

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-001

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # 22-001

SUPPL #

HFD # 510

Trade Name Activella 0.5 mg/.01 mg

Generic Name estradiol, 0.5mg/norethindrone acetate, 0.1 mg

Applicant Name Novo Nordisk

Approval Date, If Known: [REDACTED]

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

YES NO

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

505(b)(1)

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

YES NO

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

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

d) Did the applicant request exclusivity?

YES NO

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

not requested

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

YES

NO

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

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

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

YES

NO

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES

NO

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

NDA#

NDA#

NDA#

2. Combination product.

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

YES NO

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

NDA# 20-907	Activella
NDA# 21-885	ClimaraPro
NDA# 21-102	Femhrt

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

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

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

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

YES NO

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

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or

505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

YES NO

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

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

YES NO

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

YES NO

If yes, explain:

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

YES NO

If yes, explain:

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

KLIM/PD/11/USA

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the

agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

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

Investigation #1 YES NO

Investigation #2 YES NO

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

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

Investigation #1 YES NO

Investigation #2 YES NO

The study KLIM/PD/11/USA was submitted with the original NDA 021-071 for Aorevel. However, the low dose estrogen data (0.01 mg) was not essential for approval of the original application since it was for a high dose (0.1 mg) product. The data was re-reviewed for this application and is therefore being considered "new."

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

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

KLIM/PD/11/USA

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor

in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

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

Investigation #1
IND # 43006 YES ! NO
! Explain:

Investigation #2
IND # YES ! NO
! Explain:

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

Investigation #1
YES ! NO
Explain: ! Explain:

Investigation #2
YES ! NO
Explain: ! Explain:

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

YES NO X

If yes, explain:

Name of person completing form: Patricia Madara
Title: Regulatory Project Manager
Date: January 8, 2006

Name of Office/Division Director signing form: [REDACTED]
Title: [REDACTED]

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

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/s/

Patricia Madara
1/9/2007 09:19:09 AM

Mary Parks
1/9/2007 11:21:29 AM

Division of Metabolism and Endocrinology Products

REGULATORY PROJECT MANAGER REVIEW

Application Number: NDA 22-001 (Type 6 to NDA 20-907)
Name of Drug: Activella 0.5 mg/0.1 mg (estradiol/norethindrone acetate) Tablets
Applicant: NovoNordisk
Material Reviewed: Draft labeling (package insert)
Submission Dates: December 27 (e-mail), 2006

Background and Summary

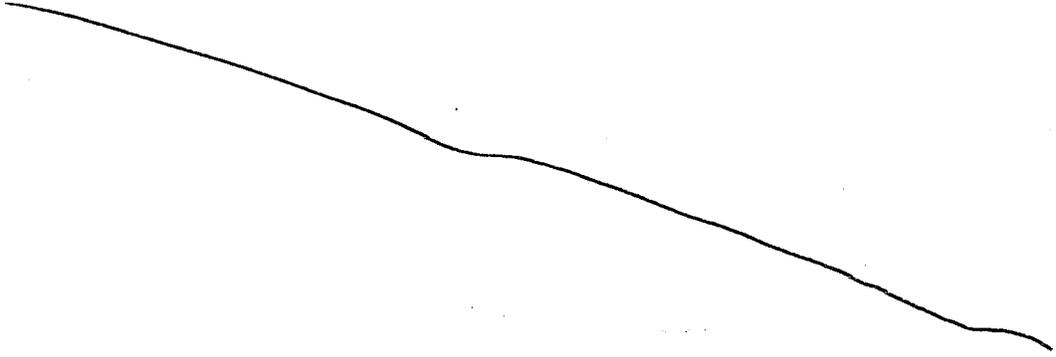
Activella 1 mg/0.5 mg (estradiol/norethindrone acetate) Tablets is currently approved in the Division of Reproductive and Urologic Products (DRUP) for treatment of moderate to severe vasomotor symptoms and severe vulvar and vaginal atrophy associated with the menopause. On April 11, 2000, a Type 6 NDA to 20-907 was approved in the Division of Metabolism and Endocrinology Products (DMEP) for Activella 1.0 mg/0.5 mg for prevention of postmenopausal osteoporosis.

On February 28, 2006, NovoNordisk submitted an efficacy supplement to NDA 20-907 and another type 6 NDA to our Division that provided for a new, lower dose of Activella. The indications are unchanged.

The patient package insert, dial-pack, shrink-wrap, and cartons for this product were reviewed by Ayoub Suliman, regulatory project manager in DRUP, and will not be discussed here.

Review

Draft Package Insert



3 Page(s) Withheld

 Trade Secret / Confidential

✓ Draft Labeling

 Deliberative Process

Withheld Track Number: Administrative- 1

Conclusions

This will be corrected before submission of FPL.

Patricia Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products

Concurrence: Lina Aljuburi

MEMORANDUM

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

DATE: December 19, 2006
TO: the file
FROM: Patricia Madara
SUBJECT: **Response to firm's question regarding labeling**
NDA 22-001, Activella

Background and Summary

On February 28, 2006, NovoNordisk submitted a type 6 NDA to our Division that provided for a new, lower dose of Activella (estradiol/norethindrone acetate) Tablets. The indication sought was for prevention of postmenopausal osteoporosis. (Note that the original NDA resides in the Division of Reproductive and Urologic Products and is indicated for treatment of moderate to severe vasomotor symptoms and severe vulvar and vaginal atrophy associated with the menopause.)

The studies were reviewed by Medical Officer, Dr. William Lubas. While the data was deemed sufficient for approval, Study EST/PD/4/N+S was found to be unacceptable for labeling.

Combined draft labeling revisions (this Division and DRUP) were sent to NovoNordisk on December 8, 2006. On December 11, 2006, I received a phone call from Dr. Rima Nassar, my contact at the firm. She requested an explanation as to why the study above was considered unacceptable for labeling. I relayed her question to Dr. Lubas. He responded to the question via email (with concurrence from his team leader, Dr. Theresa Kehoe).

I have attached his explanation (emailed to the firm) to this memo.

Madara, Patricia

From: Madara, Patricia
Sent: Monday, December 11, 2006 2:28 PM
To: 'rimn@novonordisk.com'
Subject: RE Activella NDA 22-001: question regarding Study EST/PD/4/N+S

Importance: High

NDA 22-001.

Novo Nordisk Inc.
Attention: Rima B. Nassar, Ph.D.
Director, Regulatory Product Development
100 College Road West
Princeton, NJ 08540

Dear Dr. Nassar:

Please refer to your February 28, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella 0.5/0.1 (0.5 mg estradiol/0.1 mg norethindrone acetate).

Today, by telephone, you asked why study EST/PD/4/N+S is not acceptable for labeling. The response from the DMEP Clinical Review Team is:

1. The study included perimenopausal women and there is no current indication for the prevention of PMO in perimenopausal women.
2. The study included only hysterectomized women, and there would be no reason to treat hysterectomized women with a combination estrogen progestin product, so this subset of women would not be directly generalizable to the population that would be expected to receive Activella in the US, who would all still have intact uteri.
3. The study was performed in Sweden and Norway which did not routinely supplement dairy products with Vitamin D, and there was no calcium and Vitamin D supplementation in this trial. So baseline calcium levels were likely to be lower in this trial than in the general US population.

In summary, these data could not be directly generalized to the US population of post menopausal women who are likely to receive treatment with this low dose combination product.

Please confirm receipt of this email.

If you have any questions, call me at (301) 796-1249.

Sincerely,

Pat Madara
Regulatory Project Manager
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

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/s/

Patricia Madara
12/19/2006 04:00:59 PM
CSO



MEMORANDUM

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

DATE: October 26, 2006

TO: Daniel Shames, M.D., Director
Division of Reproductive and Urologic Products (DRUP), HFD-580

Mary Parks, M.D., Director
Division of Metabolic and Endocrine Products (DMEP), HFD-510

FROM: OSE Risk Management Team

DRUG: Activella — (0.5mg estradiol (E2) and 0.1mg norethindrone (NETA))

NDA #: 22-001 and 20-907/S009

SPONSOR: Novo Nordisk

SUBJECT: Review of Proposed Risk Management Plan (RMP) submitted
February 28, 2006

PID #: D060400

Introduction/Background

The Office of Surveillance and Epidemiology (OSE) has received a consult request from the Division of Reproductive and Urologic Products to review the proposed Risk Management Plan (RMP) for Activella —

Activella low dose (— tablet contains 0.5mg estradiol (E2) and 0.1mg norethindrone (NETA). This is a lower dose of the marketed Activella which contains 1mg estradiol and 0.5mg norethindrone. Activella was originally approved on November 18, 1998 for the treatment of moderate to severe vasomotor symptoms associated with the menopause and for the treatment of vulvar and vaginal atrophy in women with an intact uterus. It was approved on April 11, 2000 for the prevention of postmenopausal osteoporosis. This new product is intended for once daily oral administration to postmenopausal women with an intact uterus for the treatment of moderate to severe vasomotor symptoms and the prevention of postmenopausal osteoporosis.

The Sponsor's safety summary identified no safety concerns with the Activella — in the pivotal clinical trial. In this study, the numbers and types of adverse events (AEs) were evenly distributed between treatment groups ALD 0.1 (0.5 mg E2 + 0.1 mg NETA), ALD 0.25 (0.5 mg E2 + 0.25 mg NETA), and placebo. The most frequently reported AEs in all treatment groups were headache, vaginal hemorrhage, and nasopharyngitis. The incidence of postmenopausal bleeding was low for both ALD 0.1 and ALD 0.25. Transvaginal ultrasound findings did not identify any safety concern. One subject was diagnosed with breast cancer during the study. No increases in mammographic density were observed for any of the treatment groups. There were no reports of thromboembolic events in any treatment group.¹

Proposed RMP

The Sponsor's RMP submission includes a summary of the risk assessment or safety specification conducted during the preclinical and clinical development program as well as a pharmacovigilance plan which describes the Company's routine pharmacovigilance practices and their plan to update product information as necessary. The Sponsor does not identify any potential safety issues that warrant a Risk Minimization Action Plan (RiskMAP) for Activella —.

Conclusion

OSE has reviewed the submitted RMP and has determined that it does not identify a specific safety concern for which a RiskMAP to minimize risk would be normally associated. The measures proposed by the sponsor seem reasonable but would appear to be routine given the potential risk. A separate review by the Division of Surveillance, Research, and Communication Support (DSRCS) of patient labeling for Activella and Activella — was completed May 25, 2006 by Jeanine Best, the Patient Product Information Specialist. If the sponsor or the review division identifies a safety concern and determines that a RiskMAP is warranted or should the review division wish OSE to review any proposed Phase IV protocols or epidemiological post-marketing studies, please provide a consult request.

OSE Risk Management Team

Mary Dempsey, Risk Management Program Officer, OSE-IO

Claudia B. Karwoski, Pharm.D., Scientific Coordinator for Risk Management, OSE-IO

¹ NDA 20902/009 Activella —, Module 2.7.4 Summary of Clinical Safety and Module 1.16 Clinical Risk Management Plan —

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/s/

Mary Dempsey
10/26/2006 11:02:26 AM
DRUG SAFETY OFFICE REVIEWER

Claudia Karwoski
10/26/2006 11:55:24 AM
DRUG SAFETY OFFICE REVIEWER

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 22-0001 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: March 1, 2006 PDUFA Goal Date: January 1, 2007

HFD 510 Trade and generic names/dosage form: Activella .5/1 (0.5 mg estradiol/0.1 mg norethindrone acetate)

Applicant: Novo Nordisk Therapeutic Class: 3020425 – osteoporosis - HRT

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

- Yes. Please proceed to the next section.
- No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): _____

Each indication covered by current application under review must have pediatric studies: *Completed, Deferred, and/or Waived.*

Number of indications for this application(s): one

Indication #1: prevention and treatment of postmenopausal osteoporosis

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
- No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
- No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA 22-001

Page 3

This page was completed by:

{See appended electronic signature page}

Pat Madara

Regulatory Project Manager

cc: NDA 22-001

HFD-960/ Rosemary Addy or Grace Carmouze

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG
DEVELOPMENT, HFD-960, 301-594-7337.**

(revised 6-23-2005)

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/s/

Patricia Madara
9/29/2006 03:23:49 PM



NDA 22-001

INFORMATION REQUEST LETTER

Novo Nordisk Inc.
Attention: Mary Ann McElligott, Ph.D.,
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your February 28, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella 0.5/0.1 (estradiol 0.5mg/norethindrone acetate 0.1 mg) Tablets.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following information request. We request a prompt written response in order to continue our evaluation of your NDA.

- Please provide calculations of the estimated concentrations of the active moieties at the point of entry into the aquatic environment to support the request for a categorical exclusion from the requirements to prepare an environmental assessment under 21 CFR 25.31(b) for the proposed drug product.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology
Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
9/21/2006 12:49:48 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-001

Novo Nordisk, Inc.
Attn: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your submission dated February 28, 2006, requesting a full waiver for pediatric studies for Activella — (estradiol 0.5 mg/norethindrone acetate 0.1 mg).

We have reviewed the submission and agree that a waiver is justified for Activella — for prevention of postmenopausal osteoporosis for the entire pediatric population. This indication does not have sufficient frequency in the pediatric population to constitute a meaningful therapeutic benefit for pediatric patients or to be used in a substantial number of pediatric patients.

Accordingly, at this time, a waiver for pediatric studies for your application is granted under section 2 of the Pediatric Research Equity Act.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Mary H. Parks, M.D.
Director
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Mary Parks
8/22/2006 07:48:06 AM

MEMORANDUM

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

DATE: August 18, 2006
TO: The file
FROM: Pat Madara, Project Manager
SUBJECT: Complete waiver of pediatric studies
NDA 22-001, Activella

Background and Summary:

On February 28, 2006, Novo Nordisk submitted new drug application (NDA), NDA 22-001, for Activella (estradiol 0.5 mg / morethindrone acetate 0.1 mg). This is a Type 6 NDA to NDA 20-907, approved on November 18, 1998 and held by the Division of Reproductive and Urology Products. NDA 22-001 provides for a lower strength product of Activella for the indication of prevention of postmenopausal osteoporosis.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred.

Novo Nordisk's February 28, 2006 submission contains a request for a complete waiver for pediatric studies for this application. The Division of Metabolism and Endocrinology Products routinely grants this request since postmenopausal osteoporosis does not have sufficient frequency in the pediatric population to constitute a meaningful therapeutic benefit for pediatric patients or to be used in a substantial number of pediatric patients.

It is recommended that a complete waiver be granted for NDA 22-001.

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/s/

Patricia Madara
8/21/2006 02:16:21 PM
CSO

memo approved by clinical team leader, Dr. Theresa Kehoe



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-001

Novo Nordisk, Inc.
Attn: Mary Ann McElligott, Ph.D.
Associate Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Dr. McElligott:

Please refer to your February 28, 2006 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella — (0.5 mg estradiol / 0.1 mg norethindrone acetate).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on April 30, 2006 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

- You have not provided the raw data for study EST/PD/4/N+S.
- You have not provided the financial disclosure information for study EST/PD/4/N+S.

We request that you submit the information described above.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Pat Madara, Regulatory Project Manager, at (301) 796-1249.

Sincerely,

{See appended electronic signature page}

Kati Johnson
Chief, Project Management Staff
Division of Metabolism and Endocrinology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

Patricia Madara
5/4/2006 10:19:28 AM
Pat Madara signing for Kati Johnson

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-001 Supplement # Efficacy Supplement Type SE-

Trade Name: Activella —
Established Name: estradiol / norethindrone acetate
Strengths: 0.5 mg / 0.1 mg
Applicant: Novo Nordisk
Agent for Applicant: N/A
Date of Application: February 28, 2006
Date of Receipt: March 1, 2006
Date clock started after UN: N/A
Date of Filing Meeting: April 19, 2006
Filing Date: April 30, 2006
Action Goal Date (optional): December 15, 2006 User Fee Goal Date: January 1, 2007

Indication requested: Prevention of post menopausal osteoporosis in women with an intact uterus.

Type of Original NDA: (b)(1) (b)(2)
OR
Type of Supplement: (b)(1) (b)(2)

NOTE:

- (1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2), complete Appendix B.
- (2) If the application is a supplement to an NDA, please indicate whether the NDA is a (b)(1) or a (b)(2) application:

X NDA is a (b)(1) application OR NDA is a (b)(2) application

Therapeutic Classification: S XXX P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES X NO

User Fee Status: Paid XX Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the user fee staff.

Version: 12/15/2004

This is a locked document. If you need to add a comment where there is no field to do so, unlock the document using the following procedure. Click the 'View' tab; drag the cursor down to 'Toolbars'; click on 'Forms.' On the forms toolbar, click the lock/unlock icon (looks like a padlock). This will allow you to insert text outside the provided fields. The form must then be relocked to permit tabbing through the fields.

- Is there any 5-year or 3-year exclusivity on this active moiety in an approved (b)(1) or (b)(2) application? YES NO X
If yes, explain:

- Does another drug have orphan drug exclusivity for the same indication? YES NO X

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO X
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES X NO

- Was form 356h included with an authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES X NO
If no, explain:

- If an electronic NDA, does it follow the Guidance? N/A YES NO
If an electronic NDA, all forms and certifications must be in paper and require a signature.
Which parts of the application were submitted in electronic format? Index, labeling, summary, chemistry, clinical, clinical pharmacology, statistical, CRFs, case report tabulations

Additional comments:

- If an electronic NDA in Common Technical Document format, does it follow the CTD guidance? YES X NO

- Is it an electronic CTD (eCTD)? YES NO X
If an electronic CTD, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments: forms and certifications were in paper

- Patent information submitted on form FDA 3542a? YES X NO

- Exclusivity requested? YES, _____ Years NO X
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES X NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and 3455 must be included and must be signed by the APPLICANT, not an agent.)
NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.
- Field Copy Certification (that it is a true copy of the CMC technical section)? Y NO
- PDUFA and Action Goal dates correct in COMIS? YES X NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers:
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

Project Management

- Was electronic "Content of Labeling" submitted? YES X NO
If no, request in 74-day letter.
- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC?
YES X NO
- Risk Management Plan consulted to ODS/IO? TBD YES NO
N/A
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? Y X NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES X NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted?
N/A X YES NO

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A x YES NO
- Has DOTCDP been notified of the OTC switch application? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?
YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to Florian Zielinski (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: April 30, 2006

BACKGROUND: Activella (1 mg estradiol / 0.5 mg norethindrone acetate) was approved by DRUP on November 18, 1998 (NDA 20-907) and is indicated for use in the treatment of moderate to severe vasomotor symptoms associated with menopause. A Type 6 NDA (new indication) for Activella was approved by DMEP on June 11, 2000 for an indication of prevention of post menopausal osteoporosis.

On February 28, 2006, Novo Nordisk submitted a supplement to NDA 20-907 which provides for a new, lower dose of Activella for treatment of moderate to severe vasomotor symptoms associated with menopause. Concurrently, a new Type 5 NDA was submitted to DMEP which provided for the lower dose of Activella to be used for prevention of post menopausal osteoporosis.

ATTENDEES: Theresa Kehoe, M.D. Clinical Team Leader
William Lubas, M.D. Clinical Reviewer
Johnny Lau, Ph.D. Clinical Pharmacology Reviewer
Su Tran, Ph.D. CMC PAL
Todd Sahlroot, Ph.D. Statistics Team Leader

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline</u>	<u>Reviewer</u>
Medical:	William Lubas, M.D.
Secondary Medical:	N/A
Statistical:	Cynthia Liu, Ph.D.
Pharmacology:	NN
Statistical Pharmacology:	NN
Chemistry:	Yvonne Yang, Ph.D.
Environmental Assessment (if needed):	NN
Biopharmaceutical:	Johnny Lau, Ph.D.
Microbiology, sterility:	NN
Microbiology, clinical (for antimicrobial products only):	NN
DSI:	Pat Madara
Regulatory Project Management:	
Other Consults:	

Per reviewers, are all parts in English or English translation? YES X NO
If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site inspection needed? YES X NO
- Advisory Committee Meeting needed? YES, date if known _____ NO X
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

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

/s/

Patricia Madara
5/3/2006 06:26:54 PM
CSO

Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.

DEPARTMENT OF HEALTH AND HUMAN
SERVICES
FOOD AND DRUG ADMINISTRATIONPRESCRIPTION DRUG USER FEE
COVERSHEET

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: <http://www.fda.gov/cder/pdufa/default.htm>

1. APPLICANT'S NAME AND ADDRESS NOVO NORDISK PHARMACEUTICALS INC Patricia Robson 100 College Road West Princeton NJ 08540 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 022001				
2. TELEPHONE NUMBER 609-919-7790		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:				
3. PRODUCT NAME Activella (estradiol/norethindrone acetate tablets 1mg/0.5mg)		6. USER FEE I.D. NUMBER PD3006278				
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY						
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO						
<p>Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:</p> <table border="0"> <tr> <td>Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448</td> <td>Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852.</td> <td>An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.</td> </tr> </table>				Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852.	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.
Department of Health and Human Services Food and Drug Administration CBER, HFM-99 1401 Rockville Pike Rockville, MD 20852-1448	Food and Drug Administration CDER, HFD-94 12420 Parklawn Drive, Room 3046 Rockville, MD 20852.	An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.				
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE 		TITLE <i>Associate Vice President, Reg. Affairs</i>	DATE 2/28/06			
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$767,400.00						
Form FDA 3397 (12/03)						

(IBE PRMT CLOSE G) (Print Cover sheet)

ACTION PACKAGE CHECKLIST

Application Information		
# 22-001	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: Activella; 0.5 mg/0.1 mg Established Name: estradiol/norethindrone acetate Dosage Form: Tablets		Applicant: Novo Nordisk
RPM: Patricia Madara		Division: 510 Phone # 301-796-1249
<p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) NDAs and 505(b)(2) NDA supplements: - Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:</p>
❖ User Fee Goal Date		January 1, 2007
❖ Action Goal Date (if different)		December 29, 2006
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input checked="" type="checkbox"/> None
❖ Advertising (approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed (indicate dates of reviews)		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

❖ Application Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): Type 5 (new formulation)	
NDAs, BLAs and Supplements: <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2 <input type="checkbox"/> Orphan drug designation	
NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
NDAs and NDA Supplements: <input type="checkbox"/> OTC drug	
Other:	
Other comments: This is a Type 6 NDA for the existing NDA 20-907 in DRUP. It is for a lower strength and for an indication generally reviewed by DMEP (prevention of postmenopausal osteoporosis).	
❖ Application Integrity Policy (AIP)	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> Exception for review (<i>file Center Director's memo in Administrative Documents section</i>) OC clearance for approval (<i>file communication in Administrative Documents section</i>) 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Public communications (approvals only)	
<ul style="list-style-type: none"> Office of Executive Programs (OEP) liaison has been notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Press Office notified of action 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> Indicate what types (if any) of information dissemination are anticipated 	<input checked="" type="checkbox"/> None <input type="checkbox"/> FDA Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

notice of certification?

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

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

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

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

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

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

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

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

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

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

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced

<p>within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.</i></p>	
SUMMARY REVIEWS	
<p>❖ Summary Reviews (e.g., Office Director, Division Director) <i>(indicate date for each review)</i></p>	<p>clin team lead: December 21, 2006 (co-signed by Div Director)</p>
<p>❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) <i>(indicate date)</i></p>	
LABELING	
<p>❖ Package Insert</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>December 27, 2006 (e-mail)</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>❖ Patient Package Insert</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	<p>December 27, 2006 (e-mail)</p>
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
<p>Medication Guide</p>	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) 	
<ul style="list-style-type: none"> • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
<p>❖ Labels (full color carton and immediate-container labels)</p>	
<ul style="list-style-type: none"> • Most-recent division-proposed labels (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	<p>December 19, 2006</p>
<p>❖ Labeling reviews and minutes of any labeling meetings <i>(indicate dates of reviews and meetings)</i></p>	<p><input checked="" type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input checked="" type="checkbox"/> DDMAC <input type="checkbox"/> SEALD <input checked="" type="checkbox"/> Other reviews 10/26/06 <input type="checkbox"/> Memos of Mtgs</p>

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	filing review: 5/3/06
❖ NDA and NDA supplement approvals only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> Center Director's Exception for Review memo If AP: OC clearance for approval 	
❖ Pediatric Page (all actions)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent. (<i>Include certification.</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Commitment Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> Outgoing Agency request for post-marketing commitments (<i>if located elsewhere in package, state where located</i>) Incoming submission documenting commitment 	
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	included
❖ Internal memoranda, telecons, email, etc.	
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) Pre-NDA/BLA meeting (<i>indicate date</i>) EOP2 meeting (<i>indicate date</i>) Other (e.g., EOP2a, CMC pilot programs) 	<input checked="" type="checkbox"/> No mtg
	<input checked="" type="checkbox"/> No mtg
❖ Advisory Committee Meeting	<input checked="" type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> Date of Meeting 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Parenteral Quality/Integrity	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	9/3/06; 11/1/06; 11/14/06
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ BLAs: Product subject to lot release (APs only)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Environmental Assessment (check one) (original and supplemental applications)	
<ul style="list-style-type: none"> <input checked="" type="checkbox"/> Categorical Exclusion (<i>indicate review date</i>) (<i>all original applications and all efficacy supplements that could increase the patient population</i>) <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) <input type="checkbox"/> Review & Environmental Impact Statement (<i>indicate date of each review</i>) 	
❖ NDAs: Microbiology reviews (sterility & apyrogenicity) (<i>indicate date of each review</i>)	<input type="checkbox"/> Not a parenteral product
❖ Facilities Review/Inspection	
<ul style="list-style-type: none"> NDAs: Facilities inspections (include EER printout) 	Date completed: 12/15/06 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

❖ BLAs: Facility-Related Documents <ul style="list-style-type: none"> • Facility review (<i>indicate date(s)</i>) • Compliance Status Check (approvals only, both original and supplemental applications) (<i>indicate date completed, must be within 60 days prior to AP</i>) 	<input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	NN
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	
❖ Nonclinical inspection review Summary (DSI)	<input type="checkbox"/> None requested
Clinical Information	
❖ Clinical review(s) (<i>indicate date for each review</i>)	December 15, 2006
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	clin rev, pg 13
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ Safety Update review(s) (<i>indicate location/date if incorporated into another review</i>)	
❖ Risk Management Plan review(s) (including those by OSE) (<i>indicate location/date if incorporated into another review</i>)	October 26, 2006 (OSE)
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input checked="" type="checkbox"/> Not needed
❖ DSI Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	<input checked="" type="checkbox"/> None requested
<ul style="list-style-type: none"> • Clinical Studies • Bioequivalence Studies • Clin Pharm Studies 	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 12/01/06
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 11/30/06

Comment [11]:

Appendix A to Action Package Checklist

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

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

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

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

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

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

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

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

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