



**FOOD AND DRUG ADMINISTRATION
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH**

Memorandum

Date: August 26, 2008

To: IND/NDA: NDA 22-196 ZolpiMist

Teleconference Date: August 6, 2008

Meeting Sponsor: _____

b(4)

Product: ZolpiMist (zolpidem tartrate oral spray)

From: Cathleen Michaloski, BSN, MPH

Telecon Minutes

FDA Attendees:

Russell Katz, MD Director, DNP

Devanand Jillapalli, MD, Medical Team Leader, DNP

Cathleen Michaloski, Regulatory Project Manager, DNP

Shastri Bhamidipati, PhD Chemist, ONDQA

Martha Heimann, PhD Chemist, ONDQA

Jagan Parepally, PhD Clinical Pharmacologist, ORA

Silvia Calderon, PharmD Clinical Pharmacologist, CSS

Suzanne Berkman, OSE Drug Risk Evaluation

Sandra J. Griffith, OSE Drug Risk Evaluation

Linda Kim-Jung, OSE DMEPA

Sponsor Attendees:

NovaDel Pharma Inc.

David Bergstrom, PhD Sr. VP and Chief Operating Officer

Frank Blondino, PhD, Exec Dir, Formulation and Process Development

Enrique Dilone, PhD Executive Director, Quality and Analytics

NovaDel Pharma Inc. Advisors

b(4)

Summary of Discussion:

1. Child-Resistant (CR) packaging

The ZolpiMist packaging submitted in the original NDA is not compliant with the Poison Prevention Act (PPPA). However, FDA has no authority to enforce these regs

_____ FDA is concerned about approving a product that may not meet the CPSC requirements.

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NovaDel stated it understands the requirements of the PPPA for certain drugs and

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2. Drug Abuse Liability

FDA stated that it believes that zolpidem tartrate has the potential for drug abuse in several forms (illicit or accidental) and that the oral spray formulation of ZolpiMist may add to the potential of abuse or misuse. The Division and NovaDel plan to work together to minimize any potential diversion or misuse. NovaDel acknowledged the Divisions' concerns and committed to a surveillance mechanism whereby any reports of abuse and/or overdose will be submitted. Existing monitoring and surveillance systems such as DAWN may be incorporated to help identify emerging problems

3. Intentional Swallowing

NovaDel indicated that the label directions to _____
_____ was inserted to be consistent with the patient administration instructions
from the ZolpiMist clinical trials where this direction was meant to have patients
avoid eating or drinking in order to minimize intra-subject and inter-subject
variability within the trials. NovaDel acknowledged that _____
_____ was not meant to be addressed because _____
would likely be impossible to prohibit.

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NovaDel will submit an amendment to the NDA, as soon as possible and prior to
the PDUFA action date, to provide information to show that _____
_____ would not affect product performance and that
appropriate administration instructions can be provided in the patient medication
guide.

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4. Sample Packaging

The Division requested actual ZolpiMist drug product. NovaDel committed to
provide samples of the ZolpiMist product (but with placebo, not active ingredient)
to FDA as soon as possible.

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/s/

Cathleen Michaloski
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CSO

Cathleen Michaloski
8/26/2008 03:49:49 PM
CSO

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Email to sponsor 8.12.08 NDA 22196

Good Afternoon _____

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Please respond to the following questions:

1. Have you any update on the requested histology information?
2. Regarding the placebo solution used in study 12230.02.01, the 28-Day Oral Irritation Study in Sprague Dawley Rats:

Please provide the composition of placebo formula 030-00 ("based on formula 027"). Is the composition of this placebo exactly the same as that of the zolpidem tartrate spray (formula 027-02), minus the active?

Please respond to me by email as well as to the NDA.

Thank you,
Cathleen

*Cathleen Michaloski, BSN / MPH
Regulatory Project Manager
CDER Division of Neurology Products
Food and Drug Administration
ph 301-796-1123
email: cathleen.michaloski@fda.hhs.gov*

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Cathleen Michaloski
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CSO

Cathleen Michaloski
8/12/2008 01:59:02 PM
CSO

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NDA 22-196

INFORMATION REQUEST LETTER

Novadel Pharma Inc.
Attention: David H. Bergstrom, Ph.D.
Senior Vice President and Chief Operating Officer
25 Minneakoning Road, Suite 101
Flemington, NJ 08822

Dear Dr. Bergstrom:

Please refer to your November 20, 2007 new drug application (NDA) submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Zolpidem Tartrate (Zolpidem Tartrate) Oral Spray.

We also refer to your submissions dated April 30, 2008 and June 20, 2008.

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

1. Please individually list and include respective acceptance limits for _____ individual unknown and total impurities in Zolpidem Tartrate specification used for accepting drug substance lots at drug product manufacturing site.
2. Please clarify if the HPLC method ATM-060 is used for the drug substance assay. It was stated that gradient HPLC method (ATM-060) is also employed for testing the raw material at the drug product manufacturing site. If the HPLC method is used for the drug substance assay, provide acceptance limits for Zolpidem tartrate assay by analytical method ATM-060 and explain as to how these assay results are utilized.
3. In regards to the validation of analytical method (ATM-060) for Zolpidem Tartrate assay, spray content and related impurities, provide intermediate precision results for variation between different instruments/labs and days.
4. In the accuracy experiments reported for spiked recovery of _____ (Section 3.2.P.5.3 MVR-038), _____ peak areas were corrected for interference from formulation in addition to response factor correction. However, the analytical method (ATM-060) procedure does not include any measures to correct the interference from product formulation in determining _____ levels in drug product and stability samples. Provide an explanation and incorporate appropriate measures with supporting data.

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b(4)

5. Please clearly indicate the stability test interval(s) at which the analytical method employed for testing the stability samples for Zolpidem Tartrate assay content and related substances was changed from ATM-044 to the current method ATM-060.
6. The acceptance limits for _____ in Drug Product specification should be tightened to no more than _____ based on the batch analyses results and the stability data presented. b(4)
7. Include an appropriate identification test for the counter-ion tartrate in the drug product specification.
8. Provide an explanation for the observed increase in Zolpidem Tartrate assay content value (96.6% to 106.3%) for the Physician Sample batch #IE0162 (Table 3.P.8.3-17).
9. Clarify the reasons for observed discrepancy in uniformity spray weight results meeting the acceptance criteria whereas uniformity of spray content results were out of specification for accelerated storage stability samples at 3 month interval (lot# 07C02 20070330M and 07C03 20070321M).
10. As post-approval commitment, the first three commercial batches of drug product should be placed on accelerated storage conditions in addition to long term storage conditions. Stability program for annual commitment batches should include both packaging sizes (Commercial and Physician' Sample) instead of one or the other.
11. The container label needs to specify the net contents (7.7 mL for Commercial and _____ for Physician's Sample) and the amount of volume (100 μ L or 0.1 mL) delivered per spray. b(4)
12. Include the following statements in the product label:
STORE IN UPRIGHT POSITION.
DO NOT FREEZE.
AVOID PROLONGED PRODUCT EXPOSURE TO ABOVE 30°C.

If you have any questions, call Scott N. Goldie, Ph.D., Regulatory Health Project Manager for Quality, at (301) 796-2055.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief
Division of Pre-Marketing Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ramesh Sood
8/7/2008 12:15:07 PM

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NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 22-196 Supplement #

Proprietary Name: ZolpiMist
Established Name: Zolpidem Tartrate oral spray
Strengths: 5 mg/100 µL metered spray; 2 sprays = 10 mg.

Applicant: Nova Del Pharma., Inc.
Agent for Applicant (if applicable):

Date of Application: 11/20/07
Date of Receipt: 11/21/07
Date clock started after UN:
Date of Filing Meeting: 1/14/08
Filing Date: 1/20/08
Action Goal Date (optional): 9/21/08 User Fee Goal Date: 9/21/08

Indication(s) requested: Insomnia; label update; negative Pediatric Indication (under PWR); safety information updated

Type of Original NDA: (b)(1) (b)(2) X
AND (if applicable)
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 or efficacy supplement is a (b)(2), complete Appendix B.

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

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

User Fee Status: Paid X 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 by contacting the User Fee staff in the Office of Regulatory Policy. 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.

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

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication N/A NO

- 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)]? N/A 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
If no, explain:

- 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:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES X
This application is: All electronic X Combined paper + eNDA
This application is in: NDA format CTD format X
Combined NDA and CTD formats

- Does the eNDA, follow the guidance? YES X NO
(<http://www.fda.gov/cder/guidance/2353fn1.pdf>)

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES X NO
If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

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

- Exclusivity requested? YES 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 . . ."

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included?
Spon req full waiver YES X NO

- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO

- Is this submission a partial or complete response to a pediatric Written Request? YES NO X

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES X NO
(Forms 3454 and/or 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) YES X NO

- PDUFA and Action Goal dates correct in tracking system? 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: #71,290 _____

- Are the trade, established/proper, and applicant names correct in COMIS? YES X NO
If no, have the Document Room make the corrections.

- End-of-Phase 2 Meeting(s)? Date(s) P-IND mtg 8/31/05 NO
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) _____ NO X
If yes, distribute minutes before filing meeting.

- Any SPA agreements? Date(s) _____ NO X
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES X NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES X NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? Pending 7/18/08 X NO
YES
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES X NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?
MG already appr under Ambien ref drug; review in progress YES NO
- Risk Management Plan consulted to OSE/IO? As above YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? Need to Verify 7/18/08 YES X NO

If Rx-to-OTC Switch or OTC application:

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? Subm cons 12/7/07 Yes X NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES X NO
If no, did applicant submit a complete environmental assessment? YES X NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: 1/14/08

NDA #: 22-196

DRUG NAMES: ZolpiMist (zolpidem tartrate) oral spray 5mg delivered 100 µL.

APPLICANT: NovaDel Pharma.

BACKGROUND: This is a 505 b2 applicant for ZolpiMist (zolpidem tartrate) oral spray. Reference drug is Ambien NDA 19908- 5 and 10 mg tablets. Basis of 505 b2 is change in formulation and drug delivery system. Indication is the same: short term treatment of insomnia characterized by difficulties with sleep initiation.

ATTENDEES:

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

Discipline/Organization

Reviewer

Medical:

D. Elizabeth McNeil, M.D., June Cai, MD

Chemistry:

Martha Heimann, PhD

Statistical:

Ohid Siddiqui, Ph.D.

Pharmacology:

Melissa Banks, Ph.D.

Biopharmaceutical:

Jagan Parepally, PhD

Regulatory Project Management:

Cathleen Michaloski, BSN, MPH

Other Consults:

DSI, CSS, DMETS (EMs and Tradename)

Per reviewers, are all parts in English or English translation? YES X NO

If no, explain:

CLINICAL FILE X REFUSE TO FILE

- Clinical site audit(s) needed? Clin pharm -DSI YES X NO

If no, explain:

- Advisory Committee Meeting needed? N/A YES, date if known NO

- 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?

N/A YES NO

STATISTICS FILE X REFUSE TO FILE

| | | | | |
|---|------|--------------------------|----------------|--------------------------|
| BIOPHARMACEUTICS | FILE | X | REFUSE TO FILE | <input type="checkbox"/> |
| • Biopharm. study site audits(s) needed? | YES | X | NO | <input type="checkbox"/> |
| PHARMACOLOGY/TOX | FILE | X | REFUSE TO FILE | <input type="checkbox"/> |
| • GLP audit needed? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| CHEMISTRY | FILE | X | REFUSE TO FILE | <input type="checkbox"/> |
| • Establishment(s) ready for inspection? | YES | X | NO | <input type="checkbox"/> |
| • Sterile product? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |
| If yes, was microbiology consulted for validation of sterilization? | YES | <input type="checkbox"/> | NO | <input type="checkbox"/> |

ELECTRONIC SUBMISSION:

Any comments: no

REGULATORY CONCLUSIONS/DEFICIENCIES:

(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- X The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- X Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

- Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
- If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
- If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
- If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
- Convey document filing issues/no filing issues to applicant by Day 74.

Cathleen Michaloski, BSN, MPH
Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original 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) 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, or
- (3) 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) 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, and.
- (3) 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) 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, or
- (3) 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.

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**Appendix B to NDA Regulatory Filing Review
Questions for 505(b)(2) Applications**

1. Does the application reference a listed drug (approved drug)? YES NO

If "No," skip to question 3.

2. Name of listed drug(s) referenced by the applicant (if any) and NDA/ANDA #(s): Ambien (zolpidem tartrate) IR 5 and 10 mg; NDA 19-908

3. Is this application for a drug that is an "old" antibiotic (as described in the draft guidance implementing the 1997 FDAMA provisions? (Certain antibiotics are not entitled to Hatch-Waxman patent listing and exclusivity benefits.)

YES NO

If "Yes," skip to question 7.

4. Is this application for a recombinant or biologically-derived product?

YES NO

If "Yes" contact your ODE's Office of Regulatory Policy representative.

5. The purpose of the questions below (questions 5 to 6) is to determine if there is an approved drug product that is equivalent or very similar to the product proposed for approval that should be referenced as a listed drug in the pending application.

- (a) Is there a pharmaceutical equivalent(s) to the product proposed in the 505(b)(2) application that is already approved?

YES NO

(Pharmaceutical equivalents are drug products in identical dosage forms that: (1) contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; (2) do not necessarily contain the same inactive ingredients; and (3) meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. (21 CFR 320.1(c))

If "No," to (a) skip to question 6. Otherwise, answer part (b and (c)).

- (b) Is the pharmaceutical equivalent approved for the same indication for which the 505(b)(2) application is seeking approval?

YES NO

- (c) Is the approved pharmaceutical equivalent(s) cited as the listed drug(s)?

YES NO

If "Yes," (c), list the pharmaceutical equivalent(s) and proceed to question 6.

If "No," to (c) list the pharmaceutical equivalent and contact your ODE's Office of Regulatory Policy representative.

Pharmaceutical equivalent(s):

6. (a) Is there a pharmaceutical alternative(s) already approved? YES X NO

(*Pharmaceutical alternatives* are drug products that contain the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form or as the same salt or ester. Each such drug product individually meets either the identical or its own respective compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times and/or dissolution rates. (21 CFR 320.1(d)) Different dosage forms and strengths within a product line by a single manufacturer are thus pharmaceutical alternatives, as are extended-release products when compared with immediate- or standard-release formulations of the same active ingredient.)

If "No," to (a) skip to question 7. Otherwise, answer part (b) and (c).

- (b) Is the pharmaceutical alternative approved for the same indication for which the 505(b)(2) application is seeking approval? YES X NO
Short term treatment of difficulty w/ sleep initiation

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES X NO

If "Yes," to (c), proceed to question 7.

NOTE: If there is more than one pharmaceutical alternative approved, consult your ODE's Office of Regulatory Policy representative to determine if the appropriate pharmaceutical alternatives are referenced.

If "No," to (c), list the pharmaceutical alternative(s) and contact your ODE's Office of Regulatory Policy representative. Proceed to question 7.

Pharmaceutical alternative(s):

7. (a) Does the application rely on published literature necessary to support the proposed approval of the drug product (i.e. is the published literature necessary for the approval)? YES X NO

If "No," skip to question 8. Otherwise, answer part (b).

(b) Does any of the published literature cited reference a specific (e.g. brand name) product? Note that if yes, the applicant will be required to submit patent certification for the product, see question 12.

8. Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution"). This application provides for a new dose formulation (oral spray).

9. Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA may refuse-to-file such NDAs (see 21 CFR 314.101(d)(9)). YES NO X

10. Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application may be refused for filing under 21 CFR 314.101(d)(9)). YES NO X

11. Is the application for a duplicate of a listed drug whose only difference is that the rate at which the product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the RLD (see 21 CFR 314.54(b)(2))? If yes, the application may be refused for filing under 21 CFR 314.101(d)(9). YES NO

12. Are there certifications for each of the patents listed in the Orange Book for the listed drug(s) referenced by the applicant (see question #2)? (This is different from the patent declaration submitted on form FDA 3542 and 3542a.) YES NO

13. Which of the following patent certifications does the application contain? (Check all that apply and identify the patents to which each type of certification was made, as appropriate.)

Not applicable (e.g., solely based on published literature. See question # 7

21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA. (Paragraph I certification) None listed in Orange Book
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired. (Paragraph II certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire. (Paragraph III certification)
Patent number(s):

21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted. (Paragraph IV certification)
Patent number(s):

NOTE: IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must subsequently submit a signed certification stating that the NDA holder and patent owner(s) were notified the NDA was filed [21 CFR 314.52(b)]. The applicant must also submit documentation showing that the NDA holder and patent owner(s) received the notification [21 CFR 314.52(e)]. OND will contact you to verify that this documentation was received.

21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above).
Patent number(s):

Written statement from patent owner that it consents to an immediate effective date upon approval of the application.
Patent number(s):

21 CFR 314.50(i)(1)(ii): No relevant patents.

21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent as described in the corresponding use code in the Orange Book. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications. (Section viii statement)

Patent number(s):

14. Did the applicant:

- Identify which parts of the application rely on the finding of safety and effectiveness for a listed drug or published literature describing a listed drug or both? For example, pharm/tox section of application relies on finding of preclinical safety for a listed drug.

YES NO

If "Yes," what is the listed drug product(s) and which sections of the 505(b)(2) application rely on the finding of safety and effectiveness or on published literature about that listed drug

Was this listed drug product(s) referenced by the applicant? (see question # 2)

YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug(s)?

N/A YES NO

15. (a) Is there unexpired exclusivity on this listed drug (for example, 5 year, 3 year, orphan or pediatric exclusivity)? Note: this information is available in the Orange Book.

YES NO

If "Yes," please list:

| Application No. | Product No. | Exclusivity Code | Exclusivity Expiration |
|-----------------|-------------|------------------|------------------------|
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Cathleen Michaloski
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