CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-810

CHEMISTRY REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 29-May-2008

FROM: Xavier Ysern, PhD ONDQA/ DPA I/ Review Chemist

THROUGH: Ali Al-Hakim, PhD ONDQA/ DPA I/ Branch Chief

SUBJECT: NDA 21-810 Satisfactory Completion of CMC Requirements.

TO: NDA 21-810 NovoLog® Mix 50/50 (50 % insulin aspart protamine suspension and 50 % insulin aspart injection, [rDNA origin]

Reference is made to the Chemistry Review for NDA21-810 (DFS document).

Since 2 years have elapsed from the acceptable overall recommendation given by the Office of Compliance on 28-Apr-2006, a resubmission for the evaluation of the cGMP status of the facilities involved in the manufacture of the drug substance and drug product was requested, and an acceptable overall recommendation was given by the Office of Compliance on 27-May-2008 (EER summary report is attached).

Therefore, from the CMC viewpoint, this NDA is recommended for approval under 505(b)(1).

Filename: 21-810 29_May_2008.doc

Attached:
EER Detail report dated 29-May-2008 (2 pages)

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

/s/

Xavier Ysern
5/29/2008 12:53:39 PM
CHEMIST

Ali Al-Hakim
5/30/2008 12:23:43 PM
CHEMIST

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 13-Sep-2007

FROM: Xavier Ysern, PhD ONDQA/ DPA I/ Review Chemist

THROUGH: Ali Al-Hakim, PhD ONDQA/ DPA I/ Branch Chief

SUBJECT: NDA 21-810 Satisfactory Completion of CMC Requirements.

TO: NDA 21-810 NovoLog® Mix 50/50 (50 % insulin aspart protamine suspension and 50 % insulin aspart injection, [rDNA origin]

Reference is made to Chemistry review for NDA21-810 (DFS document). The two pending issues: (1) Satisfactory evaluation of the manufacture sterility validation procedure by the Microbiology Division, and (2) Satisfactory cGMP inspection of the facilities used to manufacture the drug substance and drug product, have been satisfactorily addressed. An approval recommendation was given by Division of Microbiology (Bryan Raley's review dated 21-Dec-2006) and an acceptable overall recommendation was given by the Office of Compliance on 28-Apr-2006 (EER detail report is attached).

Therefore, from the CMC viewpoint, this NDA is recommended for approval under 505(b)(1).

Filename: 21-810 EER acceptable memo.doc

Attached:
EER Detail report dated 13-Sep-2007 (3 pages)

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 21810/000
Stamp: 22-JUN-2005
Regulatory Due: 28-FEB-2007
Applicant: NOVO NORDISK INC
100 COLLEGE RD WEST
PRINCETOWN, NJ 08540
Priority: 3S
Org Code: 510

Action Goal:
District Goal: 21-FEB-2006
Brand Name: NOVOLOG MIX 50/50
Estab. Name:
Generic Name: BIPHASIC INSULIN ASPART 50/50
Dosage Form: (INJECTION)
Strength: 100 U/ML 3ML

Application Comment: DRUG SUBSTANCE USED IN SEVERAL APPROVED DRUG PRODUCTS (on 21-NOV-2005 by X. YSERN () 301-796-2410)

FDA Contacts: ID = 108091 , Project Manager
X. YSERN 301-796-2410 , Review Chemist
S. MOORE 301-796-1718 , Team Leader

Overall Recommendation: ACCEPTABLE on 28-APR-2006by S. ADAMS (HFD-322)301-827-9051

Establishment: CFN 9610097 FEI 3002807748
NOVO NORDISK A/S
HAGEDORNSVEJ 1
GENTOFTE, , DA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER
Profile: SVS OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-AUG-2005				YSERNX
SUBMITTED TO DO	11-AUG-2005	GMP			ADAMSS
DO RECOMMENDATION	19-AUG-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	19-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9610699 FEI 3002807751
NOVO NORDISK A/S
HALLAS ALLE
KALUNDBORG, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE LABELER
FINISHED DOSAGE PACKAGER
Profile: CFN OAI Status: NONE

Estab. Comment:

DRUG SUBSTANCE USED IN SEVERAL APPROVED DRUG PRODUCTS (on 21-NOV-2005 by X. YSERN () 301-796-2410)

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	21-NOV-2005				YSERNX
SUBMITTED TO DO	21-NOV-2005	GMP			ADAMSS
ASSIGNED INSPECTION T	14-DEC-2005	GMP			ADAMSS
INSPECTION PERFORMED	21-APR-2006		21-APR-2006		ADAMSS
INSPECTION SCHEDULED	26-APR-2006		21-APR-2006		ADAMSS
DO RECOMMENDATION	28-APR-2006			ACCEPTABLE INSPECTION	ADAMSS
BASED ON REVIEW OF 483 OBSERVATIONS AND INVESTIGATOR'S RECOMMENDATION. AWAITING EIR AND FIRM'S RESPONSE.					
OC RECOMMENDATION	28-APR-2006			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9613234 FEI 3003234571
NOVO NORDISK A/S
SYDMARKEN 5
SOEBERG, , DA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER

FINISHED DOSAGE STABILITY TESTER
Profile: SVS OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-AUG-2005				YSERNX
SUBMITTED TO DO	11-AUG-2005	GMP			ADAMSS
DO RECOMMENDATION	19-AUG-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	19-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9616213 FEI 3000151819
NOVO NORDISK A/S
KROGSHOEJVEJ 49
BAGSVAERD, , DA

DMF No: AADA:
Responsibilities: FINISHED DOSAGE LABELER
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER
FINISHED DOSAGE RELEASE TESTER
FINISHED DOSAGE STABILITY TESTER

Profile: SVS OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	11-AUG-2005				YSERNX
SUBMITTED TO DO	11-AUG-2005	GMP			ADAMSS
DO RECOMMENDATION	19-AUG-2005			ACCEPTABLE BASED ON FILE REVIEW	ADAMSS
OC RECOMMENDATION	19-AUG-2005			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

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/s/

Xavier Ysern
9/13/2007 03:29:54 PM
CHEMIST

Ali Al-Hakim
9/13/2007 05:09:02 PM
CHEMIST

NovoLog® Mix 50/50
(50 % insulin aspart protamine suspension
and 50 % insulin aspart injection, [rDNA origin])
3 mL cartridge, 100 U/mL

NDA 21-810

Summary of the Basis for the Recommended Action
from Chemistry, Manufacturing, and Controls

Applicant: Novo Nordisk Inc.
100 College Road West
Princeton, New Jersey 08540

Indication: Treatment of patients with diabetes mellitus for the control of hyperglycemia.

Presentations: (1) NovoLog® Mix 50/50 Penfill® 3 mL cartridge, 100 U/mL, to be used with compatible delivery device NovoPen 3,
(2) Discardable NovoLog® Mix 50/50 FlexPen® Prefilled Syringe.

EER Status: Pending

Consults: DMETS – Pending
Tradename: NovoLog® Mix 50/50
EA –Categorical exclusion granted under 21 CFR §25.31(b)
Microbiology – Pending
Methods Validation – Revalidation by Agency not requested

Original Submission: **22-JUN-2005**

Post-Approval Agreements: None

Drug Substance

The drug substance, insulin aspart, is manufactured by:

Novo Nordisk A/S
Hallas Alle
Kalundborg, Denmark

The CMC information is referred to the approved NDA 20-986, volumes 2,3,4, and 5 pages 1-104 and subsequent CMC amendments for complete chemistry, manufacturing and controls drug substance documentation. In addition to NovoLog®, NDA 20-986,

insulin aspart is also the drug substance of approved product NovoLog® Mix 70/30, NDA 21-172.

Insulin aspart, B28-Asp-*human* Insulin, is an analog of human insulin that differs from human insulin by the substitution of a single amino acid. In insulin aspart, the amino acid proline in position B28 of the human insulin molecule has been replaced by the amino acid aspartic acid. The single substitution of the amino acid proline with aspartic acid was engineered to obtain an insulin analog with a faster onset (rapid-acting insulin) than regular insulin.

Insulin aspart is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) that has been modified for addition of a gene coding for a precursor form of insulin aspart, insulin aspart NN2000 precursor. The NN2000 precursor is folded by chemical methods, and purified by standard separation and chromatographic methods after enzymatic treatment.

Insulin aspart drug substance specifications include, Description (appearance), Identity

b(4)

; Testing and acceptance criteria are consistent with those for compendial insulin drug products. Analytical methods have been appropriately validated for their intended use of lot release and, where applicable, stability indicating.

In standard biological assays in mice and rabbits, one unit of insulin aspart has the same glucose lowering effect as one unit of regular human insulin. Biological activity of insulin aspart is: 6 nmol or 1 U.

The shelf-life for insulin aspart is 24 months when stored in HDPE containers at -30 °C to -16 °C.

Conclusion: Drug substance is satisfactory.

Drug Product

Formulation of NovoLog® Mix 50/50 and filling into 3 mL Penfill® cartridges is carried by:

Novo Nordisk A/S
Novo Allé
DK-2880 Bagsværd
Denmark

The drug product, NovoLog® Mix 50/50, is a uniform, white, sterile suspension that contains the active component insulin aspart (B28 asp regular human insulin analog) 100 Units/ml, 16 mg glycerol ; 1.50 mg phenol ; 1.72 mg

b(4)

metacresol ———, 19.6 µg zinc ———, 1.25 mg disodium hydrogen phosphate dihydrate ———, 1.17 mg sodium chloride ———, and 0.23 mg protamine sulfate ——— NovoLog® Mix 50/50 has a pH of 7.10 - 7.44. It addition it contains hydrochloric acid or sodium hydroxide added to adjust pH during manufacture. b(4) b(4)

Four different formulations of NovoLog® Mix 50/50 were used during development. These formulations have differed with respect to composition and/or method of manufacture.

——— ——— ———on ——— ———a. NovoLog® Mix 50/50 (50 % insulin aspart protamine suspension and 50 % insulin aspart injection) contains about 0.23 mg/mL of protamine sulfate.

The manufacturing process consists o——steps:——— ——— different manufacturing methods have been used during development. ——— b(4)

b(4)

Specifications for NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL, include:

b(4)

[illegible] The acceptance criteria, where applicable, are similar to those for approved insulin and other insulin analogs, and consistent with parenteral regulatory requirements.

Stability studies showed that NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL has a similar degradation behavior to that observed for approved insulin aspart drug products, in particular, NovoLog® Mix 70/30. Based on the stability studies performed with the validation batches at long term (5 °C), accelerated (25 °C) and severe (37 °C, 0 °C and - 18 °C) conditions, and supportive stability carried out with formulation 3, an 18 month shelf life period for NovoLog® Mix 50/50 Penfill 3 mL 100 U/mL when stored at 2 - 8 °C protected from light is granted. Based in the rotation stability studies, an in-use period of 14 days at temperatures not exceeding 30 °C is granted.

Conclusion:

Drug product is satisfactory.

Additional Items:

- Validation package, describing the test methods and validation procedures, including information supporting the reference standard, is adequately provided. As the analytical methods used in the testing procedures (release, stability and in-process) are well known and widely used by the biopharmaceutical industry, revalidation by Agency laboratories will not be requested

- Labeling is acceptable. NovoLog® Mix 50/50 found prone to confusion with approved trade name NovoLog® Mix 70/30. Proposed alternate trade name ——— – not acceptable. Recently proposed trade name ——— is still under consideration by DMETS. Until an agreeable new trade name is decided, NovoLog® Mix 50/50 is considered acceptable. b(4)

- Overall Compliance recommendation is still pending. Besides the Kalundborg facility, which is still pending for inspection, all other facilities have been found acceptable by the Office of Compliance. Kalundborg's responsibilities for NovoLog® Mix 50/50 are the same, that the facility has, for approved and currently marketed drug product NovoLog® Mix 70/30.

- All associated DMFs are acceptable.

Overall Conclusion

From a CMC perspective, this NDA is recommended for approval under 505(b)(1) pending the cGMP inspection and the Microbiology review.

Blair A. Fraser, Ph.D.
Chief
Branch II/ DPA I/ ONDQA

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/s/

Blair Fraser
3/28/2006 10:39:45 AM
CHEMIST

3.28.06

CHEMISTRY REVIEW

NDA 21-810

Novolog Mix 50/50

50 % insulin aspart protamine suspension and 50 % insulin aspart injection, [rDNA origin]

Novo Nordisk

Xavier Ysern, PhD
ONDQA/ DPA I/ Branch II DMEP

CHEMISTRY REVIEW

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA 21-810

2. REVIEW #: 1

3. REVIEW DATE: 23-MAR-2006

4. REVIEWER: Xavier Ysern, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents		Document Date
NDA 20-986	NovoLog® (insulin aspart [rDNA origin] injection)	07-JUN-2000 (approval date)
NDA 21-172	NovoLog® Mix 70/30 (70% insulin aspart [rDNA origin] protamine suspension and 30 % insulin aspart [rDNA origin] injection)	01-NOV-2001 (approval date)
IND 65,182	NovoLog Mix 50/50	30-AUG-2002 (Serial # 0000) b(4)

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	22-JUN-2005
Amendment(s)	05-JAN-2006 (update stability data)
	19-JAN-2006 (new proprietary tradename [redacted] b(4)
	09-FEB-2006 (labeling amendments)
	16-FEB-2006 (manufacturing sites clarification)
	13-MAR-2006 (new proprietary tradenam [redacted]

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk® Inc.
Address:	100 College Road West Princenton, New Jersey 08540
Representative:	Mary Ann McElligott, PhD Associate Vice President, Regulatory Affairs
Telephone:	609 987-5831

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Novolog® Mix 50/50
Non-Proprietary Name (USAN): 50 % insulin aspart protamine suspension and 50 % insulin aspart injection, [rDNA origin]
b) Code Name/# (ONDC only):
c) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Hypoglycemic Agent. Adjunct to diet to improve glycemic control in patients with NIDDM.

11. DOSAGE FORM: Sterile parenteral suspension

Chemistry Review Data Sheet

12. STRENGTH/POTENCY: 100 U/mL

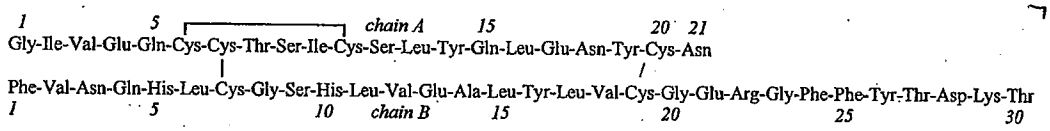
13. ROUTE OF ADMINISTRATION: Subcutaneous Injection

14. Rx/OTC DISPENSED: _x_Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM): __x__SPOTS product Form Completed

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Insulin Aspart (B28-Asp-*human* Insulin) $C_{256}H_{381}N_{65}O_{79}S_5$ MW = 5825.8



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

Cross reference to approved NDA 20-986 for DMF #s. Letters of Authorization are provided on page 1 of Form FDA 356h. Penfill® 3 mL Cartridge used in Novo Nordisk's insulin drug products approved under NDAs 20-986 and 21-172. Sufficient and adequate information provided under NDAs 20-986 and 21-172.

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	LOA Date

[1] Action codes for DMF Table: 1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF; 3 – Reviewed previously and no revision since last review; 4 – Sufficient information in application
5 – Authority to reference not granted; 6 – DMF not available; 7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-809	Novo Nordisk's NovoLog Mix 30/70 Submitted 22-JUN-2005

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--		
EES	Pending		
Pharm/Tox	--		
Biopharm	--		
ODS/ DMETS	Pending. Ongoing issues with proprietary name.		
Methods Validation	Revalidation by Agency laboratories will not be requested	23-MAR-2006	Xavier Ysern, PhD
EA	Acceptable	23-MAR-2006	Xavier Ysern, PhD
Microbiology	Pending		

Chemistry Assessment
The Chemistry Review for NDA 21-810

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application can be approved pending: (1) Satisfactory evaluation of the manufacture sterility validation procedure by the Microbiology Division, and (2) Satisfactory cGMP inspection of the facilities used to manufacture the drug substance and drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance Insulin aspart

Insulin aspart, an analog of human insulin, is the same drug substance used in two other Novo Nordisk's insulin aspart drug products; NovoLog®, described under NDA 20-986, approved on November 07, 20001, and NovoLog® Mix 70/30, NDA 21-172, approved on June 01, 2001.

Insulin aspart (NovoLog®), chemical name AspB28 insulin human, empirical formula $C_{256}H_{381}N_{65}O_{79}S_6$ and molecular weight of 5825.8 Da, is homologous with regular human insulin with the exception of a single substitution of the amino acid proline by aspartic acid in position B28.

The single substitution of the amino acid proline with aspartic acid at position B28 in insulin aspart (NovoLog®) was engineered to obtain an insulin analog with a faster onset (rapid-acting insulin) than regular insulin. The amino acid substitution was designed to reduce the molecule's tendency to form hexamers as observed with regular human insulin. NovoLog® is, therefore, more rapidly absorbed after subcutaneous injection compared to regular human insulin.

Drug substance is produced by recombinant DNA technology utilizing *Saccharomyces cerevisiae* (baker's yeast) as the production organism. The *S. cerevisiae* insulin aspart production strain, named yAKI214.6, contains the expression plasmid pAK1214.6.2D engineered for the expression of the insulin aspart NN2000 precursor.

b(4)

b(4)

Chemistry Assessment

Insulin aspart drug substance specifications include.

[redacted] b(4)

Testing and acceptance criteria are consistent with those for compendial insulin drug products. Analytical methods have been appropriately validated for their intended use of lot release and, where applicable, stability indicating.

In standard biological assays in mice and rabbits, one unit of insulin aspart has the same glucose lowering effect as one unit of regular human insulin. Biological activity of insulin aspart is: 6 nmol or 1 U.

Based on the available stability data the requested shelf-life for insulin aspart, 24 months when stored in HDPE containers at -30 °C to -16 °C, was granted.

Drug Product NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL

The drug product, NovoLog® Mix 50/50, is a uniform, white, sterile suspension that contains the active component insulin aspart (B28 asp regular human insulin analog) 100 Units/ml, 16 mg glycerol [redacted] 1.50 mg phenol [redacted] 1.72 mg metacresol [redacted], 19.6 µg zinc [redacted] 1.25 mg disodium hydrogen phosphate dihydrate [redacted], 1.17 mg sodium chloride [redacted], and 0.23 mg protamine sulfate [redacted]. NovoLog® Mix 30/70 has a pH of 7.10 - 7.44. It addition it contains hydrochloric acid or sodium hydroxide added to adjust pH during manufacture. b(4)

NovoLog® Mix 50/50 is a biphasic insulin solution which contains 50 % soluble insulin aspart. The rapid absorption characteristics of NovoLog® are maintained by NovoLog® Mix 50/50. The insulin aspart in the soluble component of NovoLog® Mix 30/70 is absorbed more rapidly from the subcutaneous layer than regular human insulin. The remaining 50 % is in crystalline form as insulin aspart protamine which has a prolonged absorption profile after subcutaneous injection.

Four different formulations of NovoLog® Mix 50/50 were used during development. These formulations have differed with respect to composition and/or method of manufacture. [redacted] b(4)

[redacted]

NovoLog® Mix 30/70 contains about [redacted] mg/mL of protamine sulfate compared to about 0.23 mg/mL in NovoLog® Mix 50/50. Approved NovoLog® Mix 70/30 (70 % insulin aspart protamine suspension and 30 % insulin aspart injection) contains about 0.33 mg/mL of protamine sulfate.

The manufacturing process consists of [redacted] different manufacturing methods have been used during development [redacted] b(4)

b(4)

NovoLog® Mix 50/50 biphasic solution primary container closure is the currently approved Penfill® 3 mL glass cartridge. The closure of the Penfill cartridge consists of a cap with a latex free laminated rubber. The laminated rubber consists of [redacted]. The cartridge contains a glass bead to facilitate the resuspension of the biphasic solution.

Specifications for NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL include [redacted]

b(4)

NovoLog® Mix 70/30, the proposed specifications are similar to approved specifications for NovoLog® Mix 70/30 3 mL cartridge, 100 U/mL. The acceptance criteria, where applicable, are similar to those for approved insulin and other insulin analogs, and consistent with parenteral regulatory requirements.

The drug product is delivered using the 3 mL Penfill® cartridge compatible device NovoPen® 3, or using the pre-filled multi-use disposable pen delivery device FlexPen® (3 mL NovoLog® Mix 30/70 FlexPen® Prefilled Syringe). The Penfill 3 mL glass cartridge is also the primary packaging for the disposable FlexPen® delivery device. These two devices, including the Penfill® 3 mL cartridge, are currently used for the delivery of approved NovoLog® and NovoLog® Mix 70/30 insulin products.

Stability studies showed that NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL has a similar degradation behavior to that observed for approved insulin aspart drug products NovoLog® and NovoLog® Mix 70/30. Based on the stability studies performed with the validation batches at long term (5 °C), accelerated (25 °C) and severe (37 °C, 0 °C and -18 °C) conditions, and supportive stability carried out with formulation 3, a 18 months shelf life period for NovoLog® Mix 30/70 Penfill 3 mL 100 U/mL when stored at 2 - 8 °C protected from light is granted. Based in the rotation stability studies, an in-use period of 14 days at temperatures not exceeding 30 °C is granted.

B. Description of How the Drug Product is Intended to be Used

NovoLog® Mix 50/50 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

NovoLog® Mix 50/50 is intended only for subcutaneous injection into the abdominal wall, thigh, or upper arm. The drug product should not be administered intravenously. As indicated in the Dosage and Administration section of the package insert, NovoLog® Mix 50/50 should be administered within 15 minutes of meal initiation up to three times daily. As other insulin products, dose regimens will vary among patients and should be determined by the health care professional familiar with the patient's metabolic needs, eating habits, and other lifestyle variables.

Drug product delivery and appropriate storage are adequately described in both package insert and patient package insert. Drug product shelf-life is 18 months at 2 - 8 °C, protected from light. In-use shelf-life period is 14 days at temperatures not exceeding 30 °C

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing of the drug substance, insulin aspart, has been provided by cross reference to applicant's approved NDAs 20-986 and 21-172. The manufacture of the drug product NovoLog® Mix 50/50 3 mL cartridge, 100 U/mL, and stability protocol are described adequately. Based on the available stability information, an 18 month expiry, stored at 2 - 8 °C, protected from light, is granted. An in-use shelf-life period is 14 days at temperatures not exceeding 30 °C was also granted.

Based in the information provided this NDA is recommended for approval under 505(b)(1) if an acceptable overall evaluation from the cGMP inspection and an acceptable recommendation for the sterile process validation procedure are received.

III. Administrative

A. Reviewer's Sign ature

B. Endorsement Block

Xavier Ysern, PhD	Review Chemist/ CDER/ ONDQA/ DPA I/ Branch II
Blair Fraser, PhD	Branch Chief/ CDER/ ONDQA/ DPA I/ Branch II

C. CC Block

30 Page(s) Withheld

✓ Trade Secret / Confidential (b4)

_____ Draft Labeling (b4)

_____ Draft Labeling (b5)

_____ Deliberative Process (b5)

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/s/

Xavier Ysern
3/27/2006 02:52:39 PM
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Blair Fraser
3/28/2006 10:32:20 AM
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Appears This Way
On Original