CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-406

CHEMISTRY REVIEW(S)

Chemistry Review Data Sheet

NDA 21-406

Fortical®
calcitonin-salmon (rDNA origin)
Nasal Spray

Unigene Laboratories, Inc.

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

1. NDA 21-406

2. REVIEW #: #2

3. REVIEW DATE: Feb-04-2005

4. REVIEWER: Yvonne Yang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
CMC Review #1	Dec-24-2003 in DFS

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Volumes 1.1-1.9, 1.9A, 1.9B	Mar-05-2003
Amendment (Comparability protocol)	Sept-18-2003
Amendment (Comparability protocol-resubmitted)	Oct-03-2003
Amendment (Change in Release Specifications for Drug Product-Particulate Matter)	Dec-12-2003
Amendment (Nov-20-2003 Meeting Minutes)	Dec-16-2003
Amendment (Complete Response)	Sept-15-2004
Amendment (Revised Specifications for Drug Substance)	Feb-07-2005

7. NAME & ADDRESS OF APPLICANT:

Name:	Unigene Laboratories, Inc.
Address:	110 Little Falls Road, Fairfield, NJ 07004
Representative:	Heike Maaser, Ph.D.
Telephone:	(973) 331-9650, Ext. 252

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Fortical® Nasal Spray
b) Non-Proprietary Name (USAN): Salmon calcitonin
c) Code Name/# (ONDC only): CAS-47931-85-1
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 3
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY:

Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: Spray, Metered

12. STRENGTH/POTENCY: 200 IU/actuation (2,200 IU/ml)

13. ROUTE OF ADMINISTRATION: Intranasal

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:

Recombinant salmon calcitonin (rsCT)
$C_{145}H_{240}N_{44}O_{48}S_2$ (MW [redacted])
See also Chemist's Review Notes

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
14426	III	Unigene Laboratories, Inc.	**Drug Substance**	1	**Adequate**	**Jan-31-2005**	Reviewed by Yvonne Yang
13966	III	Unigene Laboratories, Inc.	α-Amidating enzyme (α-AE)	1	Adequate	Dec-22-2003	Reviewed by Yvonne Yang
[redacted]	III			3	Adequate	Apr-12-2000	Reviewed by Milton Sloan
	III			1	Adequate (for nasal spray)	Dec-22-2003	Reviewed by Arthur Shaw
	III			1	Adequate	Dec-22-2003	Reviewed by Elsbeth Chikhale
	III			1	Adequate	Nov-17-2003	Reviewed by Elsbeth Chikhale

[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
IND	59,664	Fortical® Nasal Spray

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES	**Acceptable**	**Sept-30-2004**	Yvonne Yang
Pharm/Tox	Approval	Dec-04-2003	Gemma Kuijpers
Biopharm	Approval	Dec-17-2003 (sign off date)	Wei Qiu Jaya Vaidyanathan
Methods Validation	Pending Suitable for release and stability studies	Dec-24-2003 (sign off date)	Yvonne Yang
ODS/DMETS	DMETS has no objection to the use of the proposed proprietary name Fortical	May-09-2003 Dec-18-2003	Jinhee L. Jahng Alina R. Mahmud
EA	Categorical exclusion granted	Dec-24-2003 (sign off date)	Yvonne Yang
Microbiology	**Approval**	**Nov-09-2004**	David Hussong

19. ORDER OF REVIEW N/A

The Chemistry Review for NDA 21-406

The Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability

NDA 21-406 is recommended for **Approval** from the standpoint of chemistry, manufacturing and controls.

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

N/A

II. Summary of Chemistry Assessments:

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

Drug Product:

Fortical® Nasal Spray is a non-sterile aqueous solution containing calcitonin-salmon (rDNA origin) intended for intranasal administration for the treatment of postmenopausal osteoporosis. Each carton of the drug product contains one 3.5 ml fill bottle and one nasal spray applicator (pump). The nasal spray pump is attached to the 3.5 ml fill bottle before first use. Fortical® Nasal Spray contains 2,200 IU/ml calcitonin-salmon (rDNA origin), sodium chloride ——, citric acid, ——————, phenylethyl alcohol ——, benzyl alcohol ——, polysorbate 80 ——), hydrochloric acid or sodium hydroxide (added as necessary to adjust pH), and purified water. Each spray of the drug product dispenses 0.09 ml of Fortical® Nasal Spray containing 200 IU (per dose) of calcitonin-salmon (rDNA origin). Each bottle of Fortical® Nasal Spray is intended to deliver at least — doses. **The proposed expiry for Fortical® Nasal Spray is 24 months (Storage at 2-8 °C, Prevent from freezing). A 24 month expiration date is recommended based on the submitted stability data.** The potency (biological activity) of Fortical® Nasal Spray is expressed in International Units (IU) based on the *in vivo* rat hypocalcemia assay in comparison with the current International Standard for calcitonin-salmon, distributed by the National Institute for Biologic Standards and Control, potters Bar, United Kingdom.

Drug Substance:

The drug substance recombinant salmon calcitonin is synthesized in genetically engineered E. coli in which the gene encoding for salmon calcitonin was introduced

through recombinant DNA technology. The primary amino acid sequence of recombinant salmon calcitonin is identical to that of salmon calcitonin from natural sources. Salmon calcitonin is the official name used by United States Adopted Name (USAN) for salmon calcitonin manufactured by either recombinant DNA technology or by chemical synthesis. Calcitonin (salmon) or calcitonin-salmon is the official name used by International Non-Proprietary Name (INN) for salmon calcitonin manufactured by either recombinant DNA technology or by chemical synthesis. Salmon calcitonin is a single chain non-glycosylated polypeptide containing 32 amino acids with a molecular mass of

All information with respect to the chemistry and manufacturing controls (CMC) of recombinant salmon calciton is provided in two Drug Master Files: DMF provides the CMC information for rsCT, and DMF provides for the CMC information for α-AE. Both DMFs have been reviewed and found adequate to support this NDA. The proposed interim expiration date for the bulk drug substance is (storage at -20°C).

An *in vitro* cell-based bioassay is developed by the sponsor to establish the biological activity of recombinant salmon calciton at the release of the drug substance and at the end of shelf life of the drug product (DMF).

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

Fortical® Nasal Spray is intended to be used for the treatment of postmenopausal osteoporosis. The recommended dose is one spray [200 IU of calcitonin-salmon (rDNA origin)] per day administered intranasally, alternating nostrils daily. Each carton of the drug product contains one 3.5 ml fill bottle and one nasal spray applicator (pump). Unopened bottles of Fortical® Nasal Spray should be stored in the refrigerator between 2-8 °C (36-46 °F). The nasal spray pump is attached to the 3.5 ml fill bottle before first use. The bottle in use with pump attached should be stored at 20-25 °C (68-77 °F) in an upright position at all times. Each new nasal spray pump must be primed properly before first use to ensure the delivery of a correct dose. After the new pump is primed, it is not necessary to re-prime it before each use, if the bottle in use is kept in an upright position. Each bottle of Fortical® Nasal Spray is intended to deliver at least doses. Fortical® Nasal Spray, bottle with pump attached, should be discarded 30 days after first use. Failure to keep the bottle in use in an upright position may result in the delivery of an incomplete dose. Unnecessary re-priming before use may result in the insufficient delivery of doses.

Fortical® Nasal Spray has not been shown to be bioequivalent to the marketed product Miacalcin® Nasal Spray. The two products are not interchangeable.

C. Basis for Approvability or Not-Approval Recommendation

The sponsor has provided a satisfactory response to all of the deficiencies delineated in the Draft List of Deficiencies and Information Request:

- Revised specifications for drug substance to include bioassay,
- A satisfactory response to the CMC comments in the Approvable letter dated Jan-31-2003 and Information Request (IR) under the cross-referenced DMFs,
- An overall Acceptable cGMP status by the Office of Compliance.

III. Administrative:

A. Reviewer's Signature in DFS

B. Endorsement Block: in DFS

C. CC Block: in DFS

15 Page(s) Withheld

8 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Withheld Track Number: Chemistry-_____

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/s/

Yvonne Yang
2/9/05 03:36:12 PM
CHEMIST

Mamta Gautam-Basak
2/11/05 10:31:19 AM
CHEMIST
Concur, recommended for approval from CMC standpoint

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/s/

Yvonne Yang
8/5/04 01:42:18 PM
CHEMIST

Mamta Gautam-Basak
8/5/04 02:04:06 PM
CHEMIST
Concur

MEMORANDUM

Date: June 02, 2004

To: NDA 21-406 Fortical® Calcitonin-salmon (rDNA-origin) Nasal Spray

From: Yvonne Yang, Ph.D., Chemist Reviewer, HFD-820

Subject: Unigene's proposal to characterize human immunogenecity profile (amendment dated Apr-26-2004)

In response to the Agency's request in the action letter dated Dec-31-2003 and during the teleconference on Feb-18-2004, Unigene submitted amendment dated Apr-26-2004 providing for a comprehensive draft protocol discussing the studies the company is planning to conduct to characterize the human immunogenecity profile for Fortical® Nasal Spray. An abbreviated proposal was submitted previously in amendment dated Jan-21-2004, and a comprehensive protocol with additional information is submitted in this amendment and reviewed.

The imunogenecity profile of patients after 24 weeks of treatment with Fortical® or Miacalcin Nasal Spray will be evaluated using the two assays: (1) a direct ELISA will first be used to identify patients with circulating antibodies to rsCT, and (2) an in vitro bioassay will be used to determine if those circulating antibodies are capable of neutrializing the bioactivity of sCT. The information provided in this amendment is summarized in the following three tables.

Assay	Samples	Function
Direct ELISA	• Sera samples from UGL-9904: 134 postmenopausal patients after 24 weeks of treatment with Fortical® or Miacalcin (0 time vs. 6-month time point)	[redacted]
In vitro bioassay using CHO K1 cells	• Sera with a positive anti-sCT response and a signal to noise ratio of ≥ 2 (relative responses between 6-month and 0-time)	

Direct ELISA for the detection of positive antibodies to rsCT	
Reagents	• [redacted]
Assay procedures (Attachment 1 & Attachment 2)	[redacted]

Assay Validation
(Attachment 3)

Assay cut point

Forty normal human serum samples (38 females and 2 males), at a dilution of 1:50, were analyzed, and the assessment of assay variability and the establishment of assay cut point determined in three independent runs by two operators (pp. 12, 17-19):

- Mean signal/noise ratio was 1.0, no sample has a signal/noise ratio of greater than 1.2. Mean OD for NSB (non-specific background) was established to be 0.115, and an upper 95% confidence limit above the mean NSB was calculated to be 0.123
- A negative control is incorporated in every assay (to adjust for inter-assay variability) and a normalization factor is derived from the difference in OD between the negative control and the 95% limit. Assay cut point for each assay is established by adding or subtracting the normalization factor from the OD of the negative control, and the upper 95% limit used as the cut point for the assay.

In vitro Bioassay for the detection of neutralizing antibodies to rsCT (a proposal)	
Reagents (Attachment 1, pp. 7-8)	
Assay procedures (Attachment 1, pp. 7-8)	
Assay Validation	• Not yet validated • The assay will be validated using the following parameters: - Repeatability, precision and recovery - Sensitivity, or LOQ (lower limit of quantitation) - Determination of the presence of neutralizing antibodies

Information for the development, procedure, and validation of the direct ELISA for rsCT is provided in this amendment for review. The proposed direct ELISA for rsCT is adequate to proceed.

The in vitro bioassay obviously is still under development, only limited information is provided in this amendment for review.

Recommendation:

1. Proceed with the plan for the determination of human immunogenecity profile.
2. Please provide information for in vitro bioassay for review.

Cc: NDA 21-406
HFD-510/Division file
HFD-510/Y Yang/M Gautam-Basak
HFD-510/R Hedin

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/s/

Yvonne Yang
6/15/04 07:37:23 AM
CHEMIST

Mamta Gautam-Basak
6/15/04 08:43:22 AM
CHEMIST
Concur

MEMORANDUM

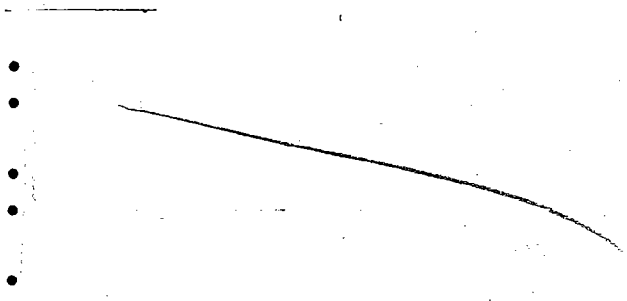
Date: February 10, 2004

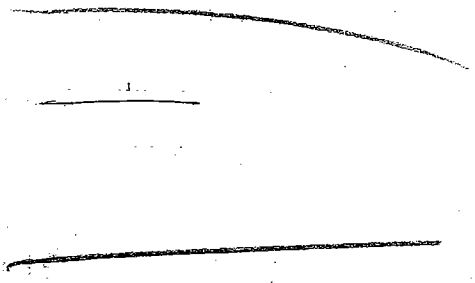
To: NDA 21-406

From: Yvonne Yang, Ph.D., Chemist Reviewer, HFD-820

Subject: Unigene's Proposal to Characterize Human Immunogenecity Profile

As requested in the Agency's action letter dated Dec-31-2003, Unigene submitted, on Jan-21-2004, a proposal describing their plan to characterize the human immunogenecity profile of Fortical Nasal Spray.





Evaluation:

1. The proposed assay is designed for the detection of antibodies against rsCT in patient sera. The conceptual proposal of the method appears to be reasonable.

2. It is premature to comment on the adequacy of the assay in the absence of any preliminary data.

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/s/

Yvonne Yang
2/11/04 02:46:33 PM
CHEMIST

Duu-gong Wu
2/20/04 05:58:08 PM
CHEMIST

NDA 21-406

Fortical®
calcitonin-salmon (rDNA origin)
Nasal Spray

Unigene Laboratories, Inc.

Yvonne Yang, Ph.D.

Division of Metabolic and Endocrine Drug Products
HFD-510

Table of Contents

Chemistry Review Data Sheet

Chemistry Review Data Sheet

1. NDA 21-406

2. REVIEW #: #1

3. REVIEW DATE: Dec-17-2003

4. REVIEWER: Yvonne Yang

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original Volumes 1.1-1.9, 1.9A, 1.9B	Mar-05-2003
Amendment (Comparability protocol)	Sept-18-2003
Amendment (Comparability protocol-resubmitted)	Oct-03-2003
Amendment (Change in Release Specifications for Drug Product-Particulate Matter)	Dec-12-2003
Amendment (Nov-20-2003 Meeting Minutes)	Dec-16-2003

7. NAME & ADDRESS OF APPLICANT:

Name: Unigene Laboratories, Inc.
Address: 110 Little Falls Road, Fairfield, NJ 07004
Representative: Heike Maaser, Ph.D.
Telephone: (973) 331-9650, Ext. 252

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Fortical® Nasal Spray
b) Non-Proprietary Name (USAN): Salmon calcitonin
c) Code Name/# (ONDC only): CAS-47931-85-1
d) Chem. Type/Submission Priority (ONDC only):
- Chem. Type: 3
- Submission Priority: S

Chemistry Review Data Sheet

9. LEGAL BASIS FOR SUBMISSION:

This NDA is submitted as a 505(b)(2) application.

10. PHARMACOL. CATEGORY:

Bone/calcium-phosphorous metabolism

11. DOSAGE FORM: Spray, Metered

12. STRENGTH/POTENCY: 200 IU/actuation (2,200 IU/ml)

13. ROUTE OF ADMINISTRATION: Intranasal

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:

Recombinant salmon calcitonin (rsCT)
$C_{145}H_{240}N_{44}O_{48}S_2$ (MW = [redacted])
See also Chemist's Review Notes

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF	Type	Holder	Item Referenced	Code[1]	Status[2]	Date Review Completed	Comments
14426	III	Unigene Laboratories, Inc.	Drug Substance	1	Inadequate	Dec-16-2003	Reviewed by Yvonne Yang
13396	III	Unigene Laboratories, Inc.	α-Amdiating enzyme (α-AE)	1	Adequate	Dec-22-2003	Reviewed by Yvonne Yang
[redacted]	III	[redacted]	[redacted]	3	Adequate	Apr-12-2000	Reviewed by Milton Sloan
[redacted]	III	[redacted]	[redacted]	1	Adequate (for nasal spray)	Dec-22-2003	Reviewed by Arthur Shaw
[redacted]	III	[redacted]	[redacted]	1	Adequate	Dec-22-2003	Reviewed by Elsbeth Chikhale
[redacted]	III	[redacted]	[redacted]	1	Adequate	Nov-17-2003	Reviewed by Elsbeth Chikhale

[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
IND	59,664	Fortical® Nasal Spray

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES		Pending	Yvonne Yang
Pharm/Tox	Approval	Dec-04-2003	Gemma Kuijpers
Biopharm	Approval	Dec-17-2003 (sign off date)	Wei Qiu Jaya Vaidyanathan
Methods Validation		Pending	Yvonne Yang
ODS/DMETS	DMETS has no objection to the use of the proposed proprietary name Fortical	May-09-2003 Dec-18-2003	Jinhee L. Jahng Alina R. Mahmud
EA	Categorical exclusion granted		Yvonne Yang
Microbiology	Approvable	Nov-18-2003	David Hussong

19. ORDER OF REVIEW

N/A

The Chemistry Review for NDA 21-406

The Executive Summary

I. Recommendations:

A. Recommendation and Conclusion on Approvability

NDA 21-406 is recommended for **Approvable** from the standpoint of chemistry, manufacturing and controls pending (1) a satisfactory response to the deficiencies delineated in the Draft List of Deficiencies and Information Request (in the CMC reviews for NDA 21-406, DMF —— and DMF ——), and (2) an overall acceptable cGMP recommendation from the Office of Compliance that was delayed due to a change in a testing facility submitted by the applicant one month before the due date.

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

N/A

II. Summary of Chemistry Assessments:

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

Drug Product:

Fortical® Nasal Spray is a non-sterile aqueous solution containing calcitonin-salmon (rDNA origin) intended for intranasal administration for the treatment of postmenopausal osteoporosis. Each carton of the drug product contains one 3.5 ml fill bottle and one nasal spray applicator (pump). The nasal spray pump is attached to the 3.5 ml fill bottle before first use. Fortical® Nasal Spray contains 2,200 IU/ml calcitonin-salmon (rDNA origin), sodium chloride ——, citric acid, monohydrate ——, phenylethyl alcohol ——), benzyl alcohol (——, polysorbate 80 (——), hydrochloric acid or sodium hydroxide (added as necessary to adjust pH), and purified water. Each spray of the drug product dispenses 0.09 ml of Fortical® Nasal Spray containing 200 IU (per dose) of calcitonin-salmon (rDNA origin). Each bottle of Fortical® Nasal Spray is intended to deliver at least — doses. **The proposed expiry for Fortical® Nasal Spray is 24 months (Storage at 2-8 °C, Prevent from freezing).** The potency (biological activity) of Fortical® Nasal Spray is expressed in International Units (IU) based on the *in vivo* rat hypocalcemia assay in comparison with the current International Standard for calcitonin-salmon, distributed by the National Institute for Biologic Standards and Control, potters Bar, United Kingdom.

Drug Substance:

The drug substance recombinant salmon calcitonin is synthesized in genetically engineered E. coli in which the gene encoding for salmon calcitonin was introduced through recombinant DNA technology. The primary amino acid sequence of recombinant salmon calcitonin is identical to that of salmon calcitonin from natural sources. Salmon calcitonin is the official name used by United States Adopted Name (USAN) for salmon calcitonin manufactured by either recombinant DNA technology or by chemical synthesis. Calcitonin (salmon) or calcitonin-salmon is the official name used by International Non-Proprietary Name (INN) for salmon calcitonin manufactured by either recombinant DNA technology or by chemical synthesis. Salmon calcitonin is a single chain non-glycosylated polypeptide containing 32 amino acids with a molecular mass of

. All information with respect to the chemistry and manufacturing controls (CMC) of recombinant salmon calciton is provided in two Drug Master Files: DMF provides the CMC information for rsCT, and DMF provides for the CMC information for α-AE. Both DMFs have been reviewed; DMF has been found adequate, while DMF inadequate, to support this NDA. The proposed interim expiration date for the bulk drug substance is (storage at -20°C).

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

Fortical® Nasal Spray is intended to be used for the treatment of postmenopausal osteoporosis. The recommended dose is one spray [200 IU of calcitonin-salmon (rDNA origin)] per day administered intranasally, alternating nostrils daily. Each carton of the drug product contains one 3.5 ml fill bottle and one nasal spray applicator (pump). Unopened bottles of Fortical® Nasal Spray should be stored in the refrigerator between 2-8 °C (36-46 °F). The nasal spray pump is attached to the 3.5 ml fill bottle before first use. The bottle in use with pump attached should be stored at 20-25 °C (68-77 °F) in an upright position at all times. Each new nasal spray pump must be primed properly before first use to ensure the delivery of a correct dose. After the new pump is primed, it is not necessary to re-prime it before each use, if the bottle in use is kept in an upright position. Each bottle of Fortical® Nasal Spray is intended to deliver at least doses. Fortical® Nasal Spray, bottle with pump attached, should be discarded 30 days after first use. Failure to keep the

bottle in use in an upright position may result in the delivery of an incomplete dose. Unnecessary re-priming before use may result in the insufficient delivery of ~ doses.

Fortical® Nasal Spray has not been shown to be bioequivalent to the marketed product Miacalcin® Nasal Spray. The two products are not interchangeable.

C. Basis for Approvability or Not-Approval Recommendation

This application is Approvable pending the following:

- revised specifications for drug substance (to include bioassay)
- a satisfactory response to the CMC deficiencies delineated in the Draft List of Deficiencies and Information Request (in the CMC reviews for NDA 21-406, DMF —, and DMF —.)
- overall recommendation from OC which was delayed due to a change in a testing facility submitted by the applicant one month before the due date.

III. Administrative:

A. Reviewer's Signature in DFS

B. Endorsement Block: in DFS

C. CC Block: in DFS

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55 Page(s) Withheld

6 Trade Secret / Confidential

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Withheld Track Number: Chemistry-_____

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/s/

Yvonne Yang
12/24/03 10:53:19 AM
CHEMIST

Duu-gong Wu
12/24/03 11:29:35 AM
CHEMIST

NDA FILEABILITY CHECKLIST

NDA Number: 21-406 **Applicant:** Unigene Laboratories, Inc. **Stamp Date:** Mar-05-2003
Drug Name: Fortical

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		Index in volume 1, pp. 14-46
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	CFNs not provided, with the help from EES, the reviewer was able to identify all facilities for inspection
5	Is a statement provided that all facilities are ready for GMP inspection?		X	Provided in amendment dated Apr-15-2003
6	Has an environmental assessment report or categorical exclusion been provided?	X		Volume 3, pp. 167-168 Claims categorical exclusion
7	Does the section contain controls for the drug substance?	X		Volume 3, pp. 9-10
8	Does the section contain controls for the drug product?	X		Volume 3, pp. 31-33
9	Has stability data and analysis been provided to support the requested expiration date?	X		Volume 3, pp. 66-145
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?			N/A
11	Have draft container labels been provided?	X		Volume 1, pp. 61-62
12	Has the draft package insert been provided?	X		Volume 1, pp. 63-82 Volume 2, pp. 01-40
13	Has an investigational formulations section been provided?	X		Volume 3, pp. 156-166
14	Is there a Methods Validation package?	X		DS: DMF — DP: Volumes 9A and 9B
15	Is a separate microbiological section included?		X	Send specification and test methods CMC sections for consult: Vol. 1.3, pp. 1-65 Vol. 1.5 PP. 158-169

cc:
Original NDA 21-406
HFD-510/Division File/Y Yang/R Hedin
HFD-820/DG Wu

NDA Number: 21-406 **Applicant:** Unigene Laboratories, Inc. **Drug Name:** Fortical

Have all DMF References been Identified?

DMF Number	Holder	Description	LOA Included	Status
14426	Unigene	Entire drug substance section	Feb-24-2003	Pending
13966	Unigene	Manufacture of α-AE	Feb-24-2003	Pending
			Aug-28-2002	Pending
			Aug-28-2002	Pending
			Nov-08-1999	Pending
			Nov-05-2001	Pending

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/s/

Yvonne Yang
4/21/03 01:10:07 PM
CHEMIST

Duu-gong Wu
4/22/03 08:27:52 AM
CHEMIST