CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-810

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-810

NDA APPROVABLE

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

Dear Dr. McElligott:

Please refer to your new drug application (NDA) dated June 22, 2005, received June 22, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin].

We acknowledge receipt of your amendments dated: August 31, September 13, and November 20, 2006, February 16, 22, and 28, March 1, 2 (2), and 9, April 20, May 8 and 9, August 17, September 13 and 19, October 10 and 25, November 8 and 15, and December 19, 2007, and January 10, 21, 25, and 31, and March 3, 2008. The August 31, 2006, submission constituted a complete response to our April 19, 2006, action letter.

We have completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to change the color used on the NovoLog Mix 50/50 FlexPen and PenFill carton and container labels to a more contrasting color to differentiate among other NovoLog products.

Confusion among insulin products is a common type of error that is often attributed to similarity in nomenclature (proprietary and established names) and look-alike packaging. The risk of insulin confusion is particularly high within a manufacturer's product line because many manufacturers employ similar proprietary names and trade dress. Selection errors involving insulin product confusion have occurred and resulted in serious patient harm or death in some cases.

The presentation of information and design of the proposed container and carton labeling has potential for confusion that could lead to medication errors. The proposed color for NovoLog Mix 50/50 may be confused with NovoLog Mix 70/30, as both labels have similar shades of blue.

Additionally, the proposed PenFill labels are not differentiating enough from other NovoLog products since the white background and the remainder of the label is virtually identical for all NovoLog products. You should increase the prominence of the differentiating color bar on the PenFill container labels. (We note that PenFill container labels were not included in the March 3, 2008 submission made subsequent to our February 22, 2008, email.)

Submit electronic mocked-up versions of the revised labels that respond to the deficiency for the following:

- FlexPen trade and sample carton labels
- FlexPen trade and sample container labels
- PenFill trade and sample carton labels
- PenFill trade and sample container labels

PHYSICIAN AND PATIENT LABELING

- At this time, we have no additional changes to the Package Insert you submitted on January 25, 2008.

- For the Patient Package Insert, FlexPen Instructions for Use Leaflet, and PenFill Instructions for Use Leaflet, we have made minor editorial revisions that are indicated in the enclosed labeling. Please submit pdf and Word versions reflecting these changes.

CONTENT OF LABELING

Submit updated content of labeling [21 CFR 314.50 (l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html for the Package Insert, submitted on January 25, 2008, and for the revised patient labeling.

If additional information relating to the safety and effectiveness of this drug product becomes available, revision of the labeling may be required.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:

- Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
- Present tabulations of the new safety data combined with the original NDA data.
- Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
- For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide updated exposure information for the clinical trials (e.g. number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

RESPONSE OPTIONS

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request a meeting or telephone conference with this division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Rachel Hartford, Regulatory Project Manager, at (301) 796-0331.

Sincerely,

{See appended electronic signature page}

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

Enclosures:
Package Insert
Patient Package Insert
Flexpen Instructions for Use Leaflet
PenFill Instructions for Use Leaflet

30 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Mary Parks
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-809
NDA 21-810

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

Dear Dr. McElligott:

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

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

We acknowledge receipt of your submissions dated September 6, and October 21 and 26, 2005, and January 5 (NDA 21-810), 19 and 30 (NDA 21-809), February 6, 9, 10, and 16, March 13, 14, 16, and April 7, 2006, to both NDA applications.

The March 13 and 16, 2006, submissions were not reviewed for this action. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We completed our review and find the information presented is inadequate. Therefore, the applications are not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies are summarized as follows:

Clinical Pharmacology:

b(4)

b(4)

b(4)

b(4)

Microbiology:

1. The media fill acceptance criteria section in the application contains the statement "The contamination is according to US "Guidance for Industry. Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice Sep 2004" but does not further define the acceptance criteria. Merely referring to an FDA Guidance is not sufficient. You should clearly state the media fill acceptance criteria.

2. The concentration of microorganisms in the *E coli* suspension used to assess container closure and package integrity need to be provided.

Labeling:

We reserve labeling comments until the applications are otherwise approvable.

Manufacturing facility inspection:

We are taking this action before our field investigator could complete inspection of your NovoLog Mix 30/70 and NovoLog Mix 50/50 manufacturing facility located in Kalundborg, Denmark. Satisfactory inspection is required before these applications may be approved.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file amendments, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the applications under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Although not approvability issues, we have the following comments concerning your applications:

b(4)

1. We received your responses dated March 13, 2006, proposing [redacted] as a new proprietary name for NovoLog Mix 30/70 and [redacted] as a new proprietary name for NovoLog Mix 50/50. These amendments were not reviewed during this review cycle; however, we refer you to our letter dated February 27, 2006 which addressed previously proposed proprietary names for your two insulin products. In that letter, the Division of Medication Errors and Technical Support rejected previously proposed proprietary names and recommended that one proprietary name be used for all of your insulin aspart protamine suspension and insulin aspart combination products. The products should be further differentiated with a numerical modifier (e.g., 70/30) representing the concentration of each component.

2. Study BIAsp 1086 was audited by the Agency and the findings were not satisfactory:

b(4)

- The record documenting the September 20, 1999, receipt of supplies from Novo Nordisk contained calibrator concentration data which were added to the document after it was signed, by someone other than the signatory, on an unknown date.

The drug products may not be legally marketed until you have been notified in writing that these applications are approved.

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

Sincerely,

{See appended electronic signature page}

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

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

/s/

Mary Parks
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