CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-536

CHEMISTRY REVIEW(S)

NDA 21-536

Levemir FlexPen (insulin detemir rDNA origin) Injection 100 IU/mL

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Novo Nordisk Pharmaceuticals, Inc.
Princeton, NJ

Indication: Treatment of Types 1 and 2 Diabetes

Presentations: 3 mL Penfill cartridges for use in the pen injection device
10 mL vials

EER Status: Acceptable 25-SEP-2003

Consults: DMETS – Levimir tradename not acceptable 18-MAY-2005/Division has accepted the name
Statistics – none
EA – no consult - waiver requested – granted
Micro – acceptable 11-JUL-2003
CDRH – acceptable 29-APR-2003

Levimir NDA 21-536 was submitted 05-DEC-2002.

The **drug substance** is manufactured by: Novo Nordisk A/S Hallas Alle, Kalundborg Denmark (acceptable GMPs). This insulin analog is produced by — recombinant derived yeast — — The manufacturing process and controls have been found to be adequate. The specification, including 2 unique bio-assays are acceptable. A drug substance re-test period of — is supported by real-time stability data. Note that the drug substance is light sensitive.

Conclusion
Drug substance information is acceptable.

The **drug product** manufacturer is Novo Nordisk A/S Hallas Alle, Kalundborg Denmark (acceptable GMPs). The formulation is a phosphate — solution containing mannitol, zinc — and NaCl with meta cresol and phenol — . The manufacturing process and controls have been found acceptable.

Submitted stability data support the proposed 24 month expiry at 2 - 8° C. The stability protocol is in accord with ICH recommendations. Stability testing commitments are acceptable.

Labeling is acceptable.

All associated DMFs are acceptable.

Conclusion
Drug product information is acceptable.

Overall Conclusion
From a CMC perspective an approval action is recommended.

Eric P Duffy, PhD
Director, DNDC II/ONDC

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/s/

Eric Duffy
6/15/05 02:05:40 PM
CHEMIST

Memorandum

Date: June 15, 2005

From: Dr. Stephen Moore, Chemistry Team Leader, CDER/OPS/ONDC/DNDC2/DMEDP (HFD-510)

Subject: Color Branding for NDA 21-536 Levemir (insulin detemir [rDNA origin] injection), Novo Nordisk, Inc.

To: NDA 21-536 File

Background

Novo Nordisk, Inc. has submitted carton, vial, cartridge and pen labeling with revised color branding in an amendment to NDA 21-536 for Levemir (insulin detemir [rDNA origin] injection) dated 10-JUN-2005. The amendment was submitted in response to the Agency's request (see FAX communication dated 09-JUN-2005).

Recommendation

I have reviewed the amendment dated 10-JUN-2005 providing the revised color branding for Levemir. Novo Nordisk has adopted all of the recommendations communicated by the Agency to the firm on 09-JUN-2005. The specific — color Green C has been chosen by Novo Nordisk for color branding of the labeling for Levemir. The labeling is acceptable.

{see appended electronic signature page}
Stephen Moore, Ph.D.,
Chemistry Team Leader

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/s/

Stephen Moore
6/15/05 05:24:47 PM
CHEMIST

NDA 21-536

Levemir™

Novo Nordisk Pharmaceuticals, Inc.

Janice Brown, HFD-510
Division Division of Metabolic
and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-536

2. REVIEW #: 2

3. REVIEW DATE: 08-Apr-2005

4. REVIEWER: Janice Brown, HFD-510

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	05-Dec-2002
Amendment N000C	17-Apr-2003
Amendment N000(BC)	26-Jun-2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment N000(AZ)	20-Dec-2004
Amendment N000(BC)	08-Apr-2005
Amendment N000(BC)	26-Apr-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Pharmaceuticals, Inc.
Address:	100 College Road West Princeton, NJ 08540
Representative:	Barry Reit, Ph.D., Vice President, Regulatory Affairs & Quality Assurance
Telephone:	(609) 987-5940

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Levemir (Approved by 510-Division Director)
b) Non-Proprietary Name (USAN): Insulin Detemir [rDNA origin] injection
c) Code Name/# (ONDC only): NN304, 0304
d) Chem. Type/Submission Priority (ONDC only):
   - Chem. Type: 1
   - Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Treatment of Diabetes Mellitus

11. DOSAGE FORM: Sterile parenteral solution

12. STRENGTH/POTENCY: 100U/mL

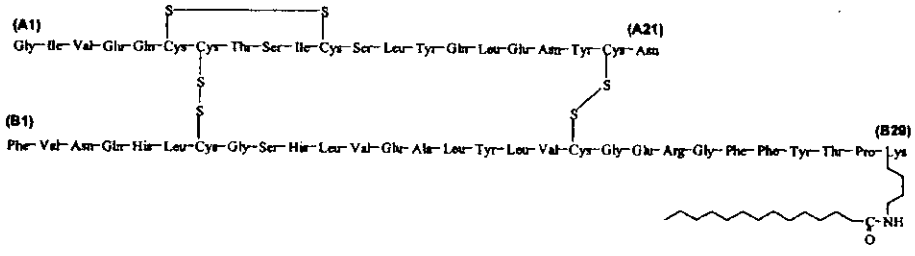
13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

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

_____Not a SPOTS product

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



The attached line represents the aliphatic C14 chain
USAN: Insulin detemir (rDNA origin)

Molecular Weight: 5916.9 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	Type III			6	Adequate	31-Jul-1998	
/	Type III			1	Adequate	14-Sept-2001	
				6	Adequate	16-Sep-2001	

[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	19-938 (Novolin R)	Referenced this application for the — — operations. Referenced this application for information on the Innolet device
NDA	20-986 (Novolog)	Referenced this application for information on the FlexPen device
IND	51,789	Insulin NN304 (insulin detemir)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Acceptable	25-Sep-2003	See attachment 3
Pharm/Tox	Acceptable	09-Mar-2005	See attachment 2
Biopharm	--	--	--
LNC	--	--	--
Methods Validation	Pending	--	--
ODS/DMETS	Acceptable	08-Aug-2003	Denise Toyer
EA	Acceptable	29-May-2003	Janice Brown
Microbiology	Approval	11-Jul-2003	Vinayak Pawar
CDRH	Acceptable	29-Apr-2003	Von Nakayama

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-536

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry standpoint, this NDA can be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – Not Applicable

II. Summary of Chemistry Assessments

This application can be Approved from a CMC viewpoint. This recommendation is based upon satisfactory response to the CMC issues listed in the 02-Oct-2003 Approvable letter.

The Office of Compliance issued an Acceptable status to Novo's manufacturing facilities (see attachment 3).

For full executive summary, see chemistry review #1.

III. Administrative

A. Reviewer's Signature

See electronic signature page

B. Endorsement Block

ChemistName/Date: J. Brown/03-May-2005
ChemistryTeamLeader: S. Moore/Date
ProjectManager: J. Rhee/Date

C. CC Block

E. Duffy, HFD-820
B. Frasier, HFD-820
HFD-510/Division File/NDA 21-536

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✓ § 552(b)(4) Trade Secret / Confidential

___ § 552(b)(5) Deliberative Process

___ § 552(b)(5) Draft Labeling

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/s/

Janice Brown
5/3/05 03:19:24 PM
CHEMIST

Stephen Moore
5/3/05 03:30:41 PM
CHEMIST

NDA 21-536
(insulin detemir injection) 100 IU

CHEMISTRY DIVISION DIRECTOR REVIEW

Applicant: Novo Nordisk Pharmaceuticals

Indication: Treatment of Diabetes mellitus

Presentations: Sterile parenteral solution containing 100IU/mL for subcutaneous injection filled and packaged in 10 mL vial or 3 mL cartridges for injection devices.

EER Status: Acceptable 9/25/2003
Consults: OPDRA (ODS/DMETS) , acceptable 8/8/2003; Microbiology, approval, 7/11/2003; EA, approval, 5/29/2003; CDRH, acceptable, 4/29/2003

is a product of insulin determir, which is an insulin analog produced by recombinant DNA technology using yeast (*Saccharomyces cerevisiae*) For production of insulin determir, the threonine in B-chain at position B30 of the human insulin molecule is eliminated and a C14 fatty acid chain is attached to the lysine at position B29 Such a modification enhances the binding of protein to albumin and as a result, prolongs the action time. The applicant intends to market the product as a long-acting insulin analog.

The drug product is filled in 10 mL vials or 3 mL glass cartridges in a clear colorless sterile parenteral solution (100 IU/mL) intended for subcutaneous injection for the treatment of diabetes mellitus. Each mL of contains 2400 nmol (14.2 mg) of insulin detemir (active). The formulation is a neutral phosphate solution with mannitol zinc and sodium chloride. The formulation is phenol and metacresol. The 3 ml PenFill cartridge will be used in either the FlexPen or InnoLet devices. The FlexPen and InnoLet devices have been reviewed by CDRH and have been found acceptable for use with the 3ml PenFill cartridge.

Drug substance and drug product are manufactured at Novo Nordisk A/S Hallas Alle, DK-4400 Kalundborg, Demark, using a

. Drug product is manufactured at Novo Nordisk A/S Novo Alle DK-2880 Bagsvaerd and assembled with the injection devices at Novo Nordisk A/S Hallas Alle DK-4400 Kalundborg , Demark.

Both sections have been reviewed and a number of deficiencies were identified. These deficiencies, however, are not considered major ones which can not be addressed by the applicant (see Chem Review #1 by Janice Brown).

It is noted that the applicant is proposing to use the *in vitro* Free Fat Cell assay (FFC assay) to determine the biological activity of insulin detemir for release testing and stability monitoring, in place of normal *in vivo* assays in mouse or rabbit normally used for biological activity determination of insulin according to the Pharmacopeias. The reason for choosing this assay method is the very low and very protracted response of insulin detemir in the two commonly used assays. To establish a correlation between the *in vitro* FFC assay and an *in vivo* mouse blood glucose assay (MBG assay), the applicant performed a study to compare two of insulin detemir secondary reference material and four clinical trial batches in the FFC assay as well as in a modified Ph.Eur. mouse blood glucose assay (MBG assay).

The re-test period for the drug substance is —
The shelf-life of the drug product is — All were supported by stability data except the in-use study for vials to support a 42-day in-use period.

Regarding consults review including EA, Microbiology, and injection devices, all are found acceptable. The original proposed tradename has been changed from Levemir to — An acceptable recommendation has been granted by the office of Compliance on 9/25/2003 for all facilities . The labeling comments related to CMC will be forwarded when the application can be approved.

Overall Conclusion:
From a chemistry perspective the application is approvable pending a satisfactory response to the CMC deficiencies.

Duu-Gong Wu, PhD
Deputy Director, DNDC II/ONDC

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/s/

Duu-gong Wu
10/1/03 03:58:53 PM
CHEMIST

NDA 21-536

Novo Nordisk Pharmaceuticals, Inc.

Janice Brown, HFD-510
Division Division of Metabolic
and Endocrine Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-536

2. REVIEW #: 1

3. REVIEW DATE: 28-May-2003

4. REVIEWER: Janice Brown, HFD-510

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original NDA	05-Dec-2002

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original NDA	05-Dec-2002
Amendment N000C	17-Apr-2003
Amendment N000(BC)	26-Jun-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Novo Nordisk Pharmaceuticals, Inc.
Address:	100 College Road West Princeton, NJ 08540
Representative:	Barry Reit, Ph.D., Vice President, Regulatory Affairs & Quality Assurance
Telephone:	(609) 987-5940

8. DRUG PRODUCT NAME/CODE/TYPE:
   Chem. Type/Submission Priority (ONDC only):
   A. Proprietary Name: —

B. Non-Proprietary Name (USAN): Insulin Detemir [rDNA origin] injection
a) Code Name/# (ONDC only): NN304, 0304
b) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 1
- Submission Priority: Standard

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

10. PHARMACOL. CATEGORY: Treatment of Diabetes Mellitus

11. DOSAGE FORM: Sterile parenteral solution

12. STRENGTH/POTENCY: 100U/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
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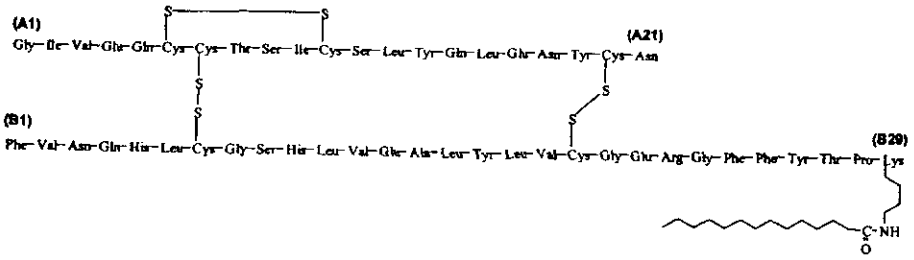

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USAN: Insulin detemir (rDNA origin)
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17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
/	Type III	/	/	6	Pending		March 29, 1996, amendment was / formulation
/	Type III	/	/	1	Adequate	14-Sept-2001	
				6	Pending		July 31, 1998, amendment was / formulation

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18. STATUS:

ONDC:

Chemistry Review Data Sheet

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	--	--	--
EES	Pending	--	--
Pharm/Tox	--	--	--
Biopharm	--	--	--
LNC	--	--	--
Methods Validation	Pending	--	--
ODS/DMETS	Acceptable	08-Aug-2003	Denise Toyer
EA	Approval	29-May-2003	Janice Brown
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CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
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Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt.
____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-536

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is APPROVABLE pending (1) submission of additional CMC information described in List of Deficiencies; and (2) Satisfactory cGMP inspection of facilities used to manufacture the drug substance and the drug product.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – Not Applicable

II. Summary of Chemistry Assessments

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

DRUG PRODUCT/DEVICES

— . (insulin detemir[rDNA origin] injection) 100U/mL is a clear colorless sterile parenteral solution intended for subcutaneous injection for the treatment of diabetes mellitus. Each mL of — . contains 2400 nmol (14.2 mg) of insulin detemir (active). The formulation is a neutral phosphate — solution with mannitol — , zinc — and sodium chloride. The formulation is — f phenol and metacresol and — —). The excipients are USP/NF grade.

There were three changes in the amount of insulin detemir (active) used in — during development. The insulin detemir concentration was increased from 600 nmol/ml (Formulation A) to 1200 nmol/ml (Formulation B) and finally to 2400 nmol/ml (Formulation C). The 600 nmol/mL formulation was developed because nonclinical studies indicated an equal molar-to-molar pharmacodynamic potency of insulin detemir vs. human insulin. However clinical trials in subjects with type 1 diabetes showed, on average, two times higher molar requirement of insulin detemir vs. insulin human to obtain the same glucose lowering effect. The 1200 nmol/ml insulin detemir formulation was subsequently developed. The most reliable estimate of the dose ratio between insulin detemir and human insulin was obtained in clinical trial no.1338 where a factor of 3.9 was obtained, corresponding to a relative efficacy of 25.6% for insulin detemir relative to human insulin. In clinical trials, the to-be-marketed 2400 nmol/mL formulation of insulin detemir was found to be equivalent to 600 nmol/mL for NPH insulin on an effect and volume basis. Thus, one unit (U) of insulin detemir (24 nmol) corresponds to one IU of human insulin (6 nmol). The 2400 nmol/mL insulin detemir formulation contains 100 U/mL.

There were three formulation changes (Formulation A, B, and C) of the excipients in the drug product during development to reduce the formation rate of — (impurity). Stability studies on the batches used for initial preclinical studies revealed relatively high formation rates of this degradation product. Excipient changes included the elimination of — and the addition of mannitol (30 mg/ml) as an — , an increase in the — phenol from — to 1.80 mg/mL and metacresol from — to 2.06 mg/ml, the — zinc from —) to —), and a decrease in the — disodium phosphate from — to 0.89 mg/ml (5 mM) which results in a pH change from — to 7.4. These formulations were all used in the clinical studies (see attachment 4 for batches used in the clinical trials).

The proposed release specifications includes —

). The proposed regulatory methods have been validated.

The drug product is filled into a 3 ml PenFill cartridge and a 10 ml vial. The 3ml PenFill is comprised of a 3mL glass cartridge, cap with rubber closure, and plunger. The 3 ml PenFill cartridge will be used in either the FlexPen or InnoLet devices. The FlexPen and InnoLet devices have been reviewed by CDRH and have been found acceptable for use with the 3ml PenFill cartridge. The PenFill will be distributed in a Marketing pack consisting of

Based on data from stability studies, the drug product in the primary container (3ml cartridge and 10ml vial) should be protected from light and is reflected in the label. The vial should be stored in the white carton (marketing pack) and the 3ml cartridges in the marketing pack (see marketing pack description above). The drug product in the 3ml cartridge in the FlexPen and InnoLet devices are stable because the devices protect the product from light. The applicant claims that the drug product is stable for 24 months when stored at 2-8°C based on — , of stability data for the 3 ml PenFill produced at pilot scale and 3 months of data for the 10 mL vial manufactured at laboratory —) and production . Based on the stability data, a — shelf life at 2-8°C is granted for the 3ml PenFill cartridge. Additional stability data manufactured at least pilot scale is required to support the vial presentation (see list of deficiencies).

The applicant has proposed a storage period of 42 days for Insulin Detemir PenFill 3 ml and 100 U/ml and Insulin Detemir 10ml, 100U/mL (vial). A rotational test at 30°C was performed on the 3ml PenFill and not for the vial presentation. Based on the results of their study the 3ml PenFill can be stored for up to 42 days at 30°C. An additional in-use study should be performed using the 10mL vial (see list of deficiencies). The applicant did not perform the rotational test at the recommended 37°C temperature because they felt it represented an excessively stressful condition. The 30°C temperature is reflected in the patient labeling for the PenFill, FlexPen and Innolet. The vial labeling states that product should be "kept as cool as possible and away from direct heat and light".

The applicant has claimed a categorical exclusion from filling an environmental assessment under 21 CFR 25.31 (b), which is also granted.

DRUG SUBSTANCE

The drug substance, insulin detemir is an analogue of human insulin. The amino acid threonine in position B30 of the human insulin molecule has been omitted and a C14 fatty acid chain has been attached to the amino acid B29. The analogue is produced using the recombinant DNA technology in Yeast (*Saccharomyces cerevisiae*) — , as the host organism — .. .n to add the 14C fatty acid chain.

The applicant explained that during development of insulin detemir, several — — were tested in animal systems with respect to albumin binding and time of action. During these investigations it turned out that the —

:The primary structure of insulin detemir was confirmed by

. The insulin detemir secondary structure was confirmed using

There were three process changes during development used to produce insulin detemir. The third process, Process C, is currently used to produce the drug substance. Process A was used for the production of the drug substance for Phase I and II clinical trials. During early development, insulin detemir was produced from a

As drug development progressed, a new method was developed using

. This process, referred to as Process C, was used for the production of the drug substance for Toxicity Testing, Phase I, Phase II and Phase III clinical trials, and is the intended commercial production process. The only difference between Process B and Process C is the rocess B has only been used for the production of primary reference material. Process B was carried out in order to

The structure of insulin detemir was elucidated by a variety of analytical and spectrophotometric techniques,

The applicant is proposing to use the *in vitro* Free Fat Cell assay (FFC assay) to determine the biological activity of insulin detemir for release testing and stability monitoring. The reason for choosing this assay method is the very low and very protracted response of insulin detemir in the *in vivo* assays in mouse or rabbit normally used for biological activity determination described in the Pharmacopeias. The applicant has not submitted comparative data on enough batches to support the routine use of the *in-vitro* FFC assay (see list of deficiencies). The modified mouse bioassay should be used to determine the bioactivity of insulin detemir.

Insulin detemir drug substance is a . It has an aqueous solubility in water at pH 7.7 more than It is pure methanol in pure ethanol The solubility is low, . in the pH range and it is lowest at pH Outside of this pH-range the solubility gradually increases to above . The pH of a 1 mg/ml aqueous solution is insulin detemir has been shown to be

There are a number of product related substances and product related impurities in insulin detemir. These are described in detail in the Drug Substance Impurity Section. The level of product related impurities are controlled by either a in-process control specifications or a drug substance specification. The applicant

has performed process validation studies demonstrating that some impurities and product related substances are reproducibly at low levels therefore, no in-process or release testing is performed.

The applicant listed — No data was presented that demonstrate — has no adverse effect on the drug substance (see list of deficiencies).

The proposed release specifications include . The impurity and degradation profiles have been investigated. Reference standards for drug substance have been developed and characterized.

Based on the stability studies on — pilot scale batches at 24 months, a re-test period of — is proposed for Insulin Detemir Drug Substance stored in — containers protected from light at the temperature range of A shelf life will replace retesting (see list of deficiencies). The drug substance is light sensitive.

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

— is supplied as 100U/ml in a 3 ml PenFill, 3 ml FlexPen, 3 ml InnoLet or a 10 mL vial. The 3ml PenFill is used with either the FlexPen or Innolet device. — . is indicated for once or twice daily subcutaneous administration for the treatment of diabetes mellitus who require basal insulin for the control of hyperglycemia.

The 3ml cartridge is stable for — at 2-8°C when stored in the marketing pack.

C. Basis for Approvability or Not-Approval Recommendation

This application is Approvable from a CMC viewpoint. This recommendation is based upon several issues identified in the review. These issues include (1) the addition of an in-vivo bioassay to test the biological activity of the drug substance; (2) add in-process controls and drug substance specifications; (3) lack of stability data to support the vial presentation; and (4) a final recommendation by the Office of Compliance is still pending.

III. Administrative

A. Reviewer's Signature

See electronic signature page

B. Endorsement Block

ChemistName/Date: J. Brown/30-May-2003
ChemistryTeamLeader: S. Moore/Date
ProjectManager: J. Rhee/Date

C. CC Block

Y. Chiu, HFD-003
E. Duffy, HFD-820

DG Wu, HFD-820
HFD-510/Division File/NDA 21-536

136 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(5) Deliberative Process

____ § 552(b)(5) Draft Labeling

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/s/

Janice Brown
9/9/03 03:24:32 PM
CHEMIST

Stephen Moore
9/9/03 04:57:36 PM
CHEMIST

NDA CMC FILEABILITY CHECKLIST

NDA Number: 21-536 **Applicant: Novo Nordisk** **Stamp Date: 9-Dec-2002**
Drug Name: Levemir (insulin detemir [rDNA origin] injection)

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	Parameter	Yes	No	Comment
1	On its face, is the section organized adequately?	X		
2	Is the section indexed and paginated adequately?	X		
3	On its face, is the section legible?	X		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full street addresses and CFNs?	X		
5	Is a statement provided that all facilities are ready for GMP inspection?	X		At the agency's request, the sponsor submitted this information on 24-Jan-2003
6	Has an environmental assessment report or categorical exclusion been provided?	X		
7	Does the section contain controls for the drug substance?	X		
8	Does the section contain controls for the drug product?	X		
9	Has stability data and analysis been provided to support the requested expiration date?	X		See summary below
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	X		
11	Have draft container labels been provided?	X		
12	Has the draft package insert been provided?	X		
13	Has an investigational formulation section been provided?	X		CTD has changed this section to Manufacturing Process Development
14	Is there a Methods Validation package?	X		
15	Is a separate microbiological section included?	X		

If the NDA is not fileable from a manufacturing and controls perspective state why it is not.

Review Chemist: Janice Brown Date: 21-Dec-2003
Team Leader: see appended signature page Date:

cc: Original NDA 21-536
HFD-510/Division File
HFD-510/JRhee
HFD-510/Orloff

Have all DMF References been identified? Yes

Stability Data Submitted:

Stage	Sponsor Requested	Stability	Data Submitted
Drug Substance	—		Pilot Scale: / Full scale –
PenFill cartridge	—	Long term	— ilot Scale: — .. @ 5°C ambient humidity Full scale – @ 5°C ambient humidity
		Accelerated	— Pilot Scale: — @ —
		Stress	— Pilot Scale: — @ —
10 mL vial	—	Long term	— Laboratory Scale — @ 5°C ambient humidity — Laboratory Scale — @ 5°C ambient humidity — Pilot – COA (release testing) — Full scale / — @ 5°C ambient humidity
		Accelerated	— Laboratory Scale — — aboratory Scale — — Full scale —): —
		Stress	— Laboratory Scale — — Laboratory Scale — idity — Full scale (—

Presentations:
PenFill 3 mL cartridge
10 mL vial
FlexPen containing PenFill 3 mL cartridge
InnoLet containing PenFill 3 mL cartridge

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

/s/

Janice Brown
1/30/03 03:12:32 PM
CHEMIST

Stephen Moore
1/30/03 05:20:59 PM
CHEMIST

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

Application : NDA 21536/000
Org Code : 510
Priority : 1S

Sponsor: NOVO NORDISK INC
100 COLLEGE RD WEST
PRINCETOWN, NJ 08540

Stamp Date : 05-DEC-2002
PDUFA Date : 20-JUN-2005
Action Goal :
District Goal: 06-AUG-2003

Brand Name : INSULIN DETEMIR 100 U/ML INJECTION
Estab. Name:
Generic Name: INSULIN DETEMIR 100 U/ML INJECTION
Dosage Form: (INJECTION)
Strength : 100U/ML

FDA Contacts:			
	H. RHEE	Project Manager (HFD-510)	301-827-6424
	J. BROWN	Review Chemist (HFD-510)	301-827-6421
	S. MOORE	Team Leader (HFD-510)	301-827-6401

Overall Recommendation: ACCEPTABLE on 25-SEP-2003by S. ADAMS (HFD-322) 301-827-9051

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

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Profile : CTL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-APR-03
Decision : ACCEPTABLE
Reason : DISTRICT RECOMMENDATION

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

DMF No: AADA:

esponsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE LABELER

Profile :	CBI	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	22-SEP-03		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		
Profile :	SVS	OAI Status:	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	25-SEP-03		
Decision :	ACCEPTABLE		
Reason :	DISTRICT RECOMMENDATION		

Establishment : CFN : 9610700 FEI :

NOVO NORDISK A/S

NORDRE FASANVEJ 215

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

COPENHAGEN DK-2200, , DA

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 22-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9613234 FEI :

NOVO NORDISK A/S

SYDMARKEN 5

SOEBERG, , DA DK 2860

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER

FINISHED DOSAGE OTHER TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9613244 FEI : 3003131673

NOVO NORDISK A/S

BERNNUM PARK, DK-3400

HILLEROED, , DA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 25-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : 9616213 FEI : 3001392218

NOVO NORDISK A/S

BAGSVAERD, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

ESTABLISHMENT EVALUATION REQUEST

SUMMARY REPORT

rofile : SVS OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 17-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

Establishment : CFN : FEI :

NOVO NORDISK A/S

NORDRE FASANVEJ 215 (FUGLEBAKKEN)

FREDERIKSBERG, , DA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile : CTL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

lestone Date: 25-SEP-03

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application:	NDA 21536/000	Action Goal:	
Stamp:	05-DEC-2002	District Goal:	06-AUG-2003
Regulatory Due:	05-OCT-2003	Brand Name:	INSULIN DETEMIR 100 U/ML
Applicant:	NOVO NORDISK PHARMACEUTICALS I	Estab. Name:	INJECTION
	100 COLLEGE RD WEST	Generic Name:	INSULIN DETEMIR 100 U/ML
	PRINCETON, NJ 08540		INJECTION
Priority:	1S	Dosage Form:	(INJECTION)
Org Code:	510	Strength:	100U/ML

Application Comment: QUALITY CONTROL TESTING OF THE DRUG PRODUCT AND RAW MATERIALS (on 29-JAN-2003 by J. BROWN (HFM-71) 301-827-1296)

FDA Contacts:	H. RHEE	(HFD-510)	301-827-6424	, Project Manager
	J. BROWN	(HFD-510)	301-827-6421	, Review Chemist
	S. MOORE	(HFD-510)	301-827-6401	, Team Leader

Overall Recommendation: ACCEPTABLE on 25-SEP-2003by S. ADAMS (HFD-322)301-827-9051

Establishment: CFN 9610097 FEI 3002807748

NOVO NORDISK A/S

GENTOFTE, , DA

MF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Profile: CTL OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
ITED TO DO	13-JAN-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	GMP			DAMBROGIOJ
INSPECTION SCHEDULED	04-FEB-2003		27-FEB-2003		IRIVERA
INSPECTION PERFORMED	27-FEB-2003		27-FEB-2003		IRIVERA
INSPECTION PERFORMED	27-FEB-2003		27-FEB-2003		DAMBROGIOJ

INSPECTION SCHEDULED	25-MAR-2003	27-MAR-2003		DAMBROGIOJ
DO RECOMMENDATION	23-APR-2003		ACCEPTABLE	ADAMSS
			INSPECTION	
[illegible]RECOMMENDATION	23-APR-2003		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

Establishment: CFN 9610699 FEI 3002807751

NOVO NORDISK A/S
HALLAS ALLE
KALUNDBORG, , DK

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER

FINISHED DOSAGE LABELER

Appears This Way
On Original

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Profile: CBI OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO DO	13-JAN-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	PS			DAMBROGIOJ
INSPECTION SCHEDULED	26-MAR-2003		09-MAY-2003		DAMBROGIOJ
INSPECTION PERFORMED	09-MAY-2003		09-MAY-2003		DAMBROGIOJ

The inspection of this API manufacturer was made in response to a pre-approval request from HFD-322 for the manufacturing and related testing of the Insulin Detemir API and the finished Insulin Detemir final dosage form. The NDA number for Insulin Detemir is 21-536.

The following Danish Novo Nordisk facilities were inspected during this inspection for [redacted] operations that relate to Insulin Detemir:

1. Kalundborg (FEI #3002807751) - The manufacturing of the API; Assembly, Labeling and Packaging of Insulin Detemir InnoLet; and Labeling and Packaging of Insulin Detemir 10ml, 100 U/ml vials and Insulin Detemir PenFill 3 ml, 100U/ml cartridges
2. Bagsvaerd (FEI #3000151819) - Formulation; Filling and Inspection of Insulin Detemir 10 ml, 100 U/ml vials and Insulin Detemir PenFill 3ml, 100 U/ml cartridges; Labeling and Packaging of Insulin Detemir 10ml, 100 U/ml and Insulin Detemir PenFill 3 ml, 100 U/ml; Labeling and packaging of PenFill blister packs
3. Soeborg (FEI #3003234571) - DBP Chemistry Laboratory performing chemical testing of the drug substance.
4. Gentofte (FEI #3002807748) - Laboratory performing [redacted] testing for [redacted] of the drug substance and the finished product.
5. Copenhagen - Fuglebakken (FEI #10841) - Insulin Chemical Control performs chemical testing for finished product.

The previous inspection of this firm, on 12/6-10/99, was classified as "NAI" and was a follow-up to a violative inspection conducted on 6/14-7/2/99.

During this current inspection, an FDA-483 was issued for the following observations: 1) [redacted] validation of [redacted] was approved even though not all test results met the validation acceptance criteria; 2) extensive [redacted] for Insulin Detemir,

batch #MK0DHP006; and 3) computerized batch production records do not always accurately reflect production information.

There were no objection conditions notes at the other sites inspected.

RECOMMENDATION	22-SEP-2003		ACCEPTABLE	ADAMSS
			INSPECTION	
OC RECOMMENDATION	22-SEP-2003		ACCEPTABLE	ADAMSS
			DISTRICT RECOMMENDATION	

Profile: SVS [redacted] OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO OC	09-JAN-2003				BROWNJA

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

SUBMITTED TO DO	13-JAN-2003	PS		DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	PS		DAMBROGIOJ
INSPECTION SCHEDULED	26-MAR-2003	09-MAY-2003		DAMBROGIOJ
OC RECOMMENDATION	26-MAR-2003		ACCEPTABLE BASED ON PROFILE	ADAMSS
INSPECTION PERFORMED	09-MAY-2003	09-MAY-2003		DAMBROGIOJ

The inspection of this API manufacturer was made in response to a pre-approval request from HFD-322 for the manufacturing and related testing of the Insulin Detemir API and the finished Insulin Detemir final dosage form. The NDA number for Insulin Detemir is 21-536.

following Danish Novo Nordisk facilities were inspected during this inspection for operations that relate to Insulin Detemir:

1. Kalundborg (FEI #3002807751) - The manufacturing of the API; Assembly, Labeling and Packaging of Insulin Detemir InnoLet; and Labeling and Packaging of Insulin Detemir 10ml, 100 U/ml vials and Insulin Detemir PenFill 3 ml, 100U/ml cartridges
2. Bagsvaerd (FEI #3000151819) - Formulation; Filling and Inspection of Insulin Detemir 10 ml, 100 U/ml vials and Insulin Detemir PenFill 3ml, 100 U/ml cartridges; Labeling and Packaging of Insulin Detemir 10ml, 100 U/ml and Insulin Detemir PenFill 3 ml, 100 U/ml; Labeling and packaging of PenFill blister packs
3. Soeborg (FEI #3003234571) - DBP Chemistry Laboratory performing chemical testing of the drug substance.
4. Gentofte (FEI #3002807748) - Laboratory performing — testing for — the release of the drug substance and the finished product.
5. Copenhagen - Fuglebakken (FEI #10841) - Insulin Chemical Control performs chemical testing for finished product.

revious inspection of this firm, on 12/6-10/99, was classified as "NAI" and was a follow-up to a violative inspection conducted on 6/14-7/2/99.

During this current inspection, an FDA-483 was issued for the following observations: 1) — validation of — was approved even though not all test results met

the validation acceptance criteria; 2) extensive — for Insulin Detemir, batch #MK0DHP006; and 3) computerized batch production records do not always accurately reflect production information.

, were no objection conditions notes at the other sites inspected.

DO RECOMMENDATION	25-SEP-2003	ACCEPTABLE	ADAMSS
		INSPECTION	
OC RECOMMENDATION	25-SEP-2003	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

Establishment: CFN 9610700 FEI

NOVO NORDISK A/S

NORDRE FASANVEJ 215

COPENHAGEN DK-2200, , DA

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DMF No: AADA:

Responsibilities: INTERMEDIATE OTHER TESTER

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO DO	13-JAN-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	GMP			DAMBROGIOJ
INSPECTION PERFORMED	09-MAY-2003		09-MAY-2003		ADAMSS
INSPECTION SCHEDULED	26-AUG-2003		09-MAY-2003		IRIVERA
DO RECOMMENDATION	22-SEP-2003			ACCEPTABLE INSPECTION	ADAMSS
ECOMMENDATION	22-SEP-2003			ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS

Establishment: CFN 9613234 FEI

NOVO NORDISK A/S
SYDMARKEN 5
SOEBERG, , DA DK 2860

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE LABELER

FINISHED DOSAGE OTHER TESTER

Profile: CTL OAI Status: NONE

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
ITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO DO	13-JAN-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	GMP			DAMBROGIOJ
INSPECTION PERFORMED	09-MAY-2003		09-MAY-2003		ADAMSS
INSPECTION SCHEDULED	26-AUG-2003		09-MAY-2003		IRIVERA

DO RECOMMENDATION	25-SEP-2003	ACCEPTABLE	ADAMSS
		INSPECTION	
OC RECOMMENDATION	25-SEP-2003	ACCEPTABLE	ADAMSS
		DISTRICT RECOMMENDATION	

Establishment: CFN 9613244 FEI 3003131673

NOVO NORDISK A/S

BERNNUM PARK, DK-3400

HILLEROED, , DA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE PACKAGER

Profile: SVS OAI Status: NONE

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO DO	13-JAN-2003	GMP			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	GMP			DAMBROGIOJ
DO RECOMMENDATION	25-SEP-2003			ACCEPTABLE	ADAMSS
				BASED ON FILE REVIEW	
BASED ON AC GMP EI 6/2003					
OC RECOMMENDATION	25-SEP-2003			ACCEPTABLE	ADAMSS
				DISTRICT RECOMMENDATION	

Establishment: CFN 9616213 FEI 3001392218

NOVO NORDISK A/S

BAGSVAERD, , DA

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE OTHER TESTER

FINISHED DOSAGE LABELER

FINISHED DOSAGE MANUFACTURER

Profile: SVS OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	09-JAN-2003				BROWNJA
SUBMITTED TO DO	13-JAN-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	22-JAN-2003	GMP			DAMBROGIOJ
INSPECTION PERFORMED	09-MAY-2003		09-MAY-2003		ADAMSS
INSPECTION SCHEDULED	26-AUG-2003		09-MAY-2003		IRIVERA
DO RECOMMENDATION	17-SEP-2003			ACCEPTABLE	ADAMSS
				INSPECTION	
OC RECOMMENDATION	17-SEP-2003			ACCEPTABLE	DAMBROGIOJ
				DISTRICT RECOMMENDATION	

Establishment: CFN FEI

NOVO NORDISK A/S
NORDRE FASANVEJ 215 (FUGLEBAKKEN)
FREDERIKSBERG, , DA

DMF No: AADA:

Responsibilities: FINISHED DOSAGE RELEASE TESTER

Profile: CTL OAI Status: NONE

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	30-JAN-2003				BROWNJA
SUBMITTED TO DO	03-FEB-2003	PS			DAMBROGIOJ
ASSIGNED INSPECTION T	05-FEB-2003	PS			DAMBROGIOJ

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

DO RECOMMENDATION	25-SEP-2003	ACCEPTABLE BASED ON FILE REVIEW	ADAMSS

FIRM WILL BE MERGED WITH 9610700 SINCE THIS IS THE SAME FACILITY. RECEIVED AN ACCEPTABLE EI 5/2003.

OC RECOMMENDATION	25-SEP-2003	ACCEPTABLE DISTRICT RECOMMENDATION	ADAMSS
