CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-930

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

EXCLUSIVITY SUMMARY FOR NDA # **21-930**

Trade Name **none**

Generic Name **fluocinolone acetonide oil, 0.01% ear drops**

Applicant Name **Hill Dermaceuticals, Inc.** HFD # **520**

Approval Date If Known **November 9, 2005**

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 question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /X/ NO /___/

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

505(b)(2)

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 /X/ 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 /X/ NO /___/

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

Not specified

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

YES /___/ **NO /X/**

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen 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 /X/**

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 /X/ NO /___/

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

NDA# 19-452 **fluocinolone acetonide oil, 0.01%**

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# _____ _____

NDA# _____ _____

NDA# _____ _____

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 NDA'S 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 /X/ 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 /X/ 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 /X/**

(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 /X/**

If yes, explain:

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:

Investigation #1, Study # 31 A
Investigation #2, Study # 31 B

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 /X/**

Investigation #2 YES /___/ **NO /X/**

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 /X/**

Investigation #2 YES /___/ **NO /X/**

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"):

Investigation #1, Study # 31 A
Investigation #2, Study # 31 B

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 # **62,690** **YES /X/** ! NO /___/ Explain: _____

Investigation #2 !

IND # **62,690** **YES /X/** ! 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 /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ 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: _____

Preparer: **Michael Puglisi**
Title: **Project Manager**

Concurrence by: **Wiley A. Chambers, M.D.**
Title: **Deputy Division Director**

Form OGD-011347 Revised 05/10/2004

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

/s/

Wiley Chambers
11/21/2005 01:56:57 PM

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA # : 21-930

Stamp Date: May 9, 2005 Action Date: November 9, 2005

HFD-520

Trade and generic names/dosage form: Fluocinolone Acetonide Topical Oil, 0.01%

Applicant: Hill Dermaceuticals, Inc. Therapeutic Class: Corticosteroid

Indication(s) previously approved: treatment of atopic dermatitis in children and adults; treatment of scalp psoriasis in adults

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1:

Treatment of chronic eczematous external otitis

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:

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:

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:

Min _____	**kg**_____	**mo.**_____	**yr.** 2	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** adult	**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.

This page was completed by:

{See appended electronic signature page}

_____
Michael Puglisi
Consumer Safety Officer

cc: NDA 21-930
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: 9/23/05

TO: Michael Puglisi, Title, Regulatory Project Manager
Wiley Chambers, M.D., Clinical Reviewer
Division of Anti-infective and Ophthalmic Drug Products, HFD-520

THROUGH: Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

FROM: Dianne D. Tesch, Consumer Safety Officer

SUBJECT: Evaluation of Clinical Inspections

NDA: #21-930

APPLICANT: Hill Dermaceuticals, Inc.

DRUG: [redacted]

THERAPEUTIC CLASSIFICATION: 6P

INDICATION: Treatment of chronic eczematous external otitis.

CONSULTATION REQUEST DATE: June 13, 2005

DIVISION GOAL DATE: August 31, 2005

PDUFA GOAL DATE: November 5, 2005

I. BACKGROUND:

Chronic eczematous external otitis is most commonly associated with other typical atopic eczematous conditions. It is characterized by itching, plugging of the ear, ear pain, enlarged tender lymph nodes, a red ear canal, purulent discharge and eczematous changes of the pinna.

Treatment consists of thorough cleansing of the ear canal to remove debris, then application of anti-itch, anti-inflammatory topical treatment.

Fluocinolone acetonide is a topical corticosteroid which has been used for many years as a topical anti-inflammatory in a variety allergic type skin conditions. It has anti-inflammatory, anti-pruritic and vasoconstrictive properties. [redacted] is in the low to medium range of potency for topical steroids. The sponsor is seeking approval for new indication, and with the inclusion of some pediatric patients aged 2-6.

The primary efficacy variable is an index of total signs and symptoms severity score in the affected area(s) to include: area of the ear involved, erythema or redness on a scale of 0-3, scaling from 0-3, erosion/oozing, crusting from 0-3, description of appearance of the skin from 0-2, and degree of pruritis from 0-3.

The investigators were chosen for the high enrollment at their sites. The medical officer does not have any special concerns about data integrity. Dr. Bradley Reese has three studies listed in the Clinical Investigator System (CIS) data base. He has no inspection history. Dr. Jack Anon has ten studies listed in CIS. He has had one prior inspection which took place September 28 to October 4, 2004. The inspection was issued as a for cause investigation surrounding allegations made by a study coordinator who said that Dr. Anon made false statements regarding the efficacy of a device and drug he was investigating during the Open Public Hearing portion of the Anti-Infective Drug Advisory Committee Meeting on October 29, 2003. The coordinator also claimed that Dr. Anon: misstated the microbiological results of specimens obtained during the study, falsely stated how specimens were obtained, made false claims about the success of the device, and failed to report adverse events (AEs) experienced by the subjects. The case remains under review, but most likely will be classified VAI for failure to maintain adequate and accurate records, and failure to follow the investigational plan.

RESULTS (by protocol/site):

Name of CI and site #, if known	City, State	Protocol	Insp. Date	EIR Recd.	Classn.
Bradley Reese, M.D.	Orlando, FL	31	8/3,4/05	8/17/05	NAI
Jack Anon, M.D.	Erie, PA	31	8/9,10,11, 18/05	9/21/05	VAI

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

A. Protocol #31 "Safety and Efficacy of [redacted] in the Treatment of Pediatric Patients with Chronic Eczematous External Otitis"

1. Site #1 Bradley Reese, M.D., Orlando, FL. The data were acceptable:

   a. The inspection took place August 3 and 4, 2005. Sixty subjects were consented, forty nine were randomized, and forty six subjects completed the study. Seventeen records were reviewed in depth for the inspection.

   b. There were no limitations to the inspection.

   c. There was only one minor discrepancy between the source documents and the data listings supplied by the sponsor. The records were well organized and legible. No 483 was issued.

   d. The data are acceptable for consideration in the NDA review decision.

2. Site #2 Jack Anon, M.D., Erie, PA. The data were acceptable

   a. The inspection took place August 9, 10, 11, and 18, 2005. 63 subjects were enrolled at the site. Twenty-two records were reviewed in depth for the inspection.

   b. There were no limitations to the inspection.

   c. The single observation on the Form FDA 483 was lack of IRB approval for the study from 12/9/03 through 1/13/04. IRB approval expired 12/9/03. Re-approval was not granted until 1/13/04. During that period two subjects were enrolled and dispensed study drug. The lapse is most likely due to clerical oversight. The lapse did not affect subject safety or data quality.

   d. The data are acceptable for consideration in the NDA review decision.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

There were no deficiencies found at Dr. Reese's site. There was a one month lapse in IRB approval at Dr. Anon's site which is most likely attributable to clerical oversight rather than clinical deficiency. It did not impact patient safety or data integrity and reliability.

No follow up action is indicated other than routine surveillance.

Dianne D. Tesch, CSO
GCPB Reviewer

CONCURRENCE:

Supervisory comments

Leslie K. Ball, M.D.
Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations

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

/s/

Dianne Tesch
9/27/2005 08:09:16 AM
CSO

Leslie Ball
9/28/2005 08:33:23 PM
MEDICAL OFFICER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-930

Hill Dermaceuticals, Inc.
Attention: Rosario G. Ramirez, M.D.
Director, Medical and Regulatory Affairs
2650 South Mellonville Avenue
Sanford, Florida 32773

Dear Dr. Ramirez:

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

Name of Drug Product: [redacted] (fluocinolone acetonide)

Review Priority Classification: Priority (P)

Date of Application: May 4, 2005

Date of Receipt: May 9, 2005

Our Reference Number: NDA 21-930

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 8, 2005, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be November 9, 2005.

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. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to one of the following address:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products, HFD-520
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Anti-Infective and
Ophthalmology Products, HFD-520
9201 Corporate Boulevard
Rockville, Maryland 20850-3202

If you have any questions, call Michael Puglisi, Project Manager, at (301) 827-2090.

Sincerely,

{See appended electronic signature page}

Maureen P. Dillon-Parker
Chief, Project Management Staff
Division of Anti-Infective and
Ophthalmology Products, HFD-520
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

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

/s/

Maureen Dillon-Parker
6/15/05 03:43:04 PM
NDA 21-930 Acknowledgement Letter

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-930		
Drug: Fluocinolone Acetonide Topical Oil, 0.01%	**Applicant: Hill Dermaceuticals, Inc.**	
RPM: Michael Puglisi	**HFD-520**	**Phone # 301-796-0791**

Application Type: ( ) 505(b)(1) **(X) 505(b)(2)** (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) *If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.* (X) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s): NDA 12-787

❖ Application Classifications:	
• Review priority	( ) Standard **(X) Priority**
• Chem class (NDAs only)	**Type 6**
• Other (e.g., orphan, OTC)	**N/A**
❖ User Fee Goal Dates	**November 9, 2005**
❖ Special programs (indicate all that apply)	**(X) None** Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	( ) Paid UF ID number -
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) **(X) Other (specify) -not a human drug application for purposes of user fee**
❖ Application Integrity Policy (AIP)	

• Applicant is on the AIP	( ) Yes **(X) No**
• This application is on the AIP	( ) Yes **(X) No**
• Exception for review (Center Director's memo)	**N/A**
• OC clearance for approval	**N/A**
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	**(X) Verified**
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	**(X) Submitted**
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) **(X) Verified** 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's 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)? *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 box below (Exclusivity).* *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 ( ) Yes ( ) No ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the 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)? *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 box below (Exclusivity).* *If "**No**," continue with question (5).*	( ) Yes ( ) No
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the 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 within the 45-day period). *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 box below (Exclusivity).* *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.*	( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	**Summary complete and in Package, No remaining exclusivity.**
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ **(X) No**

General Information	
Actions	
• Proposed action	**(X) AP** ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	**none**
• Status of advertising (approvals only)	**(X) Materials requested in AP letter** ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	**(X) Yes** ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	**(X) None** ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	**N/A**
• Most recent applicant-proposed labeling	**In Package - submitted 11/8/05**
• Original applicant-proposed labeling	**In Package - submitted 5/4/05**
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	**DDMAC- 9/1/05** **DMETS- 8/25/05**
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	**N/A**
• Applicant proposed	**In Package – submitted 5/4/05**
• Reviews	**DDMAC- 9/1/05** **DMETS- 8/25/05**
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	**N/A**
• Documentation of discussions and/or agreements relating to post-marketing commitments	**N/A**
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	**In Package**
❖ Memoranda and Telecons	**N/A**
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	**N/A**
• Pre-NDA meeting (indicate date)	**N/A**
• Pre-Approval Safety Conference (indicate date; approvals only)	**N/A**
Other	**N/A**
❖ Advisory Committee Meeting **N/A**	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	**N/A**
❖ Postmarketing Safety Review	**N/A**
❖ Office Director's Memo	**N/A**
Deputy Division Director's Memo	**11/8/05**
Clinical Team Leader's Memo	**N/A**

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	**11/8/05**
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	**N/A**
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	**In 11/8/05 Clinical Review**
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	**N/A**
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	**In Package**
❖ Demographic Worksheet *(NME approvals only)*	**N/A**
❖ Statistical review(s) *(indicate date for each review)*	**N/A**
❖ Biopharmaceutical review(s) *(indicate date for each review)*	**N/A**
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	**N/A**
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	**9/28/05**
• Bioequivalence studies	**N/A**
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	**10/4/05**
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	**In 10/4/05 CMC Review**
• Review & FONSI *(indicate date of review)*	**N/A**
• Review & Environmental Impact Statement *(indicate date of each review)*	**N/A**
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	**N/A**
❖ Facilities inspection (provide EER report)	**Date completed: 9/30/05** **(X) Acceptable** ( ) Withhold recommendation
❖ Methods validation	**(X) Completed** ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	**N/A**
❖ Nonclinical inspection review summary	**N/A**
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	**N/A**
❖ CAC/ECAC report	**N/A**