CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-907/S-004

Trade Name:	Activella 1mg/0.5mg Tablets
Generic Name:	estradiol / norethindrone acetate
Sponsor:	Novo Nordisk
Approval Date:	November 14, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-907/S-004
NDA 20-908/S-003

APPROVAL LETTER

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Dear Dr. Reit:

Please refer to your supplemental new drug applications dated August 16, 2000, received August 21, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella™ (1 mg/0.5 mg) and Vagifem® (25 µg).

These "Changes Being Effected in 30 days" supplemental new drug applications provide for:

A Microbiology Testing site change from the current facility in Gentofte to the PSM Quality Control Laboratory (Dept. 414) in Maaloev in Q3/Q4, 2000.

We have completed the review of these supplemental applications, and they are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader,
Division of Reproductive and Urologic
Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

/s/

Moo-Jhong Rhee
11/14/00 01:32:00 PM

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-004

CHEMISTRY REVIEW(S)

CHEMIST REVIEW
OF **SUPPLEMENT**

1. **ORGANIZATION:** DRUDP HFD-580
2. **NDA NUMBER:** 20-907/SCM-004
3. **SUPPLEMENT NUMBERS/DATES:**
   Letterdate: 16-AUG-2000
   Stampdate: 21-AUG-2000
4. **AMENDMENTS/REPORTS/DATES:**
   Letterdate:
   Stampdate:
5. **RECEIVED BY CHEMIST:** 28-AUG-2000

6. **APPLICANT NAME AND ADDRESS:**
   Novo Nordisk Pharmaceuticals, Inc.
   Suite 200, 100 Overlook Center
   Princeton, NJ 08540-7810

7. **NAME OF DRUG:**
   Activella

8. **NONPROPRIETARY NAME:**
   Estradiol/Norethindrone acetate Tablets

9. **CHEMICAL NAME/STRUCTURE:**
   a. Estradiol: estra-1,3,5(10)-triene-3,17β-diol hemihydrate
   b. Norethindrone acetate: 17β-acetoxy-19-nor-17α-pregn-4-en-20-yn-3-one

   See USP Dictionary of Drug Names for structures.

10. **DOSAGE FORM(S):**
    Tablet

11. **POTENCY:**
    1 mg estradiol/0.5 mg norethindrone acetate

12. **PHARMACOLOGICAL CATEGORY:**
    Estrogen and progestin/Treatment of Post Menopausal Vasomotor Symptoms

13. **HOW DISPENSED:**
    RX

14. **RECORDS & REPORTS CURRENT:**
    Yes

15. **RELATED IND/NDA/DMF:**
    NDA 20-908/SCM-003, ANDA 40-312

16. **SUPPLEMENT PROVIDES FOR:**
    Change in Microbiology Testing from the current facilities in Gentofte, Denmark to the PSM Quality Control Laboratory in Maaloev, Denmark.

17. COMMENTS

This supplement has been filed to provide for the change in Microbiology Testing from the current facilities in Gentofte, Denmark to the PSM Quality Control Laboratory in Maaloev, Denmark. The proposed facility will perform the same tests as the current facility, and those tests are as follows: 1) testing of drug product tablets for Activella, Vagifem and Innofem, 2) [redacted] 3) testing of environmental samples, and 4) testing of primary packaging for Vagifem. The sponsor states that the analytical testing equipment in the proposed facility is the same as in the current facility. In addition, the same technicians will perform the analyses using the same analytical methods and SOP's. Finally, the proposed Microbiology Testing facilities are located in the same building as the PSM Quality Control Laboratory approved for chemical analysis.

The sponsor has met all the criteria for this supplement to qualify as a CBE supplement under PAC-ALTS (Postapproval Changes-Analytical Testing Laboratory Sites). An EER was submitted on August 28, 2000 and returned as acceptable by the Office of Compliance on September 5, 2000 (see attached EER). The recommendation was acceptable based on file review.

The Microbiology Staff was consulted to review this supplement. Dr. Bryan Riley recommended approval pending satisfactory cGMP status of the proposed testing facility (see Micro. Review dated October 16, 2000).

18. CONCLUSIONS AND RECOMMENDATIONS:

This CBE-30 Supplement may be approved. **Issue an approval letter.**

19. REVIEWER NAME	**SIGNATURE**	**DATE COMPLETED**
David T. Lin, Ph.D. Review Chemist		30-OCT-2000

cc: Original: NDA 20-907/SCM-004
HFD-580/Division File
HFD-580/DSpell-LeSane
HFD-580/MRhee/DLin

INIT by MJ Rhee

Filename: S20907.004 (doc)

APPEARS THIS WAY
ON ORIGINAL

06-SEP-2000 FDA CDER EES Page 1 of 1

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application: NDA 20907/004
Stamp: 21-AUG-2000
Regulatory Due: 21-FEB-2001
Applicant: NOVO NORDISK
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 08540
Priority: 4S
Org Code: 580

Action Goal:
District Goal: 17-JAN-2001
Brand Name: ACTIVELLE (ESTRADIOL 1MG/NORETHINDRONATE
Estab. Name:
Generic Name: ESTRADIOL 1MG/NORETHINDRONATE ACETATE 0.

Dosage Form: (AEROSOL)
Strength: 1 MG/0.5 MG

Application Comment: THIS SUPPLEMENT IS FOR A CHANGE IN MICROBIOLOGY TESTING SITE TO NOVO NORDISK'S FACILITY IN MAALOEV, DENMARK. IT IS BUNDLED WITH NDA 20-908/S-003 AND ANDA 40-312. (on 28-AUG-2000 by D. LIN (HFD-580) 301-827-4230)

FDA Contacts: D. LIN (HFD-580) 301-827-4230 , Review Chemist
M. RHEE (HFD-580) 301-827-4237 , Team Leader

Overall Recommendation: ACCEPTABLE on 05-SEP-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: 9613235
NOVO NORDISK A/S
NOVO NORDISK PARK
MAALEOV, , DA DK-2760

DMF No: AADA:
Responsibilities: FINISHED DOSAGE RELEASE TESTER
Profile: CTL OAI Status: NONE
Estab. Comment:

Milestone Name	Date	Req. Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	28-AUG-2000				LINDAV
SUBMITTED TO DO	29-AUG-2000	GMP			EGASM
DO RECOMMENDATION	05-SEP-2000			ACCEPTABLE BASED ON FILE REVIEW	EGASM
BASED ON EI OF 10/2/98					
OC RECOMMENDATION	05-SEP-2000			ACCEPTABLE DISTRICT RECOMMENDATION	EGASM

APPEARS THIS WAY
ON ORIGINAL

/s/

David T. Lin
11/2/00 02:55:48 PM
CHEMIST

Moo-Jhong Rhee
11/2/00 03:13:11 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-004

MICROBIOLOGY REVIEW

REVIEW TO HFD-580
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF/HFD-805
MICROBIOLOGY REVIEW #1 OF NDA

16 October 2000

A. 1. NDA: 20-908/S-003
20-907/S-004
ANDA: 40-312/S-001

2. TYPE OF SUPPLEMENT: Changes Being Effected in 30 Days

3. SUPPLEMENT PROVIDES FOR: Change in Microbiology Testing Site

4. APPLICANT/SPONSOR: Novo Nordisk
Suite 200
100 Overlook Center
Princeton, New Jersey 08540-7810

5. MANUFACTURING SITE:

6. DRUG PRODUCT NAME:
Proprietary: Vagifem®, Activella™, Innofem™
Nonproprietary: estradiol
Drug Priority Classification: Standard

7. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: tablet

8. METHOD(S) OF STERILIZATION: NA

9. PHARMACOLOGICAL CATEGORY: Estrogen

B. 1. DOCUMENT/LETTER DATE: August 16, 2000
2. RECEIPT DATE: August 16, 2000
3. CONSULT DATE: September 19, 2000
4. DATE OF AMENDMENT: na
5. ASSIGNED FOR REVIEW: September 28, 2000
6. SUPPORTING/RELATED DOCUMENTS:

C. REMARKS: This review also covers NDA 20-907 and ANDA 40-312.

D. CONCLUSIONS: This submission is recommended for approval pending satisfactory cGMP status of the alternate testing facility at Novo Nordisk A/S, Novo Nordisk Park, DK-2760 Maaloev.

Bryan S. Riley, Ph.D.
Microbiology Reviewer

cc.: Original NDAs 20-908, 20-907 ANDA 40-312
HFD 580/Division File
HFD 580/Spell-LeSane/Lin/Rhee/Rumble
HFD 805/Consult File
HFD 805/ B. Riley

Drafted by: Bryan Riley, Ph.D.
R/D initialed by: Peter Cooney, Ph.D.

filename: C:\data\data\word\nda\s\20908s3.doc

APPEARS THIS WAY
ON ORIGINAL

E. REVIEW NOTES: The microbiology testing is being transferred from one facility to another.

Current Facility: Novo Nordisk A/S
Hagedornsvej 1
DK-2820 Gentofte

New Facility: Novo Nordisk A/S
Novo Nordisk Park
DK-2760 Maaloev

The tests being transferred are the Microbial Limit Tests. The test methods in the approved application are not being changed. This supplement was submitted as a CBE-30 under PAC-ATLS. Therefore, no data is necessary, only satisfactory GMP.

ADEQUATE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-004

CORRESPONDENCE

NDA 20-907/S-004

CBE-30 SUPPLEMENT

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center Suite 200
Princeton, NJ 08540

Dear Dr. Reit:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug: Activella™

NDA Number: 20-907

Supplement Number: S-004

Date of Supplement: August 16, 2000

Date of Receipt: August 21, 2000

This supplemental application, submitted as "Supplement - Changes Being Effected in 30 days" proposes the following change:

> A Microbiology Testing site change from the current facility in Gentofte to the PSM Quality Control Laboratory (Dept. 414) in Maaloev in Q3/Q4, 2000.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 20, 2000, in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Reproductive and, Urologic Drug Products HFD-580
Office of Drug Evaluation III
Attention: Division Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and, Urologic Drug Products HFD-580
Office of Drug Evaluation III
Attention: Document Room 17B-20
5600 Fishers Lane
Rockville, Maryland 20857

If you have any question, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Terri F. Rumble
Chief, Project Management Staff
Division of Reproductive and Urologic
Drug Products, HFD-580
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-907
HFD-580/division file
HFD-580/ Spell-LeSane
HFD-580/Allen/Slaughter/Bennett/Rhee/Lin/Parekh/Jordan/Rumble
DISTRICT OFFICE

Drafted by: DSL-8.24.00
Initialed by Rumble, 8.24.00
Final: Spell-LeSane, 8.24.00
Filename: NDA/20907/letter/ackcbe004.doc