CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-810

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 21-810 SUPPL # n/a HFD # 510

Trade Name NovoLog Mix 50/50

Generic Name 50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)

Applicant Name NovoNordisk

Approval Date, If Known August 26, 2008

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES ☒ NO ☐

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES ☐ NO ☒

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

The pivotal studies for approval were bioequivalence studies. The key endpoints for these studies were the pharmacokinetics (insulin concentrations) and pharmacodynamics (glucose infusion rates) during an insulin clamp following single doses of NovoLog 50/50 or comparator insulins.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES ☐ NO ☒

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES ☒ NO ☐

NDA 20-986 NovoLog (insulin aspart [rDNA origin] injection) was granted Pediatric Exclusivity (expires 13Mar09).

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES ☐ NO ☒

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES ☐ NO ☐

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES ☒ NO ☐

NOTE: Insulin aspart protamine suspension has not been approved as a stand alone product, but is present along with insulin aspart in NovoLog 70/30 and NovoLog 50/50. The differing proportions of protamine, excipient and insulin aspart in these products results in a different pharmacokinetic/pharmacodynamic pattern. Therefore we consider this a combination product. Both Humalog 75/25 and Humalog 50/50 were considered combination products.

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-986 NovoLog (insulin aspart [rDNA origin] injection)

NDA# 21-172 NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 50% insulin aspart injection [rDNA origin])

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES ☐ NO ☒

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES ☐ NO ☒

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

Because the 2 key ingredients in NovoLog 50/50 have already been approved (NovoLog and NovoLog 70/30 both contain insulin aspart; NovoLog 70/30 contains protamine excipient), there was no requirement for the company to establish the efficacy and safety of these ingredients in clinical trials. Instead, the sponsor was required to show that the pharmacokinetics and pharmacodynamics of NovoLog 50/50 differ sufficiently from the pharmacokinetics and pharmacodynamics of NovoLog and NovoLog 70/30 to justify approval of NovoLog 50/50. The type of investigation needed to achieve this objective is a bioequivalence study, which is the pivotal evidence that FDA relied upon to make its determination about the approvability of NovoLog 50/50.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES ☒ NO ☐

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES ☐ NO ☒

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES ☐ NO ☐

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 !

IND # YES ☐ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! Explain:

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 !

IND # YES ☐ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! Explain:

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1 !

IND # YES ☐ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! Explain:

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !

IND # YES ☐ ! NO ☐

! Explain:

Investigation #2 !

IND # YES ☐ ! NO ☐

! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1 !

YES ☐ ! NO ☐

Explain: ! Explain:

Investigation #2	!
YES ☐	! NO ☐
Explain:	! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES ☐ NO ☐

If yes, explain:

Name of person completing form: Rachel Hartford
Title: Regulatory Project Manager
Date: 27Aug08

Name of Office/Division Director signing form: Mary H. Parks, M.D.
Title: Director Division of Metabolism and Endocrinology Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

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

/s/

Rachel E Hartford
8/27/2008 02:50:46 PM

Mary Parks
8/27/2008 05:23:01 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-810 | Supplement Number: n/a | NDA Supplement Type (e.g. SE5): n/a

Division Name:Division of Metabolism and Endocrinology Products | PDUFA Goal Date: 26AUG2008 | Stamp Date: 26JUN2008

Proprietary Name: NovoLog Mix 50/50

Established/Generic Name: 50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)

Dosage Form: injection

Applicant/Sponsor: NovoNordisk

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) n/a
(2) n/a
(3) n/a
(4) n/a

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s):1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: treat patients with diabetes mellitus for the control of hyperglycemia

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #:_____ PMR #:_____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☒ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☐ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

☐ Yes. PREA does not apply. **Skip to signature block.**

☒ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☒ Yes: (Complete Section A.)

☐ No: Please check all that apply:

- ☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)
- ☐ Deferred for some or all pediatric subpopulations (Complete Sections C)
- ☐ Completed for some or all pediatric subpopulations (Complete Sections D)
- ☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
- ☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

☐ Necessary studies would be impossible or highly impracticable because:

- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease/condition to study
- ☐ Other (e.g., patients geographically dispersed): _____

☒ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.

☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☒ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

JUSTIFICATION for NDA 21-810 NovoLog Mix 50/50

NovoLog 50/50, an insulin mix, does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of all pediatric age groups. Excellent glycemic control has been shown to reduce some of the complications of type 1 and type 2 diabetes. However, the fixed ratio of short-acting insulin to long-acting insulin in NovoLog 50/50 limits the ability to achieve tight glycemic control because the short-acting insulin component and long-acting insulin component cannot be titrated individually. Most pediatric patients with diabetes, especially those who are prepubescent, have type 1 diabetes. These patients are typically treated with a long-acting basal insulin and a premeal, rapid-acting insulin analog. In post-pubertal patients with type 2 diabetes primarily linked to childhood obesity, metformin is the preferred anti-diabetic therapy because, unlike insulin, metformin carries a low risk of hypoglycemia and does not cause weight gain.

Therefore, a full pediatric waiver for NovoLog 50/50 is appropriate (of note, the other marketed insulin mixes also have full pediatric waivers).

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible#	Not meaningful therapeutic benefit*	Ineffective or unsafe†	Formulation failedΔ
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

\# Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

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

/s/

Rachel E Hartford
8/27/2008 11:38:40 AM

Debarment Statement

Novo Nordisk® Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.

Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs

June 22, 2005
Date

Appears This Way
On Original

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # **21-810** BLA # n/a	NDA Supplement # n/a BLA STN # n/a	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: NovoLog Mix 50/50 Established/Proper Name: 50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin] Dosage Form: injection		Applicant: Novo Nordisk Agent for Applicant (if applicable): n/a
RPM: Rachel Hartford		Division: DMEP

NDAs:	505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2) Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2) (A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)): N/A Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.** ☐ No changes ☐ Updated Date of check: **If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.** **On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.**

❖ User Fee Goal Date Action Goal Date (if different)	26AUG08 n/a
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None AE - 28Apr08 NA - 19Apr06
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics	
Review priority: ☒ Standard ☐ Priority Chemical classification (new NDAs only): 3 ☐ Fast Track ☐ Rolling Review ☐ Orphan drug designation ☐ Rx-to-OTC full switch ☐ Rx-to-OTC partial switch ☐ Direct-to-OTC NDAs: Subpart H ☐ Accelerated approval (21 CFR 314.510) ☐ Restricted distribution (21 CFR 314.520) Subpart I ☐ Approval based on animal studies BLAs: Subpart E ☐ Accelerated approval (21 CFR 601.41) ☐ Restricted distribution (21 CFR 601.42) Subpart H ☐ Approval based on animal studies ☐ Submitted in response to a PMR ☐ Submitted in response to a PMC Comments:	
❖ Application Integrity Policy (AIP) http://www.fda.gov/ora/compliance_ref/aip_page.html	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative/Regulatory Documents *section,with* Administrative Reviews*)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative/Regulatory Documents *section with* Administrative Reviews*)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC *(required for approvals only)* If PeRC review not necessary, explain: ☐	27Aug08
❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)*	☐ Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☐ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☒ No
• Press Office notified of action	☐ Yes ☒ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☐ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☒ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	☐ Yes ☐ No
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist[3]	28Aug08
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/nonconsent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) AP - 26Aug08, AE - 28Apr08, NA - 19Apr06
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	25Jan08
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	☐ Medication Guide ☒ Patient Package Insert ☒ Instructions for Use ☐ None

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	20Aug08
❖ Original applicant-proposed labeling	
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	26Jun08
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☒ RPM 25Aug08 ☒ DMEDP 4Aug08 / 22Feb08 / 23Dec05 ☒ DRISK 12Aug08/ 27Dec07 / 17Feb06 ☐ DDMAC ☐ CSS ☐ Other reviews
Administrative/ Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	RPM Filing Review - 05Aug08 Memo of Filing Mtg - 05Aug05
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☒ 27Aug08
❖ AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	☒ Not on AIP
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	☒ 27Aug08
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	☒ Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	Included
❖ Internal memoranda, telecons, etc.	N/A
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing *(indicate date)*	☒ No mtg

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Type C - R 05Sep06 End of Review Mtg - 11May06
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 28Apr08 & 19Apr06
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None 23Aug08
Clinical Information	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	23Aug08 / 17Apr06
• Clinical review(s) *(indicate date for each review)*	02Nov07 / 06Apr06
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	20Aug08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	06Apr06 pg28
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not needed
❖ REMS • REMS Document and Supporting Statement *(indicate date(s) of submission(s))* • Review(s) and recommendations (including those by OSE and CSS) *(indicate location/date if incorporated into another review)*	☒ None 21Aug08 – Safety Team Memo
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	25May07 / 2Feb06 / 16Nov05
• Bioequivalence Studies	N/A
• Clinical Pharmacology Studies	N/A
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☒ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☒ None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 15Jun07 / 05Feb07 / 10Mar06
❖ DSI Clinical Pharmacology Inspection Review Summary	☒ None
Nonclinical ☒ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☐ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☐ No carc
❖ ECAC/CAC report/memo of meeting	☐ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	☐ None requested
CMC/Quality ☐ None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None 28Mar06
• Branch Chief/TeamLeader Review(s) *(indicate date for each review)*	☒ None
• CMC/product quality review(s) *(indicate date for each review)*	☐ None 13Sep07 / 28Mar06
• BLAs only: Facility information review(s) *(indicate dates)*	☒ None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology	21Dec06 / 20Mar06 ☐ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☒ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	28Mar06 pg36
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: 27May08 ☒ Acceptable ☐ Withhold recommendation

• BLAs: ➢ TBP-EER ➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: ☐ Acceptable ☐ Withhold recommendation Date completed: ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☒ Not needed

NOTES:

1 – Items from the first/second cycle are separated by pink pages. Items from the third cycle are separated by green pages.

2 – Tabs that intentionally do not have any information contain Yellow pages with the text "Section is Intentionally Blank."

3 – Note to FOI included in both volumes of the Action Package. "Many of the documents in these volumes for NDA 21-810 (NovoLog Mix 50/50) apply to an unapproved and withdrawn application NDA 21-809 (NovoLog Mix 30/70).

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

Rachel E Hartford
8/28/2008 09:01:16 AM

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 21-810

Name of Drug: NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin])

Applicant: Novo Nordisk Inc.

Material Reviewed:

Submission & Receipt Date	Document Type
June 22, 2005	PenFill container labels (trade and sample)
January 25, 2008	PI, PPI, PenFill Prefilled syringe Patient Instructions for Use Leaflet (PIFUL), and FlexPen Cartridge PIFUL
March 3, 2008	PenFill carton labels (trade and sample) and FlexPen carton and container labels (trade and sample)
June 26, 2008	PPI, PenFill Prefilled syringe Patient Instructions for Use Leaflet (PIFUL), PenFill carton labels (trade and sample) , PenFill container labels (trade and sample), FlexPen Cartridge PIFUL, FlexPen carton labels (trade and sample), and FlexPen container labels (trade and sample)
August 20, 2008	PPI, PenFill Prefilled syringe Patient Instructions for Use Leaflet (PIFUL), and FlexPen Cartridge PIFUL,

Material Referenced:

Date Finalized	Author (Discipline)	Document Type
December 27, 2007	Sharon Mills Division of Risk Management (DRISK)	Review of Patient Instructions for Use Leaflets (PenFill and FlexPen) and Patient Package Insert submitted November 15, 2007
January 16, 2008	Enid Galliers Division of Metabolism and Endocrinology Products (DMEP)	Email containing FDA proposed revisions for: PI, PPI, Penfill PIFUL, and FlexPen PIFUL
February 22, 2008	Judy Park Division of Medication Error and Technical Support (DMETS)	Review of carton and container labeling submitted January 21, 2008

February 22, 2008	Rachel Hartford	Email containing comments from the DMETS 22FEB08 review
August 4, 2008	Melina Griffis Division of Medication Error Prevention and Anaysis (DMEPA)	Review of carton and container labeling submitted June 26, 2008
August 12, 2008	Sharon Mills DRISK	Review of Patient Instructions for Use Leaflets (PenFill and FlexPen) and Patient Package Insert submitted June 26, 2008

Background and Summary

NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]) is for the treatment of patients with diabetes mellitus, for the control of hyperglycemia. The NDA 21-810 for NovoLog Mix 50/50 was submitted on June 22, 2005. A not approvable letter was issued on April 19, 2006. NovoNordisk submitted a complete response on August 31, 2006. An approvable letter was issued was issued on April 28, 2008. NovoNordisk submitted a complete response on June 26, 2008.

Review

Package Insert

1. The Package Insert submitted on January 25, 2008, was compared to the FDA revised Package Insert sent on January 16, 2008. The following changes have been made and were acceptable to DMEP:

   a. Two figures were numbered 1; corrected and renumbered subsequent figures.

   b. Added an *s* to *formulation* in the following sentence in the first paragraph under Pharmacodynamics: "There was diminishing distinction in pharmacodynamics between the two NovoLog Mix formulations at later time points (See Figure 3)."

   c. Added underlined text to the following sentence in the last paragraph under General in PRECAUTIONS: "Insulin may cause sodium retention and edema (swelling of hands and feet), particularly if previously poor metabolic control is improved by intensified insulin therapy."

   d. [redacted] b(4)

   [redacted]. It is now the

last sentence in the first paragraph under Information for Patients in PRECAUTIONS and reads: "Patients should be informed that hypoglycemia may impair the ability to concentrate and react, which may present a risk in situations where these abilities are especially important, such as driving or operating other machinery."

e. Added the following sentence to the first paragraph in Information for Patients in PRECAUTIONS: "Patients should be informed that alcohol, including beer and wine, may affect their blood sugar when taking NovoLog® Mix 50/50."

f. Added the unerlined text to the first sentence under DOSAGE AND ADMINISTRATION: "The written prescription for NovoLog® Mix 50/50 should include the full name, to avoid confusion with NovoLog® (insulin aspart) and NovoLog® Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection, (rDNA origin)."

b(4)

g. Changed [redacted]o *light* in the following sentence in the second paragraph under RECOMMENDED STORAGE: "Keep all PenFill® cartridges and NovoLog® Mix 50/50 FlexPen® Prefilled syringes away from direct heat and [redacted]ight."

Patient Package Insert

2. The Patient Package Insert submitted on January 25, 2008, was compared to the FDA revised Patient Package Insert sent on January 16, 2008. The following changes have been made:

   a. Deleted the [redacted]or the following: NovoLog® Mix 50/50 (NO[redacted]og-MIX-FIF-tee-FIF-tee).

   b. Changed the first sentence in *Know your insulin* from 1 to 2.

      1. [redacted]

      b(4)

      2. Do not change the type of insulin you *take* unless told to do so by your healthcare provider.

   c. Changed the *What is NovoLog Mix 50/50?* Section from 1 to 2.

      1. NovoLog® Mix 50/50 is a mixed man-made insulin. It is similar to the insulin made by the human body. NovoLog Mix 50/50 is both a fast-acting and long-acting insulin.

      2. NovoLog® Mix 50/50 is similar to the insulin made by the body. NovoLog®

Mix 50/50 is both a rapid-acting and long-acting insulin.

d. Changed the first bullet under *What is NovoLog Mix 50/50?* from 1 to 2.

1. [redacted] b(4)

2. 3 mL PenFill® cartridges for use with Novo Nordisk 3 mL PenFill® cartridge compatible insulin delivery devices. These may be used with or without the addition of a NovoPen® 3 PenMate® and NovoFine® disposable needles.

e. Added the underlined text to the following sentence under *What is NovoLog Mix 50/50?:* "Only use NovoLog® Mix 50/50 if all of the medicine looks white and cloudy after you mix it (resuspension) (see "Patient Instructions for Use")"

f. Changed from 1 to 2 under *How should I take NovoLog Mix 50/50.*

1. [redacted] b(4)

2. Although you can inject insulin in the same area, do not inject into the exact same spot for each injection.

g. Changed the bullets under *Your insulin dosage may need to change because of* from 1 to 2.

1. [redacted] b(4)

2. change in food intake

h. Added *surgery* as a bullet under *Your insulin dosage may need to change because of.*

i. Changed [redacted] to *taking* and *take* in the following sentence under *Other possible side effect include*: "If you keep having skin reactions or they are serious, you may need to stop *taking* NovoLog® Mix 50/50 and *take* a different insulin." b(4)

j. Added the underlined text:

1. **Unopened NovoLog Mix 50/50:**
   - Keep all unopened NovoLog® Mix 50/50 in the refrigerator between 36° to 46° F (2° to 8° C). Do not store in the freezer or next to the refrigerator cooling element. **Do not freeze.**

- Keep unopened NovoLog® Mix 50/50 in the carton to protect from light.
- [redacted] b(4)

3. The Patient Package Insert submitted on August 20, 2008, was compared to the one submitted on June 26, 2008.

   a. DRISK recommended changing the font to enhance readability in their August 12, 2008, review. NovoNordisk changed the font to Arial for enhanced readability.

   b. Changed the *What is NovoLog Mix 50/50?* Section from 1 to 2.

      1. [redacted] b(4)

      2. NovoLog Mix 50/50 is both a rapid-acting and long-acting man-made insulin.

   c. Per DMEP's recommendation, changed the first entry under *NovoLog Mix comes in:* list from 1 to 2.

      1. 3 mL PenFill cartridges for use with Novo Nordisk 3 mL PenFill cartridge compatible insulin delivery devices. These may be used with or without the addition of a NovoPen 3 PenMate and NovoFin disposable needles.

      2. 3 mL PenFill cartridges.

   d. Per DRISK's recomendation, revised the following bullet in the *How should I take NovoLog Mix 50/50* section: [redacted] b(4) It now states, "Change (rotate) sites with each dose. Although you can inject insulin in the same area, do not inject into the exact same spot for each injection."

   e. Per DRISK's recommendation, inserted the following statement to the *What are the most common side effects of NovoLog Mix 50/50* section: "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."

   f. [redacted] b(4)

   g. Changed the copyright to 2002-2008 from [redacted] b(4)

PenFill Cartridge Instructions for Use

4. The PenFill Cartridge Patient Instructions for Use submitted on January 25, 2008, was compared to the FDA revised PenFill Cartridge Patient Instructions for Use sent on January 16, 2008. The following changes have been made:

   a. Added the underlined text in the following sentence in *How to use the NovoLog Mix 50/50 cartridge* #2: "NovoLog® Mix 50/50 should look white and cloudy (after being mixed)."

   b. Did not add a picture for each type of supply listed in #3 of *How to use the NovoLog Mix 50/50 cartridge* as requested by Division of Risk Management (DRM).

   c. Revised the first and second sentences in #8 in *How to use the NovoLog Mix 50/50 cartridge* from 1 to 2.

      1. [redacted] b(4)

      2. Dial the number of units you need to inject on the device (see Diagram 6 below). Inject right away as you were shown by your healthcare provider.

   d. Changed #11 in *How to use the NovoLog Mix 50/50 cartridge* from 1 to 2.
      1 [redacted] b(4)

      2. These containers should be sealed and thrown away safely.

   e. Changed #2 in *After the first use of the 3 mL PenFill cartridge* from 1 to 2

      1. [redacted] b(4)

      2. Before you inject, there must be at least 12 units of insulin left in the cartridge to make sure the remaining insulin is evenly mixed.

   f. Changed the first two sentences immediately following IMPORTANT NOTES into the first bullet under IMPORTANT NOTES.

   g. Changed bullet 5 under IMPORTANT NOTES from 1 to 2.

      1. [redacted] b(4)

      2. NovoLog mix 50/50 cartridges are designed for use with NovoFine disposable needles.

h. Added the underlined second sentence to the following bullet under IMPORTANT NOTES: "Always carry an extra NovoLog® Mix 50/50 cartridge with you in case the NovoLog® Mix 50/50 cartridge is damaged or lost. Always keep the NovoLog Mix 50/50 cartridge in the outer carton when you are not using it in order to protect it from light."

i. Changed [redacted] to *they he or she* in the last sentence in the last bullet under IMPORTANT NOTES: "Do not share it with anyone else even if *they he or she* also has diabetes." b(4)

5. The PenFill Cartridge Patient Instructions for Use submitted on August 20, 2008 was compared to the June 26, 2008 submission.

   a. DRISK recommended changing the font to enhance readability in their August 12, 2008, review. NovoNordisk changed the font to Arial for enhanced readability.

   b. Per DRISK recommendation, changed all reference[redacted] to "3 mL PenFill cartridge." b(4)

   c. Per DMEP recommendation added the following sentences to number three in the *How to use the NovoLog Mix 50/50 cartridge* section. "Be sure to use an insulin delivery device that is made to work with NovoLog Mix 50/50 PenFill cartridges. These insulin delivery devices can be used with a NovoPen 3 PenMate if you would like to hide the needle from view during injection."

FlexPen Instructions for Use

6. The FlexPen Prefilled syringe Patient Instructions for Use submitted on January 25, 2008, was compared to the FDA revised FlexPen Prefilled syringe Patient Instructions for Use sent on January 16, 2008. The following changes have been made:

   a. In Figure 1 the identifier [redacted] was changed to 'rubber stopper' which is consistent with the text. b(4)

   b. Added the underlined text in the following sentence under item 1: "NovoLog® Mix 50/50 should look white and cloudy (after being mixed)."

   c. Added the underlined text in the following sentence in the fourth bullet under item 1: "Hold the NovoLog® Mix 50/50 FlexPen® Prefilled syringe in a horizontal (level) position between your palms (see diagram A above). "

   d. Changed [redacted] to *is* in the following sentence in the fifth bullet under item 1: "Mixing (resuspension) *is* easier when the insulin is at room temperature." b(4)

e. Changed the second bullet under item 2 *Setting the Dose* from 1 to 2

1. [redacted] b(4)

2. Dial the number of units you need to inject by turning the dose selector

f. Changed the second sentence in the third bullet under item 2 *Setting the Dose* from 1 to 2

1. [redacted] b(4)

2. When dialing back, be careful not to press the push button. Pressing the button will cause the insulin to come out.

g. Changed the fourth sentence in the first bullet in *After the injection* in item 3 GIVING THE INJECTION from 1 to 2.

1. [redacted] b(4)

2. These containers should be sealed and thrown away safely.

h. Changed the first sentence in the second paragraph under section 4 FUTURE INJECTIONS from 1 to 2.

1. [redacted] b(4)

2. Before you inject, there must be at least 12 units of insulin left in the insulin cartridge to make sure the remaining insulin is evenly mixed.

7. The Flex Pen Prefilled syringe Patient Instructions for Use submitted on August 20, 2008 was compared to the June 26, 2008 submission. The following change was made.

   a. DRISK recommended changing the font to enhance readability in their August 12, 2008, review. NovoNordisk changed the font to Arial for enhanced readability.

FlexPen Carton labels

8. The FlexPen Retail and Sample Carton labels submitted on March 3, 2008, were compared to the February 22, 2008 DMETS review. The following changes have been made:

a. Per DMETS recommendation "New Product Strength" is to appear for a period of time not to exceed 6 months.

b. Increased the prominence of color on areas previously colored white.

c. Added an image of the FlexPen and added the brand name on the side panel containing expiration date and lot number as part of the global harmonization with other Novo Nordisk insulin products.

d. The NovoLog Mix 50/50 color was not changed to a more contrasting color.

9. The FlexPen Retail and Sample Carton labels submitted on June 26, 2008, were compared to the ones submitted on March 3, 2008.

   a. Differentiating color changed from purple to grey; DMEPA indicates the color is acceptable in their August 4, 2008, review.

   b. The barcode was removed from the back panel.

FlexPen Container labels

10. The FlexPen Retail and Sample Container labels submitted on March 3, 2008, were compared to the February 22, 2008, DMETS review. The following changes have been made:

    a. Per DMETS recommendation revised the strength to include "(U-100)" [i.e. 100 units/mL (U-100)].

    b. The NovoLog Mix 50/50 color was not changed to a more contrasting color.

11. The FlexPen Retail and Sample Container labels submitted on June 26, 2008, were compared to the ones submitted on March 3, 2008.

    a. Differentiating color changed from purple to grey; DMEPA indicates the color is acceptable in their August 4, 2008, review.

PenFill Carton labels

12. The PenFill Retail and Sample Carton labels submitted on March 3, 2008, were compared to the February 22, 2008, DMETS review. The following changes have been made:

    a. Per DMETS recommendation the prominence of the secondary expression of

strength, "100 units/mL (U-100)" was increased.

b. Per DMETS recommendation "New Product Strength" is to appear for a period of time not to exceed 6 months.

c. Novo Nordisk also updated patent information and removed references to InDuo and Innovo which will not be marketed with NovoLog Mix 50/50.

d. Did not follow DMETS recommendation to increase the prominence of the differentiating color to clearly distinguish from other NovoLog products. Novo Nordisk states NovoLog PenFill is the only other Novo Nordisk PenFill product currently marketed in the US and it has an orange band.

e. The NovoLog Mix 50/50 color was not changed to a more contrasting color.

13. The PenFill Retail and Sample Carton labels submitted on June 26, 2008, were compared to the ones submitted on March 3, 2008.

    a. Differentiating color changed from purple to grey; DMEPA indicates the color is acceptable in their August 4, 2008, review.

    b. As requested by DMEPA, the prominence of the differentiating color was increased to distinguish from other NovoLog products.

PenFill Container labels

14. The PenFill Retail and Sample Container labels submitted on June 22, 2008, were approved by DMEPA in their August 4, 2008 review. The June 22, 2008, labels were compared to the June 25, 2005 labels. The following changes have been made:

    a. Differentiating color changed from medium blue to grey.

    b. As requested by DMEPA, the prominence of the differentiating color was increased to distinguish from other NovoLog products.

    c. Added the phrase "For subcutaneous use only."

Conclusion

An approvable letter should be drafted for NDA 21-0810.

Reviewed by:
Rachel Hartford
Regulatory Project Manager

Supervisory concurrence:
Enid Galliers
Chief, Project Management Staff

Drafted: 23Apr08
Revised: 27Jun08, 20Aug08, and 25Aug08
Finalized:25Aug08

CSO LABELING REVIEW

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

/s/

Rachel E Hartford
8/25/2008 01:44:38 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 12, 2008
To:	Mary Parks, M.D., Director **Division of Metabolism and Endocrinology Products**
Through:	Jodi Duckhorn, M.A., Team Leader **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
From:	Sharon R. Mills, BSN, RN, CCRP Patient Product Information Specialist **Patient Labeling and Education Team** **Division of Risk Management (DRISK)**
Subject:	Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use) #2
Drug Name(s):	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin))
Application Type/Number:	NDA 21-810
Applicant/sponsor:	NovoNordisk
OSE RCM #:	2008-1061

1 INTRODUCTION

Novo Nordisk submitted a Complete Response on August 31, 2006 in response to an Agency Not Approvable letter issued on April 19, 2006 for their New Drug Application, NDA 21-810, NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)). On November 15, 2007, the sponsor submitted two revised proposed Patient Package Inserts (PPIs) including Patient Instructions for Use of this NDA, one for each presentation. The two proposed presentations are a 3 mL cartridge and a FlexPen Prefilled Syringe. OSE/DSRCS reviewed the PPI and Patient Instructions for Use on December 27, 2007.

The Review Division took an Approvable Action for NDA 21-810 on April 28, 2008. The sponsor submitted a Complete Response to the Agency's Approvable Action on June 26, 2008. This submission includes revised patient labeling (Patient Package Insert (PPI) and Patient Instructions for Use), revised carton and container labeling, and spl labeling. The Patient Labeling and Education Team received a request from the review division to review the submitted patient labeling for this submission. The comments below are in response to that request.

2 MATERIAL REVIEWED

- NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)) Patient Package Insert (PPI) submitted June 26, 2008.
- NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)) Patient Instructions for Use for the NovoLog Mix 50/50 3 mL cartridge and for the NovoLog Mix 50/50 FlexPen Prefilled Syringe, submitted June 26, 2008.

3 DISCUSSION

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision.

All future relevant changes to the PI should also be reflected in the PPI and Patient Instructions for Use.

4 CONCLUSIONS AND RECOMMENDATIONS

1. We suggest that the sponsor reformat the PPI and Patient Instructions for Use documents using one of the three fonts listed above to enhance readability specifically for low vision readers.
2. In our prior review dated December 27, 2007, we requested that the sponsor have only one PPI for the product and separate Patient Instructions for Use for each product presentation. In this submission, we found that there were two separate Patient Instructions for Use attached to an identical Patient Package Insert. Please inform the sponsor for review purposes, the Patient Package Insert should be provided separately from the Patient Instructions for Use. This will avoid the need for a line-by-line review

to determine that the Patient Package Inserts are identical. For distribution purposes, the sponsor may attach the Patient Package Insert to each Patient Instructions for Use.

3. In the PPI:
   - In the section, "How should I take NovoLog Mix 50/50?" the 4th bullet should be stated using active voice. Add the following to the beginning of the bullet: Change (rotate) sites with each dose."
   - At the end of section "What are the most common side effects...," add the following:
     "Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088."
     This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, *Toll-Free Number for Reporting Adverse Events on Labeling for Human Drug Products* in Federal Register Vol. 73, No. 2, p.402-404, 1/3/2008). Although not required for voluntary PPIs like NovoLog Mix 50/50, we recommend adding this language to all FDA-approved patient labeling for consistency.
   - Under "How should I store NovoLog Mix 50/50?" the last bullet under the section for Unopened product is not in the PI. Either add the information to the PI or delete this information from the PPI.
4. We have no suggested changes to the revised Patient Instructions for Use for the NovoLog Mix 50/50 Prefilled Syringe.
5. As stated in our prior review of the NovoLog Mix 50/50 cartridge Patient Instructions for Use, the term [redacted] is not patient-friendly and should be revised throughout the document. In the current submission, the language has not been adequately changed to address this concern. Specifically the word [redacted] may be too difficult for low literacy readers. The sponsor should simplify this language throughout the document. b(4)

Please let us know if you have any questions.

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/s/

Sharon Mills
8/12/2008 03:52:09 PM
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn
8/12/2008 04:04:16 PM
DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	August 4, 2008
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Division of Medication Error Prevention and Analysis
From:	Melina Griffis, R.Ph., Safety Evaluator Division of Medication Error Prevention and Analysis
Subject:	Labeling Review
Drug Name(s):	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection)
Application Type/Number:	NDA 21-810
Applicant/applicant:	NovoNordisk
OSE RCM #:	2008-1601

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EXECUTIVE SUMMARY

The Division of Medication Error Prevention and Analysis reviewed the container labels and carton labeling for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection) and acknowledges that the Applicant has addressed our concerns outlined in OSE review #2007-2559. In the Applicant's submission two versions (a preferred [grey] and backup [green]) of labels and labeling were proposed. Since the preferred version of the proposed labels were acceptable to our Division, the backup version of the labeling was not reviewed.

1 BACKGROUND

1.1 INTRODUCTION

This consult was written in response to a June 30, 2008, request from the Division of Metabolism and Endocrinology Products for a review of the revised container labels and carton labeling submitted by the Applicant in response to OSE Review #2007-2559, dated February 22, 2008.

1.2 REGULATORY HISTORY

The Division of Medication Error Prevention and Analysis previously reviewed the proposed labels, and labeling for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]) in OSE Reviews #2007-2559 and found that the proposed carton labels and container labeling were inadequate. On April 28, 2008, the Division of Metabolism and Endocrinology Products issued an approvable action requesting that the labels for NovoLog Mix 50/50 be revised. A submission dated June 26, 2008 provided a response to the approvable action and provided revised labels for our review.

1.3 PRODUCT INFORMATION

Currently, there are two NovoLog products (NovoLog and NovoLog Mix 70/30) marketed in the U.S. NovoLog (Insulin Aspart) is a faster acting insulin with a shorter duration of action than regular insulin. It is normally used together with intermediate or long acting insulin products. Because of its rapid action, Novolog is given before a meal. NovoLog Mix 70/30 is a premix containing 30% rapid-acting Novolog (insulin aspart) and a 70% modified long acting formulation (insulin aspart protamine suspension). NovoLog products are available in 10 mL vials of 100 units/mL, 3 mL PenFill cartridges for use with a pen device (i.e. NovoPen, 3 PenMate, NovoFine needles), and a prefilled pen device (FlexPen).

At present, the applicant seeks approval of a new NovoLog Mix product NovoLog Mix 50/50 which provides a therapeutic alternative with a different long-acting/short-acting insulin balance to the existing NovoLog Mix 70/30 product. NovoLog Mix 50/50 will be available in PenFill cartridges and FlexPen.

2 METHODS AND MATERIALS

This section describes the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff to conduct a label, labeling, and/or packaging risk assessment. The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to

inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [1]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[2]

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, The Division of Medication Error Prevention and Analysis staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on June 26, 2008 the following revised labels for our review (see Appendices A, B, C, and D for images):

- Retail Container: FlexPen; PenFill
- Retail Carton: FlexPen; PenFill
- Sample Container: FlexPen; PenFill
- Sample Carton: FlexPen; PenFill

The sponsor provided two versions, a preferred and backup, of the above labels.

3 RESULTS

The revised labels submitted included 1) a change in color in all the proposed labels from the previous color blue and 2) increased prominence of the differentiating color bar on the PenFill container labels. Two different versions of labels and labeling were proposed by the Applicant, a preferred version (grey in color) and a backup version (green in color).

4 DISCUSSION

Based upon our assessment of the labels and labeling, the Division of Medication Error Prevention and Analysis acknowledges that our concerns outlined in OSE review #2007-2559, dated February 22, 2008 have been addressed and that the proposed labels (see Appendix A, B, C, and D) are consistent with our recommendations. It should be noted that the Applicant provided two versions of labeling (a preferred [grey] and backup [green]) for our review. Since the

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[1] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

[2] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

preferred version (grey in color) of the proposed labels addressed our concerns, the backup version of the labels and labeling were not reviewed.

5 CONCLUSIONS AND RECOMMENDATIONS

The Division of Medication Error Prevention and Analysis reviewed the container labels and carton labeling for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection) and acknowledges that the Applicant has addressed our concerns outlined in OSE review #2007-2559. The Applicants preferred version of the proposed labels and labeling (grey in color; see Appendix A, B, C, and D) are acceptable.

The Division of Medication Error Prevention would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy our division on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

2 Page(s) Withheld

_____ Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Melina Griffis
8/4/2008 11:36:47 AM
DRUG SAFETY OFFICE REVIEWER

Kellie Taylor
8/4/2008 02:47:57 PM
DRUG SAFETY OFFICE REVIEWER
Signing on behalf of D. Toyer also

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # NDA # **21-810**	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type N/A	
Proprietary Name: **NovoLog Mix 50/50** Established Name: 50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin] Dosage Form: injection		Applicant: Novo Nordisk	
RPM: Rachel Hartford		Division: DMEP	Phone # 301-796-0331

NDAs:
NDA Application Type: ☒ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

☐ If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

☐ No changes ☐ Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

❖ User Fee Goal Date ❖ Action Goal Date (if different)	28-FEB-07
❖ Actions	
• Proposed action	☐ AP ☐ TA ☒ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None Not Approvable /19-APR-06
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☐ Requested in AP letter ☐ Received and reviewed N/A

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be filed in the Action Package.

❖ Application Characteristics

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☐ Fast Track
☐ Rolling Review

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• If yes, exception for review granted *(file Center Director's memo in* Administrative Documents *section)*	☐ Yes
• If yes, OC clearance for approval *(file communication in* Administrative Documents *section)*	☐ Yes ☐ Not an AP action
❖ Date reviewed by PeRC (required for approvals only) If PeRC review not necessary, explain: ☐	N/A
❖ BLAs only: RMS-BLA Product Information Sheet for TBP has been completed and forwarded to OBPS/DRM (approvals only)	N/A ☐ Yes, date
❖ Public communications (approvals only)	N/A
• Office of Executive Programs (OEP) liaison has been notified of action	☐ Yes ☐ No
• Press Office notified of action	☐ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs and sNDAs only (not BLA's): Exclusivity Summary (approvals only) *(file Summary in* Administrative Documents *section)*	☐ Included **N/A**
• Is approval of this application (includes a supplemental application) blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☒ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **N/A** ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	☐ No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  If "Yes," skip to question (4) below. If "No," continue with question (2).

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

  If "No," continue with question (3).

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? ☐ Yes ☐ No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? ☐ Yes ☐ No

  If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

  If "No," continue with question (5).

  (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? ☐ Yes ☐ No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).* *If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*	
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist	**28Apr08**
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list.	**N/A**
❖ Documentation of consent/non-consent by officers/employees	**N/A**
Decisional Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	**N/A**
❖ Division Director Summary Review *(indicate date for each review)*	28Apr08 & 19APR06
❖ Cross-Discipline Team Leader Review *(indicate date for each review)*	**N/A**
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approvable 28-APR-08 Not Approvable 19-APR-06
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	25JAN08
• Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	**N/A**
❖ Patient Package Insert *(write submission/communication date at upper right of first page of PPI)*	
• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	25JAN08

• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	N/A
❖ Medication Guide *(write submission/communication date at upper right of first page of MedGuide)*	N/A
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	N/A
• Most recent applicant-proposed labeling	03MAR08
❖ Patient Instructions for Use Leaflet(s) *[write submission/communication date at upper right of first page of Leaflet(s)]* • Most-recent division proposal for (only if generated after latest applicant submission) • Most recent applicant-proposed labeling	 N/A 25JAN08
❖ Labeling reviews and any minutes of internal labeling meetings *(indicate dates of reviews and meetings)*	☐ RPM ☒ DMEDP 22FEB08/23DEC05 ☒ DRISK 27DEC07/17FEB06 ☐ DDMAC ☐ SEALD ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) *(indicate date of each review)*	RPM Filing Review 05AUG05 Memo of Filing Meeting 05AUG05
❖ NDA and NDA supplement approvals only: Exclusivity Summary *(signed by Division Director)*	N/A ☐ Included
• AIP-related documents • Center Director's Exception for Review memo • If approval action, OC clearance for approval	N/A
❖ Pediatric Page *(a new Pediatric Page for each review cycle)* See 27JUN05 Ack Ltr – waived requirement for peds studies for this application	☐ Included N/A
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. *(Include certification.)*	☒ Verified, statement is acceptable
❖ Postmarketing Commitment (PMC) Studies	☒ None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	
• Incoming submission documenting commitment	
❖ Postmarketing Requirement (PMR) Studies	☒ None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	

❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	**Included**
❖ Internal memoranda, telecons, etc.	**N/A**
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	☒ Not applicable
• Regulatory Briefing	☒ No mtg
• Pre-NDA/BLA meeting *(indicate date)*	☒ No mtg
• EOP2 meeting *(indicate date)*	☒ No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Type C - R 05SEP06 End of Review Meeting 11MAY06
❖ Advisory Committee Meetings	☒ No AC meeting
• Date(s) of Meetings	
• 48-hour alert or minutes, if available	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Quality Information	
❖ ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	3.28.06 ☐ None
❖ PAL/BUD Review(s) *(indicate date for each review)*	☒ None
❖ CMC/product quality review(s) *(indicate date for each review)*	13SEP07/28Mar06 ☐ None
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date for each review)*	☒ None
❖ BLAs: Product subject to lot release (APs only)	☐ Yes ☐ No **N/A**
❖ Environmental Assessment (check one) (original and supplemental applications)	
• ☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	3.28.06 pg36
• ☐ Review & FONSI *(indicate date of review)*	**N/A**
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) *(indicate date of each review)*	21DEC06/20MAR06 ☐ Not a parenteral product
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: ☒ Acceptable ☐ Withhold recommendation
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and all supplemental applications (except CBEs)) *(indicate date completed, must be within 60 days prior to AP)*	**N/A** ☐ Requested ☐ Accepted ☐ Hold
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
Nonclinical Information	
❖ ADP/T Review(s) *(indicate date for each review)*	☒ None
❖ Supervisory Review(s) *(indicate date for each review)*	☒ None
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☒ None

❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	**N/A** Included in P/T review, page
❖ Nonclinical inspection review summary (DSI)	☒ None requested
Clinical Information	
❖ Clinical Team Leader Review(s) *(indicate date for each review)*	17APR06
❖ Clinical review(s) *(indicate date for each review)*	02NOV07/06APR06
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR ❖ If no financial disclosure information was required, review/memo explaining why not	6APR06 pg28
❖ Clinical reviews from other review disciplines/divisions/Centers *(indicate date of each review)*	☒ None
❖ Clinical microbiology reviews(s) *(indicate date of each review)*	☒ Not needed
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ REMS review(s) (including those by OSE) *(indicate location/date if incorporated into another review)*	**N/A**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date of each review)*	☒ Not needed
❖ DSI Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☐ None requested
• Clinical Studies	25MAY07/2FEB06/16NOV05
• Bioequivalence Studies	**N/A**
• Clinical Pharmacology Studies	**N/A**
Biostatistics	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☒ None
❖ Statistical Team Leader Review(s) *(indicate date for each review)*	☒ None
❖ Statistical Review(s) *(indicate date for each review)*	☒ None
Clinical Pharmacology	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☒ None
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	15JUN07/5FEB07/10MAR06 ☐ None

Added a Sponsor Communications Tab

Removed the following Tabs:

Officer/Employee List	List Documentation	Exclusivity Summary
AIP	Peds Page	Postmarketing Commitment Studies
Postmarketing Required Studies	Internal Memoranda	Advisory Committee
FR/DESI/NAS/NRC	BLAs	Environmental Assessment
Facilities Review/Inspection	ASP/T Review	Supervisory Review
Pharm/Tox Review	P/T requested Reviews	Statistical Reviews of Carci Studies

ECAC/CAC	DSI-Nonclinical Inspection	Financial Disclosure
Other Disc/DIV/Ctrs Clinical Reviews	Clinical Microbiology Reviews	REMS Review
Controlled Substance Staff Review	Biostatistics Review	

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, he supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA or the OND ADRA.

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

/s/

Rachel E Hartford
4/29/2008 11:23:06 AM

ACTING DIVISION DIRECTOR MEMO

NDA #:	21-810 NovoLog Mix 50/50 21-809 NovoLog Mix 30/70
Applicant name	NovoNordisk
Date of Submission	June 22, 2005
Action Goal Date	April 22, 2006

BACKGROUND

Treatment of diabetes mellitus with insulin targets control of glucose excursions post-prandially and regulation of hepatic glucose output. In all patients with type 1 diabetes mellitus (except those treated with sc insulin pumps) and in some with type 2 diabetes mellitus, these goals are achieved through administration of a short-acting recombinant human insulin or insulin analogue before meals to mimic endogenous production of insulin in response to food intake, and through administration of an intermediate- or long-acting insulin to provide basal insulin to control hepatic gluconeogenesis and lipolysis. Frequently, patients mix these two different types of insulin into a single insulin syringe to avoid multiple injections. The process requires proper sequence of mixing to avoid contaminating the vial containing short-acting insulin with long-acting insulin, and careful attention to appropriate units of each type of insulin drawn. The availability of fixed-dose insulin combination products with specific proportions of long-acting and short-acting insulins are convenience products that obviate the need for mixing of different insulin types. Dosing with fixed-dose insulin combination products is based on the requirements of the individual. For example, those patients who may require better glycemic control post-breakfast and pre-lunch but have high fasting plasma glucose levels may opt for a combination product that contains a higher proportion of short-acting insulin in the morning and one that has a higher proportion of long-acting insulin before dinner or at bedtime.

Several fixed-dose insulin combination products have been approved which have different proportions of long to short-acting insulin to allow flexibility in dosing. These have included the recombinant human insulin mixes (Humulin 70/30, Humulin 50/50, and Novolin 70/30) and mixes containing insulin analogues (Humalog 75/25, Humalog 50/50, and Novolog 70/30).

This memorandum discusses the findings from a single pivotal study submitted in support of two new drug applications: one for NovoLog® Mix 50/50 (50% insulin aspart [rDNA origin] protamine crystals and 50% soluble insulin aspart [rDNA origin]) and another for NovoLog® Mix 30/70 (30% insulin aspart [rDNA origin] protamine crystals and 70% soluble insulin aspart [rDNA origin]). Insulin aspart (IAsp) is an analogue of human insulin that differs in a single amino acid substitution (aspartic acid for proline) at position 28 in the B-chain. This substitution allows for IAsp to dissociate rapidly into monomers and confers a faster onset of action than regular insulin. The onset of action of regular insulin is approximately 30 to 60 minutes with peak action occurring between 2 to 3 hrs after administration whereas IAsp (and other insulin analogues) has an onset of action of approximately 5 to 15 minutes with peak action occurring between 30 to 90 minutes. The addition of protamine sulfate to IAsp converts the

soluble insulin to a more crystalline state with a tendency to form hexamers with a delayed absorption after subcutaneous administration. The resulting drug products should provide different time-action profiles reflective of the properties of soluble IAsp (rapid-acting) and the protamine crystals (delayed absorption).

The applicant, NovoNordisk, holds the NDA (21-172) for the approved product NovoLog Mix 70/30. This NDA initially received an approvable letter in November 2000 and was subsequently approved in 2001. Critical to the review of these two current NDAs are the recommendations made for NDA 21-172 and the fact that the study relied upon for the approval of NovoLog Mix 70/30 (Study BAsp 1086 conducted in 1999) is the same pivotal study submitted in support of NovoLog Mix 50/50 b(4)

From the November 2000 Division Director memo for NDA 21-172, there is discussion of an "unofficial" guidance on fixed-dose combination insulin products which requires pharmacokinetic and pharmacodynamic data showing that the combination product differs from its individual components and differs from other combination products currently available. The memo further states, "*though not stated in our unofficial guidance, other combination products apt to be proposed for marketing or likely to be used by patients mixing their own rapid and long-acting insulins may be relevant comparators*". The intent was to avoid approving combination products manufactured by the same company that were considered "nominally distinct but truly duplicate". In other words, this recommendation required that a company show some difference in PK/PD between the two different dosage formulations. This 2000 memo for NovoLog Mix 70/30 further defines "different" as a minimum 20% difference in any number of parameters related to insulin kinetics or glucose utilization dynamics.

In its initial submission, NovoLog Mix 70/30 was shown to be distinct from human insulin 70/30 (Novolin 70/30). As the company was not able to manufacture IAsp containing 100% protamine (or an NPH equivalent), it was not required to compare NovoLog Mix 70/30 to its individual components. Consequently, the company was required to demonstrate pK/PD difference to IAsp and the unapproved 50/50 mix. As the pivotal Study BAsp 1086 was not yet completed, an approvable letter was issued. In 2001, data comparing NovoLog Mix 70/30 to 50/50 were submitted. Pharmacokinetic difference in Cmax was demonstrated between the two products; however, a pharmacodynamic difference of less than 20% was noted in the medical officer's review. A decision was made at that time to not inspect the study site or laboratory facilities for this trial. I was informed by the project manager that the basis for this decision was secondary to restrictions on government foreign travel immediately following the September 11, 2001 terrorist attacks in New York, Pennsylvania, and Washington, DC.

DESCRIPTION OF STUDY BIASP 1086

This study was a randomized, four-period, crossover trial conducted in healthy non-diabetic subjects to evaluate the pharmacokinetics and pharmacodynamics of IAsp, NovoLog mix 70/30, NovoLog mix 50/50, and NovoLog mix 30/70 employing a euglycemic clamp technique. Each insulin product was administered sc at a dose of 0.3 U/kg body weight on 4 different days separated by a washout period of at least 4 days. As stated earlier, this study was conducted in 1999; however, an extension study was conducted in 2000 to specifically compare the pK/PD of NovoLog mix 30/70 to 50/50. The pivotal study and its extension study were reviewed by Dr. Wei from Office of Clinical Pharmacology and Biopharmaceutics (OCPB) and Dr. Zawadzki, medical officer in the Division of Metabolism and Endocrinology Products (DMEP). Dr. Wei also reviewed the studies evaluating bioequivalence across different formulations tested and the to-be-marketed formulations. This memo will only summarize the findings from the pivotal study BIAsp 1086.

CLINICAL/BIOPHARMACEUTICAL ISSUES

The primary objective of the study was to demonstrate a pharmacodynamic difference between treatments based on the glucose infusion rate (GIR) 2 hours following the sc dose of 0.3 U/kg during the euglycemic clamp study as measured by $AUC_{GIR\ 0\text{-}2\ hrs}$. It should be noted that while this early time point was selected

as the primary efficacy parameter, additional assessments of the glucose infusion rates were also performed at subsequent time points out to 24 hours to determine if the addition of protamine sulfate conferred a difference in pharmacodynamics at intermediary timepoints. Secondary objectives included a demonstration of pharmacokinetic difference (Cmax) between treatments.

b(4)

b(4)

2 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

b(4)

b(4)

DSI
An inspection was conducted of BIAsp 1086 as part of the review of these two applications and several deficiencies were identified. They have been summarized in Dr. Zawadzki's review and the DSI report submitted into DFS which included a recommendation that the results from BIAsp 1086 not be relied upon for approval. It should be noted that the approved NovoLog 70/30 was based on results from this same study; however, as NovoLog 70/30 was previously compared to Novolin 70/30 and Novolog, there is sufficient evidence to uphold that approval.

CMC
CMC has found the drug substance and drug products acceptable. However, the reviewers recommend approval pending a satisfactory evaluation of the manufacture sterility validation procedure by the Microbiology Division and a satisfactory cGMP inspection of the facilities used to manufacture the drug substance and drug product.

TRADENAMES PROPOSED
Several tradenames have been proposed for these two products. DMETS has rejected the first submission and their recommendations were relayed to company in a letter dated February 27, 2006. As these two applications will not be approved, any decision on recently proposed tradenames will be deferred until the applicant addresses the deficiencies of the applications.

RECOMMENDATION
The deficiencies noted in these two applications extend beyond what was identified by DSI inspection.

b(4)

[ ]

As stated under *Background*, combination insulin drug products contain fixed proportions of long-acting and short-acting insulins, and different dosage formulations to allow for flexibility in dosing and adjustments based on the patient's glucose profile. The decision to use one regimen over another may be based on a requirement for more or less of a short- or long-acting insulin.

b(4)

Addendum to Memo

The applicant contacted the agency several times two weeks prior to the action goal date to determine what the deficiencies were and whether they could resolve these deficiencies. A teleconference was held between the FDA (myself and Ms. Kati Johnson) and the applicant (Janet Overholt and Liz D'amato) on Monday, April 17, 2006 in which the above deficiencies were noted but the recommended action was NOT disclosed. The applicant sent an email on April 17, 2006 at 7:35 pm with 7 attachments. The crux of NovoNordisk's argument was that they had been given advice during development that PK data alone was sufficient for approval. I have reviewed these attachments and the advice has been consistently to demonstrate a difference in pharmacokinetics/pharmacodynamics not PK data alone. The only document which may have suggested that pK data alone would be acceptable was the company's meeting minutes of a tcon between Dr. Misbin and Ms. Rhee; however, in those minutes the company acknowledge Dr. Misbin stating that his advice was "unofficial" feedback and official feedback only came from the Division. In a letter signed by Dr. Orloff dated December 20, 2002 the company was told the following:

"Clinical studies are not required. However, you need to demonstrate 20% difference in pharmacokinetic/ pharmacodynamic parameters between bracketed products. Thus, NovoLog Mix 30/70 must be different from NovoLog Mix 50/50 and different from insulin aspart."

In conclusion, the additional information submitted by email provide no additional evidence supporting approval of these two combination insulin products. I maintain that these two applications receive a non-approval action.

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
4/19/2006 11:01:49 AM
MEDICAL OFFICER

Hartford, Rachel

From: Hartford, Rachel
Sent: Monday, January 28, 2008 10:26 AM
To: 'LIZD (Liz D'Amato)'
Subject: NovoLog Mix 50/50

Good Morning Liz,

Hope you had a nice weekend. I have a couple of questions and requests for you from DMETS.

1. Is NovoLog Mix 50/50 marketed in Europe?
2. If so, how long and is the same color scheme used to differentiate the products?
3. Would you provide the European labels for comparison?
4. Do you have anything to support the 50/50 color (i.e. usability studies)?

They are not asking at this point for studies to be conducted, just the information if they have been conducted.

Thanks,

Rachel

Rachel E. Hartford
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Center for Drug Evaluation and Research
Food and Drug Administration
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301-796-0331 (phone)
301-796-9712 (fax)

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

/s/

Rachel E Hartford
4/11/2008 03:33:52 PM
CSO

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	February 22, 2008
To:	Mary Parks, MD, Director Division of Metabolism and Endocrinology Products
Thru:	Kellie Taylor, PharmD, MPH, Team Leader Denise Toyer, PharmD, Deputy Director Carol Holquist, RPh, Director Division of Medication Error and Technical Support
From:	Judy Park, PharmD, Safety Evaluator Division of Medication Error and Technical Support
Subject:	Labeling Review
Drug Name(s):	NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection)
Application Type/Number:	NDA 21-810
Applicant/applicant:	NovoNordisk
OSE RCM #:	2007-2559

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EXECUTIVE SUMMARY

DMETS reviewed the container labels and carton labeling for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection) and identified several areas that contribute to medication errors.

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed pen, container label and carton labeling introduces vulnerability to confusion that could lead to medication errors. DMETS is concerned that the proposed colors for NovoLog Mix 50/50 may be confused with NovoLog Mix 70/30 which are both similar shades of blue. Additionally, we believe the proposed PenFill labels are not differentiating enough from other NovoLog products and recommend a more prominent display of the differentiating color or changing it to a more contrasting color. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

1 BACKGROUND

Insulin products have a high risk of medication error, and the risks are well-documented in the medication safety literature. When insulin is used in error it can result in permanent patient harm or death; as a result, insulin is considered a high-alert medication[1].

Although many different types of errors may occur with insulin products, confusion among insulin products is a common type of error that often is attributed to similarity in nomenclature (brand 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 in the United States and other countries, and resulted in serious patient harm or death in some cases.

Historically, the use of colors on insulin labels and packaging has been limited. In fact, all text and graphics (except the company logo) and colored bars were required by the FDA to be displayed in black on a white background. The colored bars were also required to be displayed separately from any other text or graphics. Recently, the FDA has acknowledged that the incorporation of color on insulin labels and packaging may help to reduce the risk of product selection errors, if the use of color is judiciously applied and does not impede the readability of information. As such, some manufacturers have begun to develop more colorful insulin labels. However, given the high rate of medication errors associated with insulin products and the FDA's previous position limiting the use of color, such changes involving the application of color to insulin labels have not been viewed by the Agency as "minor and editorial" and have been implemented only as the result of prior approval supplement.

1.1 INTRODUCTION

This consult was written in response to a request from the Division of Metabolism and Endocrinology Products to evaluate the container label and carton labeling to identify areas that could lead to medication errors.

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[1] Cohen, Michael. *Medication Errors.* American Pharmaceutical Association, 1999. pp 5.27 to 5.29.

1.2 REGULATORY HISTORY

DMETS previously reviewed the proposed name, labels, and labeling for NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, [rDNA origin]) in OSE Reviews #05-0164 and 06-0165, dated December 23, 2005. At that time, DMETS did not recommend the use of the proprietary name. The Applicant submitted the same proposed labels again on February 9, 2006 for review and comment but DMETS did not review them because they were found to be the identical to the ones previously reviewed (see OSE Review #0165-01). The Applicant received a Not Approvable letter on April 19, 2006 and submitted a complete response on August 31, 2006.

Subsequently, the Applicant revised the FlexPen container and carton labels for NovoLog, NovoLog Mix 70/30 and Levemir in the 2006 Annual Report without submitting a prior-approval labeling supplement. These labels are currently being marketed and the Agency was not given an opportunity prior to implementation (i.e. prior approval supplement) to review them to determine the impact the changes would have on medication errors. The Applicant subsequently submitted on December 19, 2007 and January 21, 2008 container labels and carton labeling for NovoLog Mix 50/50 in the same labeling format as the other currently marketed labels for review and comment.

1.3 PRODUCT INFORMATION

Currently, there are two NovoLog products (NovoLog and NovoLog Mix 70/30) marketed in the U.S. NovoLog (Insulin Aspart) is a faster acting insulin with a shorter duration of action than regular insulin. It is normally used together with intermediate or long acting insulin products. Because of its rapid action, Novolog is given before a meal. NovoLog Mix 70/30 is a premix containing 30% rapid-acting Novolog (insulin aspart) and a 70% modified long acting formulation (insulin aspart protamine suspension). NovoLog products are available in 10 mL vials of 100 units/mL, 3 mL PenFill cartridges for use with a pen device (i.e. NovoPen, 3 PenMate, NovoFine needles), and a prefilled pen device (FlexPen).

At present, the applicant seeks approval of a new NovoLog Mix product NovoLog Mix 50/50 which provides a therapeutic alternative with a different long-acting/short-acting insulin balance to the existing NovoLog Mix 70/30 product. NovoLog Mix 50/50 will be available in PenFill cartridges and FlexPen.

2 METHODS AND MATERIALS

This section describes the methods and materials used by DMETS medication error staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Container Label, Carton Labeling, and Insert Label Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. DMETS defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. [2]

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The container labels and carton labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to

[2] National Coordinating Council for Medication Error Reporting and Prevention. http://www.nccmerp.org/aboutMedErrors.html. Last accessed 10/11/2007.

communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.[3]

Because DMETS staff analyze reported misuse of drugs, DMETS staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. DMETS uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on December 19, 2007 and January 21, 2008 the following labels for DMETS review (see Appendices A, B, C, and D for images):

- Retail Container: FlexPen; PenFill
- Retail Carton: FlexPen; PenFill
- Sample Container: FlexPen; PenFill
- Sample Carton: FlexPen; PenFill

3 RESULTS

The proposed labels for NovoLog Mix 50/50 follow the same label format as currently marketed NovoLog and NovoLog Mix 70/30. The background of the FlexPen container labels matches the color stripe that differentiates the NovoLog products. However, the NovoLog Mix 50/50 label is similar in color to the already marketed NovoLog Mix 70/30 labels which are shades of blue (see Table 1 on page 6).

The NovoLog PenFill labels for NovoLog products have a similar appearance to one another with the white background and are only differentiated by the color stripes on the side of the label (see Table 1). The proposed label for NovoLog Mix 50/50 employs a color stripe in mild purple on the principal display panel to differentiate the product from other NovoLog products.

This format has been modified from the layout reviewed previously in OSE review #05-0164 and #05-0165. We noted the labeling recommendations from our previous review were not implemented in the proposed labels.

[3] Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

Table 1: NovoLog FlexPen and PenFill Label Comparison

	NovoLog	*NovoLog Mix 70/30*	*NovoLog Mix 50/50*
FlexPen			
PenFill			

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Additionally, the color branding used by the applicant is not consistent with the insulin color coding initiative by the International Diabetes Federation (IDF).[4] Table 2 below illustrates the difference.

Table 2: Color Difference between NovoLog Products and IDF Color Coding

	Regular Insulin	*70/30 (or 30/70) Mix*	*50/50 Mix*
NovoLog color name (Pantone color #)			
IDF color name (Pantone color #)			

b(4)

4 DISCUSSION

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors with NovoLog Mix 50/50.

DMETS is concerned the similar shade of blue for NovoLog Mix 50/50 and NovoLog Mix 70/30 may not afford adequate differentiation of the products especially since the FlexPen itself is also in the shade of blue (see Table 3 on page 7). For example, if a doctor asks which insulin a patient is using the patient may answer, "The blue one." In that case, the patient could be referring to NovoLog Mix 70/30 or NovoLog Mix 50/50 since their color stripes are similar color. The patient can even be referring to NovoLog FlexPen or Levemir FlexPen since all the FlexPens are the same color blue. However, since the differentiating color fills the entire background of the

[4] http://www.idf.org/home/index.cfm?node=1211

FlexPen container label, we believe this may help in minimizing the risk for confusion. However, DMETS does not believe that the color stripe on PenFill label affords adequate differentiation from other NovoLog products since the white background and the remainder of the labels is virtually identical for all NovoLog products. Additionally, the similarity of color stripes of NovoLog 70/30 and NovoLog 50/50 increases the potential for confusion between these products.

Table 3: NovoLog Colors

NovoLog	*NovoLog Mix 70/30*	*NovoLog Mix 50/50*	*FlexPen Color*

b(4)

Although FDA does not support the International Diabetes Federation (IDF) as a means of color coding for insulin products, DMETS recognizes that this initiative is increasingly being implemented and approval of color banding inconsistent with IDF's color coding may be a source of confusion. However, at this point, our primary concern is to ensure that the use of color on insulin labels helps to differentiate insulin products, reduces errors and not contribute to further medication errors.

5 CONCLUSIONS AND RECOMMENDATIONS

The Label and Labeling Risk Assessment findings indicate that the presentation of information and design of the proposed pen, container labels and carton labeling introduces vulnerability to confusion that could lead to medication errors. DMETS believes the risks we have identified can be addressed and mitigated prior to drug approval, and provides recommendations in Section 5.2 that aim at reducing the risk of medication errors.

5.1 COMMENTS TO THE DIVISION

Based upon our assessment of the labels and labeling, DMETS has identified areas of needed improvement. We have provided recommendations in section 5.2 and request this information be forwarded to the Applicant.

Given the high rate of medication errors with insulin products, DMETS requests that DMEP and ONDQA not allow any changes on insulin labels and packaging even though the Applicant feels they are "minor and editorial" without a prior approval supplement, including a clinical safety review to determine the impact of the changes on insulin medication errors.

DMETS would appreciate feedback on the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy DMETS on any communication to the Applicant with regard to this review. If you have further questions or need clarifications, please contact Cheryl Campbell, Project Manager, at 301-796-0723.

5.2 COMMENTS TO THE APPLICANT

Due to a high rate of medication errors with insulin products, the Agency does not deem any changes on insulin labels and packaging as "minor and editorial" since any change, especially incorporation of color, can impact the safe use of these products. Therefore, any labeling or packaging changes should be submitted as a prior approval supplement (not in an Annual Report or as CBE supplement) and undergo a clinical and safety evaluation for approval prior to being implemented.

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

5.2.1 General Comments

1. Change the color of NovoLog Mix 50/50 to a more contrasting color to differentiate from other NovoLog products (for both FlexPen and PenFill labels).
2. Increase the prominence of the differentiating color on PenFill labels to clearly distinguish from other NovoLog products.
3. DMETS recommends that the statement, "New Product Strength" appears on product labels and labeling for a period of time not to exceed six months.

5.2.2 FlexPen Container (Retail and Sample)

1. Revise the strength to include "(U-100)" [i.e. 100 units/mL (U-100)].

5.2.3 PenFill Carton (Retail and Sample)

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

6 REFERENCES

1. Adverse Events Reporting System (AERS)

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufactures that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

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___✓___ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Judy Park
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DRUG SAFETY OFFICE REVIEWER

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date: December 27, 2007

To: Mary Parks, M.D., Director
Division of Metabolic and Endocrinology Products

Thru: Jodi Duckhorn, M.A., Team Leader
Patient Labeling and Education Team
Office of Surveillance and Epidemiology
Division of Risk Management

From: Sharon R. Mills, BSN, RN, CCRP
Patient Product Information Specialist
Patient Labeling and Education Team
Office of Surveillance and Epidemiology
Division of Risk Management

Subject: DSRCS Review of Patient Labeling (Patient Package Insert and Patient Instructions for Use)

Drug Name(s): NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin))

Application Type/Number: NDA 21-810

Applicant/sponsor: Novo Nordisk

OSE RCM #: 2007-2374

1 INTRODUCTION

Novo Nordisk submitted a Complete Response on August 31, 2006 in response to an Agency Not Approvable letter issued on April 19, 2006 for their New Drug Application, NDA 21-810, NovoLog Mix 50/50 (50% insulin aspart protamine suspension and 50% insulin aspart injection, (rDNA origin)). On November 15, 2007, the sponsor submitted two revised proposed Patient Package Inserts (PPIs) including Patient Instructions for Use of this NDA, one for each presentation. The two proposed presentations are a 3 mL cartridge and a FlexPen Prefilled Syringe. The sponsor states in their cover letter dated November 15, 2007 that they have revised the patient inserts based on recommendations from the Agency dated May 6, 2007 for NovoLog Mix 70/30 (NDA 21-172).

2 MATERIAL REVIEWED

Revised proposed Professional Information (PI), and Patient Package Inserts with Patient Instructions for Use for the 3 mL. cartridge and FlexPen Penfilled Syringe submitted on November 15, 2007.

3 DISCUSSION

See the attached document for our suggested revisions to the sponsor's revised PPIs and Patient Instructions for Use. We have simplified the wording where possible and ensured that both the PPI and Patient Instructions for Use are consistent with the revised proposed PI.

Comments to the review division are ***bolded, italicized, and underlined.***

4 CONCLUSIONS AND RECOMMENDATIONS

- The sponsor stated in their cover letter that based on the recommendations received from the Agency on may 6, 2007 related to NovoLog Mix 70/30 (NDA21-172), they propose two patient inserts, one for each presentation of NovoLog Mix 50/50. The sponsor's proposal to have two PPIs is unacceptable. The Agency email to the sponsor dated May 6, 2007 clearly instructs, in the case of NovoLog Mix 70/30 that there is one FPI for all NovoLog Mix 70/30 product presentations, and, therefore; The Division of Risk Management (DRM) recommends one PPI for NovoLog Mix 50/50 which corresponds with and is consistent with the one FPI. We reiterate that there can only be one PPI for each product. However, each product presentation should have its own specific Patient Instructions for Use.
- We have separated the PPI from the Patient Instructions for Use as submitted by the sponsor. Now there is one PPI for all NovoLog Mix 50/50 products and, two separate Patient Instructions for Use for the 3 mL cartridge and the FlexPen Prefilled Syringe.
- Add instructions to the PPI for patients for what to do if they take too much NovoLog Mix 50/50 or if they forget to take a dose.
- In the NovoLog Mix 50/50 Prefilled Syringe Patient Instructions for Use:

- Label the device figure, "Figure 1."
- Under the bullet "Giving the airshot before each injection," add a specific instruction on how to dial 2 units to the first sub-bullet. Include a statement that the arrow should line up with the "2" in the dosage indicator window. Add a labeled figure showing the push button being pushed in, to the last sub-bullet.
- In the second bullet under "2. Setting the dose," Add a statement that the arrow should line up with your dose.

- In the NovoLog Mix 50/50 3 mL cartridge Patient Instructions for Use:
  - Add appropriate illustrations to show the various steps in the Patient Instructions for Use. Each illustration should be numbered and referenced appropriately.
  - The term [redacted] is not patient-friendly and should be revised throughout the document. If there are other compatible devices, they should be listed. b(4)
  - We reitierate the recommendation previously conveyed to the sponsor on May 6, 2007 in regard to NovoLog Mix 70/30, which points out that the numbering system in the Instructions for Use should be revised. It is confusing for patients to have an instruction labeled "a" and a diagram labeled "A." We have revised the diagram references to diagram 1 and diagram 2.
  - We have added "Important Notes" to the end of the Patient Instructions for Use to be consistent with the NovoLog 50/50 Prefilled Syringe Patient Instructions for Use. Review and revise the "Important Notes" as appropriate.
- We are providing marked up and clean copies of our revisions to the PPI and Patient Instructions for Use to the review division as Word documents. We recommend using the clean document as the working document.

Please let us know if you have any questions.

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✓ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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Sharon Mills
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