable)
- 16. Debarment certification (FD&C Act 306(k)(1))
- 17. Field copy certification (21 CFR 314.50(k)(3))
- 18. User Fee Cover Sheet (Form FDA 3397)
- 19. Financial Information (21 CFR Part 54)
- 20. OTHER (Specify) Tradename

**CERTIFICATION**

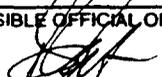
I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA.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

- 1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
- 2. Biological establishment standards in 21 CFR Part 600.
- 3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
- 4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
- 5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
- 6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
- 7. Local, state and Federal environmental impact laws.

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

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

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

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT 	TYPED NAME AND TITLE Barry Reit, PhD.	DATE 8/30 /01
ADDRESS (Street, City, State, and ZIP Code) 100 College Road West, Princeton, NJ 08540	TELEPHONE NUMBER 609-987-5822	

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services  
Food and Drug Administration  
CBER, HFM-99  
1401 Rockville Pike

Food and Drug Administration  
CDER, HFD-94  
12420 Parklawn Dr., Room 3046  
Rockville, MD 20852

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



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

---

---

**FACSIMILE TRANSMITTAL SHEET**

---

---

**DATE: July 31, 2001**

<b>To:</b> Elizabeth Tan, 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) 987-5940	<b>Phone number:</b> (301) 827-6424
<b>Subject:</b> NDA 21-172 NovoLog Mix 70/30	

---

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

---

**Comments:**

Agenda for the 8/6/01 tele-conference.

---

**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**

RE: NDA#21172 Clinical studies 038 and 067

Antibody data submitted to NDA and on spreadsheet

For the B/T % binding (percent binding--bound divided by total) for the cross-reacting antibodies, did the bound number include non-specific binding along with specific binding or did the bound number delineate only specific binding?

**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

7/31/01 11:43:10 AM

CSO

**APPEARS THIS WAY  
ON ORIGINAL**



NDA 21-172

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

Dear Dr. Reit:

We acknowledge receipt on May 1, 2001, of your April 30, 2001, resubmission to your new drug application (NDA) for NovoLog Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30% insulin aspart [rDNA origin] injection).

We also acknowledge receipt of your February 9, March 15 and 22, and April 10, 2001, resubmissions on February 12, March 16 and 23, and April 12, 2001, respectively.

These resubmissions contain additional clinical, clinical pharmacology, and chemistry information submitted in response to our November 15, 2000, action letter.

We consider these a complete class 2 response to our action letter. Therefore, the user fee goal date is November 1, 2001.

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

---

**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

5/11/01 02:05:26 PM

APPEARS THIS WAY  
ON ORIGINAL

NDA 21-172

DEC 27 1999

Novo Nordisk Pharmaceuticals, Inc.  
Attention: Barry Reit, Ph.D.  
Vice President, Regulatory Affairs  
100 Overlook Center  
Suite 200  
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:                   70/30, (insulin aspart [rDNA origin] 70% protamine suspension and 30% injection) 100 U/mL

Therapeutic Classification:    Standard (S)

Date of Application:            December 17, 1999

Date of Receipt:                December 22, 1999

Our Reference Number:        NDA 21-172

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 20, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be October 22, 2000, and the secondary user fee goal date will be December 22, 2000.

Be advised that, as of April 1, 1999, 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 (63 FR 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with

NDA 21-172

Page 2

the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

We note your request for a full waiver of this requirement in your submission and will respond by April 20, 2000.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at [www.fda.gov/cder/pediatric](http://www.fda.gov/cder/pediatric)) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will proceed with the pediatric drug development plan that you submit and notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed 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: Division Document Room, 14B-19  
5600 Fishers Lane  
Rockville, Maryland 20857

NDA 21-172

Page 3

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

Sincerely,

Enid Galliers  
Chief, Project Management Staff  
Division of Metabolic and Endocrine Drug Products  
Office of Drug Evaluation II  
Center for Drug Evaluation and Research

**APPEARS THIS WAY  
ON ORIGINAL**

NDA 21-172

Page 4

cc:

Archival NDA 21-172

HFD-510/Div. Files

HFD-510/J.Rhee

HFD-510/Reviewers and Team Leaders

DISTRICT OFFICE

Drafted by: ddk/December 27, 1999.

Initialed by: Jweber 12/27/99

final: ddk/December 27, 1999.

filename: 21172ACK

*ISI*  
*not Williams*  
*12/27/99*

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY  
ON ORIGINAL