

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-140

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

EXCLUSIVITY SUMMARY

NDA # 20-140

SUPPL #

HFD # 150

Trade Name

Generic Name levoleucovorin calcium

Applicant Name Spectrum

Approval Date, If Known

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)(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 ☒

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?

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# 8-107

Leucovorin calcium

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 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:

Lederle high dose methotrexate protocols 76-5, 76-6, 76-7, 76-13, 76-16, 76-18, 76-19, 76-21, 76-22, and 76-23.

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 ☒

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"):

same as 2 c

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: —

YES ☒

!
!
!
!

NO ☐

! Explain:

In 1990, Lederle was the applicant for NDA 20-140. Spectrum is the current applicant for NDA 20-140 and all rights have been transferred to Spectrum. Spectrum certified that the studies in 2c were sponsored and funded entirely by its predecessor in interest, Lederle under IND: —

b(4)

Investigation #2

IND #

YES ☒

!
!
!
!

NO ☐

! Explain:

same response for all investigations in 2c

(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 ☒

If yes, explain:

Name of person completing form: Paul Zimmerman

Title: Project Manager

Date: 3-7-08

Name of Office/Division Director signing form:

Title:

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

/s/

Ann Farrell

3/7/2008 02:21:52 PM



SPECTRUM
PHARMACEUTICALS

Turning Insights into Hope

March 07, 2008

SPONSOR CERTIFICATION

On behalf of the NDA 20,140 applicant, Spectrum Pharmaceuticals, Inc., I hereby certify that the clinical studies listed below were sponsored and funded entirely by its predecessor of interest, Lederle Laboratories, Inc, a Division of Ameridcan Cyanamid Company, under _____

b(4)

Protocols 76-5, 76-6, 76-7, 76-13, 76-16, 76-18, 76-19, 76-21, 76-22 and 76-23

Cynthia Letizia

I attest to the accuracy and
integrity of this document
2008.03.07 10:09:28
-08'00'

Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA #: 20-140 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: 12-14-1990 PDUFA Goal Date: _____ PrePDUFA Goal date is 3-7-2008 _____

HFD 150 Trade and generic names/dosage form: ISO-Vorin (levoleucovorin calcium) for Injection

Applicant: Spectrum Pharmaceuticals Inc. Therapeutic Class: 5

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 question.
☒ 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): _____

Indication #1: _____

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 20-140

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

**FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700**

(Revised: 10/10/2006)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

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 copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

[See appended electronic signature page]

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700

(Revised: 10/10/2006)

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

/s/

Paul Zimmerman
2/26/2008 04:38:42 PM



SPECTRUM
PHARMACEUTICALS

Turning Insights into Hope

29 June 2007

DEBARMENT CERTIFICATION

On behalf of Spectrum Pharmaceuticals, Inc., I hereby certify that Spectrum Pharmaceuticals, Inc. 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.

Cynthia Letizia

2007.06.29
14:02:31 -07'00'

Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA 20-140 is pre User Fee and was submitted 12-14-1990 and a Not Approval letter was issued 1-3-1992.
The applicant submitted an activating amendment 7-10-2007.

NDA # 20-140 Supplement # Efficacy Supplement Type SE-

Proprietary Name: ISO-Vorin
Established Name: levoleucovorin calcium
Strengths: 50 mg/ 5 mL (10 mg/mL)

Applicant: Spectrum Pharmaceuticals, Inc
Agent for Applicant (if applicable):

Date of Application: 12-14-1990

Date of Receipt: 12-18-1990

Date clock started after UN:

Date of Filing Meeting:

Filing Date:

Action Goal Date (optional): 3-7-2008

User Fee Goal Date: preUser FEE

Indication(s) requested: ISO-VorinTM rescue is indicated after high-dose methotrexate therapy in osteosarcoma.
ISO-VorinTM is also indicated to diminish the toxicity and counteract the effects of impaired methotrexate elimination and of inadvertent overdosage of folic acid antagonists

Type of Original NDA: (b)(1) ☐ (b)(2) ☒
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 ☒ P ☐
Resubmission after withdrawal? ☐ Resubmission after refuse to file? ☐
Chemical Classification: (1,2,3 etc.) 5
Other (orphan, OTC, etc.) orphan

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

User Fee Status: PreUserFee Paid ☐ 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 ☒
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? YES ☐ 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)]? 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 ☒
If yes, explain:
- If yes, has OC/DMPQ been notified of the submission? YES ☐ NO ☐
- Does the submission contain an accurate comprehensive index? YES ☒ NO ☐
If no, explain:
- Was form 356h included with an authorized signature? YES ☒ NO ☐
If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES ☒ NO ☐
If no, explain:
- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

- This application is a paper NDA YES ☐
- This application is an eNDA or combined paper + eNDA YES ☒
This application is: All electronic ☐ Combined paper + eNDA ☒
This application is in: NDA format ☐ CTD format ☐
Combined NDA and CTD formats ☒

Does the eNDA, follow the guidance?

(<http://www.fda.gov/cder/guidance/2353fnl.pdf>)

YES ☐ NO ☐

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? **The 2007 activating amendment and onward are electronic.**

Additional comments:

- This application is an eCTD NDA. YES ☐

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

- Correctly worded Debarment Certification included with authorized signature? YES ☒ 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? YES ☒ 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 ☒

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? **Pre FD requirement** YES ☐ 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 ☐ NO ☐
- PDUFA and Action Goal dates correct in tracking system? YES ☒ 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:
- Are the trade, established/proper, and applicant names correct in COMIS? YES ☐ NO ☐
 If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO ☒
 If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) 7-15-2005 NO ☐
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO ☒
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 ☐ 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 ☒ 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? YES ☒ NO ☐
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES ☒ NO ☐
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A ☒ YES ☐ NO ☐
- Risk Management Plan consulted to OSE/IO? N/A ☒ YES ☐ NO ☐
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA ☒ YES ☐ 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? YES ☐ NO ☐

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES ☐ NO ☐
If no, did applicant submit a complete environmental assessment? YES ☐ 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: N/A. NDA 20-140 is pre PDUFA and was submitted 12-14-1990 and a Not Approval letter was issued 1-3-1992. The applicant submitted an activating amendment 7-10-2007. The review team agreed soon thereafter that the 7-10-2007 was a reviewable submission.

NDA #:

DRUG NAMES:

APPLICANT:

BACKGROUND:

(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES:

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

Discipline/Organization

Reviewer

Medical:
Secondary Medical:
Statistical:
Pharmacology:
Statistical Pharmacology:
Chemistry:
Environmental Assessment (if needed):
Biopharmaceutical:
Microbiology, sterility:
Microbiology, clinical (for antimicrobial products only):
DSI:
OPS:
Regulatory Project Management:
Other Consults:

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

YES ☐ NO ☐

CLINICAL

FILE ☐

REFUSE TO FILE ☐

- Clinical site audit(s) needed?

YES ☐ NO ☐

If no, explain:

- Advisory Committee Meeting needed?

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 ☐

CLINICAL MICROBIOLOGY N/A ☐ FILE ☐ REFUSE TO FILE ☐

STATISTICS N/A ☐ FILE ☐ REFUSE TO FILE ☐

BIOPHARMACEUTICS FILE ☐ REFUSE TO FILE ☐

- Biopharm. study site audits(s) needed?
YES ☐ NO ☐

PHARMACOLOGY/TOX N/A ☐ FILE ☐ REFUSE TO FILE ☐

- GLP audit needed? YES ☐ NO ☐

CHEMISTRY FILE ☐ REFUSE TO FILE ☐

- Establishment(s) ready for inspection? YES ☐ NO ☐
- Sterile product? YES ☐ NO ☐
- If yes, was microbiology consulted for validation of sterilization? YES ☐ NO ☐

ELECTRONIC SUBMISSION:

Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

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

- ☐ The application is unsuitable for filing. Explain why:
- ☐ 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.
- ☐ 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.)

5. ☐ Convey document filing issues/no filing issues to applicant by Day 74.

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.

**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):

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 ☒ 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 ☒ NO ☐

- (c) Is the approved pharmaceutical alternative(s) cited as the listed drug(s)? YES ☐ 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 ☐ 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 is for levoleucovorin. The listed drug is leucovorin (d,l leucovorin)

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 ☒

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 ☒

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)
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

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, March 04, 2008 3:28 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for levoleucovorin - 6.2

Attachments: Picture (Enhanced Metafile)

Cynthia,

In 6.2 we would like to change the current sentence from:

For 217 adverse reactions (108 reports) where levoleucovorin was a suspected, interacting, or concomitant medication, there were 40 occurrences of "possible allergic reaction."

to:

For 217 adverse reactions (108 reports) where levoleucovorin was a suspected or interacting medication, there were 40 occurrences of "possible allergic reaction."

We would like to make this change because your submission, dated 11-12-08, revised the wording from the original NDA submission to state that there were 217 AEs (as 108 reports) with levoleucovorin as "suspected or interacting" medication. This is stated in paragraph 1 of the attached document below. In paragraph 2, there is clarification that there were 252 reports (525 events) in which levoleucovorin was mentioned as "suspected or interacting or concomitant".

- FDA Question - Please explain why you selected events "of potential concern and potentially related to allergic reaction" from a pool of only 217 "unspecified indication" events, rather than from the entire pool of 252 events. You apparently have excluded events where the indication was "non-cancer" (n=4) and "cancer" (n=31).

The report, entitled "Analysis of The Uppsala Monitoring Center (UMC) database (Vigibase) to describe the safety profile of calcium levofolinate" and dated April 2, 2007, was based on standard methods of reporting information from the Uppsala Monitoring Centre (UMC) database. This method follows CIOMS guidelines to report those events where the physician considered a medication as either a suspected or interacting cause of the events. Individual events were searched on the preferred term for the reported reaction which was assigned according to the WHOART coding system. Using this methodology, the UMC identified 108 reports (217 events) that listed Calcium Levofolinate as either a suspected or interacting medication.

The process used to identify the number of reports that mentioned the indication of calcium of levofolinate used different search criteria. For this analysis, all reports (suspected, interacting and concomitant medication) which mentioned calcium levofolinate were searched for the listing of an indication. There were 252 reports (525 events) that listed calcium levofolinate as a suspected or interacting or concomitant medication.

In the report provided (date April 2, 2007), references to 252 reports were erroneously labelled as "252 events." As a result, the table list on page 4 of the April 2, 2007 report should read as below. The term "events" has been replaced by the term "reports" in bold.

"Listed indications - all reports mentioning calcium levofolinate

		% of total (252)
Non-cancer	4	1.59%
Cancer	31	12.30%
Unspecified	217	86.11%

*Indications listed as "Rectum", "Bone and Articular Cartilage" and "Stomach" were assumed to be cancer."

Thanks
Paul

Zimmerman, Paul F

From: Cynthia Letizia [CLetizia@spectrumpharm.com]
Sent: Tuesday, March 04, 2008 3:34 PM
To: Zimmerman, Paul F
Subject: RE: NDA 20-140 for levoleucovorin - 6.2

We concur, I will make this change and get it back to you.

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Tuesday, March 04, 2008 12:28 PM
To: Cynthia Letizia
Subject: NDA 20-140 for levoleucovorin - 6.2

Cynthia,

In 6.2 we would like to change the current sentence from:

For 217 adverse reactions (108 reports) where levoleucovorin was a suspected, interacting, or concomitant medication, there were 40 occurrences of "possible allergic reaction."

to:

For 217 adverse reactions (108 reports) where levoleucovorin was a suspected or interacting medication, there were 40 occurrences of "possible allergic reaction."

We would like to make this change because your submission, dated 11-12-08, revised the wording from the original NDA submission to state that there were 217 AEs (as 108 reports) with levoleucovorin as "suspected or interacting" medication. This is stated in paragraph 1 of the attached document below. In paragraph 2, there is clarification that there were 252 reports (525 events) in which levoleucovorin was mentioned as "suspected or interacting or concomitant".

- FDA Question - Please explain why you selected events "of potential concern and potentially related to allergic reaction" from a pool of only 217 "unspecified indication" events," rather than from the entire pool of 252 events. You apparently have excluded events where the indication was "non-cancer" (n=4) and "cancer" (n=31).

The report, entitled "Analysis of The Uppsala Monitoring Center (UMC) database (Vigibase) to describe the safety profile of calcium levofolinate" and dated April 2, 2007, was based on standard methods of reporting information from the Uppsala Monitoring Centre (UMC) database. This method follows CIOMS guidelines to report those events where the physician considered a medication as either a suspected or interacting cause of the events. Individual events were searched on the preferred term for the reported reaction which was assigned according to the WHOART coding system. Using this methodology, the UMC identified 108 reports (217 events) that listed Calcium Levofolinate as either a suspected or interacting medication.

The process used to identify the number of reports that mentioned the indication of calcium levofolinate used different search criteria. For this analysis, all reports (suspected, interacting and concomitant medication) which mentioned calcium levofolinate were searched for the listing of an indication. There were 252 reports (525 events) that listed calcium levofolinate as a suspected or interacting or concomitant medication.

In the report provided (date April 2, 2007), references to 252 reports were erroneously labelled as "252 events." As a result, the table list on page 4 of the April 2, 2007 report should read as below. The term "events" has been replaced by the term "reports" in bold.

"Listed indications – all reports mentioning calcium levofolinate

		% of total (252)
Non-cancer	4	1.58%
Cancer*	31	12.30%
Unspecified	217	86.11%

*Indications listed as "Rectum", "Bone and Articular Cartilage" and "Stomach" were assumed to be cancer."

Thanks
Paul

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, March 04, 2008 3:47 PM
To: 'Cynthia Letizia'
Subject: RE: NDA 20-140 SPL restriction on PI Highlights

Cynthia,

We are OK without the modifier "Present as levoleucovorin calcium" in line two. However, you should submit a justification why you cannot modify the structured data table to include this modifier. You should note that the SPL data standards do not preclude adding additional modifiers.

Paul

From: Cynthia Letizia [mailto:CLetizia@spectrumpharm.com]
Sent: Tuesday, March 04, 2008 2:30 PM
To: Zimmerman, Paul F
Subject: NDA 20-140 SPL restriction on PI Highlights

Dear Paul,

Our SPL vendor, — cannot modify the structured data table to include 'Present as levoleucovorin calcium' in line two (following 'for INTRAVEOUS USE') as this does not conform to the SPL data standard. b(4)

The 1.1 Limitations of Use in the FPI contents and body has been corrected. Please see attached WORD files for each presentation of the proprietary name.

Regards,

Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs
Spectrum Pharmaceuticals, Inc.
157 Technology Drive
Irvine, CA 92618
(949) 788-6700 x210
(949) 788-6708 (fax)
(949) 466-2183 (blackberry)
cletizia@spectrumpharm.com

CONFIDENTIALITY NOTICE

This message may contain material that is privileged, confidential and/or protected from disclosure and is for the sole use of the recipient to which it is addressed. If the reader of this message is not the intended recipient, please be advised that any reading, copying, forwarding or dissemination of this communication or any attachments is strictly prohibited, as is any other use of or taking of any action in reliance upon the same by persons or entities other than the intended recipient. If you have received this communication in error, please notify the sender or Spectrum Pharmaceuticals, Inc. immediately and delete the message and all attachments from your computer system.

From: Zimmerman, Paul F
Sent: Friday, February 29, 2008 4:22 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 - carton and container label

Regarding the carton we have the following comments:

- b(4)

1. The size and prominence of the established name needs to be at least one-half of the size and prominence of the proposed trade name.

Thanks
Paul

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

/s/

Paul Zimmerman
2/29/2008 04:42:37 PM
CSO

Zimmerman, Paul F

From: Colangelo, Kim M
Sent: Thursday, February 21, 2008 11:49 AM
To: Abraham, Sophia
Cc: Zimmerman, Paul F; Booth, Brian P; Duvall Miller, Beth A
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Thanks! It appears that, for the record, this is a (b)(2). Don't ask the applicant to do anything as this designation has no bearing on intellectual property protections.

From: Abraham, Sophia
Sent: Thursday, February 21, 2008 11:47 AM
To: Colangelo, Kim M
Cc: Zimmerman, Paul F; Booth, Brian P
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Kim,

I do not think it is a class labeling and no brand name was cited in the literature.

From: Colangelo, Kim M
Sent: Thursday, February 21, 2008 11:38 AM
To: Abraham, Sophia
Cc: Zimmerman, Paul F; Booth, Brian P
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Hello everyone,

Thanks for the clarification on this one...

Here is what the attorneys had to say on this one:
if you want that information to be in the label, and if the support comes from the literature (meaning the data is not owned by the applicant, nor do they have right of reference to the data) then it is a (b)(2).

What does that mean? In this situation, probably not much. Given that folic acid and the anti-convulsants mentioned are all "old" drugs, there are no patent/exclusivity issues to be concerned about. We likely won't need anything additional from the applicant.

Nevertheless, a couple of follow-up questions:
Does the literature cite any specific, brand-name product?
Is this information considered "class labeling"?

Thank you!
Kim

From: Abraham, Sophia
Sent: Thursday, February 14, 2008 9:39 AM
To: Colangelo, Kim M
Cc: Zimmerman, Paul F; Booth, Brian P
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Kim,

- Yes, L-leucovorin is known as folinic acid.

- L-leucovorin (or folinic) may be used in combination with either anti-convulsants.
- Folic acid is most commonly used in combination with anti-convulsants as a replacement for folate deficiency.
- L-leucovorin (or folinic acid) can be also used as a replacement therapy for folate deficiency.

From: Colangelo, Kim M
Sent: Wednesday, February 13, 2008 5:45 PM
To: Abraham, Sophia; Zimmerman, Paul F
Cc: Booth, Brian P; Duvall Miller, Beth A
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Forgive my ignorance: is L-leucovorin considered a folinic acid? Or is L-leucovorin commonly used in combination with either anti-convulsants and/or folic acid? (Perhaps that is normal practice of medicine for rescue therapy after high dose mtx.)

Just trying to figure out how the labeling statement provided below relates to the L-leucovorin...

Thanks!
 Kim

Kim Colangelo
 Associate Director for Regulatory Affairs
 Office of New Drugs, CDER, FDA
 301-796-0700 (OND IO main)
 301-796-0140 (direct)
 301-796-9856 (facsimile)
 Kim.Colangelo@fda.hhs.gov

From: Abraham, Sophia
Sent: Thursday, February 07, 2008 3:43 PM
To: Zimmerman, Paul F
Cc: Booth, Brian P; Colangelo, Kim M
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Yes, the literature for folic acid was used to confirm a drug interaction labeling statement for levoleucovorin. So we will wait

until Kim discuss it with (b)(2) folks.

From: Zimmerman, Paul F
Sent: Thursday, February 07, 2008 3:36 PM
To: Colangelo, Kim M
Cc: Farrell, Ann T; Scher, Nancy; Booth, Brian P; Abraham, Sophia; Pease, Dorothy W; Duvall Miller, Beth A
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Sopha, Brian
 Can you reply?
 Paul

From: Colangelo, Kim M
Sent: Thursday, February 07, 2008 2:28 PM
To: Zimmerman, Paul F
Cc: Farrell, Ann T; Scher, Nancy; Booth, Brian P; Abraham, Sophia; Pease, Dorothy W; Duvall Miller, Beth A
Subject: RE: NDA 20-140 for Isovorin - 505b2?

Paul,

The literature in this case was on studies with folic acid?

I will discuss with the (b)(2) folks and get back to you. Even if it meets the definition of a (b)(2) not sure that there will be any issues (famous last words.)

Kim

From: Zimmerman, Paul F
Sent: Thursday, February 07, 2008 2:12 PM
To: Colangelo, Kim M
Cc: Farrell, Ann T; Scher, Nancy; Booth, Brian P; Abraham, Sophia; Pease, Dorothy W
Subject: NDA 20-140 for Isovorin - 505b2?

Kim,

Until this week, we considered this NDA from Spectrum a b1 but we just learned that ORP has determined that use of literature for the labeling, even if not required for approval, makes the NDA a 505(b)(2). With this determination we have the following that is b2

7 DRUG INTERACTIONS

Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children. It is not known whether folinic acid has the same effects. However, both folic and folinic acids share some common metabolic pathways. Caution should be taken when taking folinic acid in combination with anticonvulsant drugs.

This prePDUFA NDA was submitted 12-14-1990 and a Not Approval letter was issued 1-3-1992. The applicant submitted an activating amendment 7-10-2007. It is due 3-7-2008. There is no referenced listed drug. The NDA is for levoleucovorin calcium. Chemical Class 5.

Please let me know how we should proceed.

Thanks
Paul

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, February 21, 2008 5:14 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for levoleucovorin- carton and container

Dear Cynthia,

Regarding the recently submitted (2-12-08) proposed carton(s) and container(s) we have the following comments:

-the Rx Only statement needs to be more prominent.

-the regulations require that the size and prominence of the established name is at least one-half of the size and prominence of the proposed trade name. (This was previously included in the comments regarding Carton and container for ISO-Vorin.) The same should apply to the new established name(s) and trade name(s).

Please submit revised cartons and containers.

Thanks
Paul

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

/s/

Paul Zimmerman
2/21/2008 05:21:11 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, February 20, 2008 9:03 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for levoleucovorin

Dear Cynthia,

Regarding the 120-day safety update from 1991 Isovorin we have the following:

Email segments 4 and 5 of Volume 2 (of 13) of the safety update reference patients treated with 5FU and levoleucovorin, including new patients. The first 3 segments seem to contain the osteosarcoma data.

The submission is entitled I-leucovorin tablets safety update report, NDA20-141, dated May 16, 1991. It seems to include summary tables for I-leucovorin, IV and oral, not distinguishing which formulation was used for a particular patient/course.

There is no narrative explanation of the methodology used to obtain the data in volume 2. Perhaps this is in Volume 1, from which you could provide some narrative summary.

You have stated that the update submits data for **9 new patients treated with 50 courses and 8 previously reported patients who received an additional 48 courses.**

- **Please clarify that the number of new patients and new courses refers specifically to osteosarcoma patients only.**
- **Please provide us with a brief synopsis of any new and unexpected safety information contained in the 120-day safety update as it pertains to treatment of osteosarcoma.**

Thanks,
Paul

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

/s/

Paul Zimmerman
2/20/2008 09:09:40 AM
CSO

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

/s/

Paul Zimmerman
2/19/2008 04:47:52 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, February 19, 2008 4:32 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for levoleucovorin

Attachments: PI SENT TO SPECTRUM 2-19-08.doc

Dear Cynthia,

We have reviewed your proposed package insert and have made revisions. The attached is clean copy in Word of the proposed package insert with our revisions. Please note that we have asked you to revised ADVERSE REACTIONS and OVERDOSAGE. Regarding REFERENCES, I will contact you tomorrow as to whether this section should be in this package insert. We would like you to submit Package Insert labeling for _____ as soon as possible. Please let me know if you have any questions. (Please do not use a trademark symbol in the PI. SPL does not convert this symbol.)

b(4)



PI SENT TO
CTRUM 2-19-08.c

Thanks
Paul

7 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Paul Zimmerman
2/19/2008 04:46:22 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, February 08, 2008 12:07 PM
To: _____ 'Cynthia Letizia'
Subject: FW: NDA 20-140 Request for Labeling Information of 30-Jan-2008

b(6)

Attachments: 2008-02-01 Response to FDA Info Req Labeling of 2007-01-30.pdf



2008-02-01
sponse to FDA In

Cynthia,

Regarding your 2-1-08 communication:

You reference a Lederle 120-day safety update from May 16, 1991, which submits data for nine new patients treated with 50 courses and eight previously reported patients who received an additional 48 courses. We are having difficulty locating these volumes (2 of 13).

Our understanding is that the tables you have provided, 6A and 7A, demonstrate the # of doses levoleucovorin per course and total mg per course for the entire study population, incorporating the data from the original patients/courses and the new patients/courses from the 120-day update.

Please provide us with a brief synopsis of and new and unexpected safety information contained in that 120-day safety update, as well as your new proposal for the label (with explanation for numeric changes).

You also reference and submitted a copy of table 9 in the ISS (vol 33, p 14). This is the same table that we referenced as "CSR, Sponsor Table 7".

Thanks,
Paul

-----Original Message-----

From: _____
Sent: Friday, February 01, 2008 3:03 PM
To: Zimmerman, Paul F
Cc: _____
Subject: NDA 20-140 Request for Labeling Information of 30-Jan-2008

b(6)

Dear Paul,

Please find attached the response to the information request of 30-Jan-2008 regarding proposed labeling for NDA 20-140. The response incorporates NDA extracts linked from the blue text references.

Today's response and the previous email responses to labeling information requests of 17-Jan-2008 as well as the microbiology report to support sterility for the _____ reconstitution hold time will be compiled into an NDA Amendment next week. One micro test had to be repeated due to a dilution error, but results to date are negative for microbial growth.

b(4)

The request for review of the alternative tradename(s) will be sent separately on Monday.

Please do not hesitate to contact me through my personal email account at

~~_____~~ The company email server is undergoing repairs.

b(6)

I may also be reached at ~~_____~~

Regards,

Cynthia

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

/s/

Paul Zimmerman
2/8/2008 12:12:14 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, February 07, 2008 12:25 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - Label

Dear Cynthia,

As discussed, we have the following concerning labeling. Additional comments may be provided as our review continues.

Container/Carton and PI Labeling Comments:**General Comments**

1. In your proposed trade name, reflect a standard upper/lower case presentation and eliminate the use of "tall-man" lettering.
2. Your proposed proprietary and established names are currently written in dual colors. For the purposes of clarity, eliminate the use of dual colors for the proposed proprietary and established names and revise accordingly.
3. Please insert the equivalence statement in the container and carton labels.
4. The product is provided as a single-use vial without preservatives, containing 50 mg. The usual indicated dose is 7.5 mg every 6 hours. :

b(4)

 Since the vial size does not more closely match the individual dose, there is enhanced risk of administration of a contaminated product. See the comment below.

5. Please incorporate a statement in your proposed container and carton labeling to specify the maximum allowable holding time for the reconstituted solution (i.e. "reconstituted solution must be used within 4 hours").

Container Labeling Comments

1. See General Comment 1 above.
2. The swoosh that appears above and beneath the proprietary name distracts from the prominence of the proprietary name. Eliminate the swoosh that appears above and beneath the proposed proprietary name.
3. Revise "IV" to "intravenous".
4. Revise "sterile diluent" to "0.9% Sodium Chloride Injection, USP".
5. The "Rx Only" statement distracts from the prominence of the dosage strength. Reduce the prominence of the "Rx Only" statement and relocate the strength closer to the proprietary and established names to improve readability.
6. Ensure that the size and prominence of the established name is at least one-half of the size and prominence of the proposed trade name.
7. Relocate the dosage strength statement to be closer to the established name.

Carton Labeling Comments

1. See General Comments 1-5 above.
2. See Container Comments 2-7 above.

Thanks
Paul

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

/s/

Paul Zimmerman
2/7/2008 12:33:11 PM
CSO

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

/s/

Paul Zimmerman
1/30/2008 03:15:47 PM
CSO

Zimmerman, Paul F

From: Cynthia Letizia [CLetizia@spectrumpharm.com]
Sent: Tuesday, January 29, 2008 12:51 PM
To: Zimmerman, Paul F
Subject: RE: NDA 20-140 for Isovorin - label - information request for anticonvulsant interaction statement
Attachments: 2008-01-29 eml response.zip

Dear Paul,

With reference to the abstracts sent in the email response of January 17, 2008, the citations and PubMed search results are provided herein. These will be included in a forthcoming eCTD-NDA amendment.

Please let me know if there are additional questions on this or any other aspect of the proposed labeling.

Regards,

Cynthia

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Thursday, January 17, 2008 5:35 AM
To: Cynthia Letizia; John Spoden
Subject: NDA 20-140 for Isovorin - label

Dear Cynthia,

The DRUG INTERACTIONS section of the proposed Isovorin label states, "Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children."

Please provide evidence that **folinic acid may counteract the antiepileptic effect of drugs.**

Thanks
Paul

1/29/2008

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

/s/

Paul Zimmerman
1/29/2008 01:08:11 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, January 17, 2008 8:35 AM
To: 'Cynthia Letizia'; 'John Spoden'
Subject: NDA 20-140 for Isovorin - label

Dear Cynthia,

The DRUG INTERACTIONS section of the proposed Isovorin label states, "Folic acid in large amounts may counteract the antiepileptic effect of phenobarbital, phenytoin and primidone, and increase the frequency of seizures in susceptible children."

Please provide evidence that **folinic acid may counteract the antiepileptic effect of drugs.**

Thanks
Paul

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

/s/

Paul Zimmerman
1/17/2008 08:39:27 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, January 08, 2008 4:37 PM
To: 'Cynthia Letizia'; 'John Spoden'
Subject: NDA 20140 for Isovorin - Micro request

Dear John, Cynthia,

We have the following from our Microbiology review. (To facilitate the review, when you submit your response as an amendment, please also send that response to me by email as you have been doing)

Concerning drug product manufacturing,

1. Please justify the 2 year interval for requalification of the _____
2. Please provide a current copy of _____ and also a current copy of _____
3. The sterilization process validation report _____ for the _____
_____ was not received in readable form in the submission. Please re-submit the report.
4. Please provide summaries of the most recent _____, revalidations
that support the following:
 - a. _____
 - b. _____
 - c. _____

b(4)

Thanks
Paul

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

/s/

Paul Zimmerman
1/8/2008 04:40:25 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Monday, January 07, 2008 8:34 AM
To: 'Cynthia Letizia'; 'John Spoden'
Subject: NDA 20-140 for Isovoron

Dear Cynthia,

We have the following concerning the Proprietary name.

Proprietary name

DMETS does not recommend the use of the proprietary name, Iso-vorin. DMETS recommends that the sponsor propose an alternate proprietary name, and DMETS strongly suggests that the sponsor's alternate proprietary name not incorporate "vorin" in the names to avoid dosing errors related to name confusion with leucovorin calcium.

Thanks,

Paul

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

/s/

Paul Zimmerman
1/7/2008 08:58:14 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, December 19, 2007 11:50 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - Labeling

Dear Cynthia,

We have the following comments regarding the package insert. Additional comments may be provided as our review continues.

Comment 1

Please refer to the Drug Interactions section of your proposed ISO-Vorin label, and specifically to the following statement:

"Preliminary — human studies have shown that small quantities of systemically administered leucovorin enter the CSF primarily as 5-methyltetrahydrofolate and, in humans, remain 1-3 orders of magnitude lower than the usual methotrexate concentrations following intrathecal administration."

b(4)

This statement is unclear and unsupported by your NDA submission. Please provide study reports that support this statement and provide clearer, more specific wording to describe this potential drug-drug interaction and the risks it may pose to patients.

Comment 2

Please refer to Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) of your proposed ISO-Vorin label and specifically to the following statement:

"No studies have been conducted to evaluate the potential of levoleucovorin in these areas"

Please provide your literature search strategy to support this statement in the label.

Comment 3

Please refer to Section 13.2 (Animal Toxicology And/Or Pharmacology) of your proposed ISO-Vorin label, and specifically to the following statement:

b(4)

—
Please provide a clear description of high-dose levoleucovorin toxicity in the animal toxicology and/or pharmacology portion of the label. We believe that toxicities seen in animals such as rapid breathing, sedation, tremors, convulsions and seizures raise concern.

Thanks,
Paul

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

/s/

Paul Zimmerman
12/19/2007 11:54:02 AM
CSO

TELECON MINUTES

TELECON DATE: 12-12-07

NDA: 20-140 **DRUG:** Isovorin **SPONSOR:** Spectrum

FDA ATTENDEES:

Robert Mello, Ph.D., Microbiological Reviewer/12-14-07

James McVey, Ph.D., Microbiological Team Leader/12-18-07

David Hussong, Ph.D., Associate Director, OPS-Microbiology/ 12-18-07

Paul Zimmerman, R.Ph., Project Manager

APPLICANT:

Ashok Gore, PhD., Sr. Vice President, Pharmaceutical Development & Quality Assurance

Cynthia Letizia, MPH, RAC, Vice President, Regulatory Affairs

John Spoden, B.S., Director, Regulatory Affairs

Van Huynh, B.S. Associate Director, Pharmaceutical Development

Bahman Shimiæi, B.S., Associate Director, Pharmaceutical Development

Background:

The purpose of the telecon was to discuss applicant's statement in the submitted draft labeling

On 11-28-07, the FDA notified the applicant as follows:

Please be advised that labeling that recommends post-penetration reconstituted drug product holding periods **beyond 4 hours** must be supported by well defined experimental data that extend beyond the labeled holding period. Therefore, please provide microbiological data supporting the — holding period following reconstitution of the drug product. Alternatively, the labeling could be changed to indicate use within 4 hours of reconstitution.

b(4)

The applicant requested a telecom to discuss this.

Discussion:

The FDA noted that due to contamination rates observed since 1994, the safe time for reconstituted products in general is considered to be 4 hours. Product development testing is needed to support longer periods. Generally for a — claim, a — testing period (twice as long as the claim) should be used. The test should be performed by the labeled reconstitution method using low inoculum levels, using suitable timepoints (e.g., at T = 0, 4, 8, 12, 18, 24, 48 hours) and suitable controls (saline). Replicate plating should be performed and the entire test should be replicated 1-2 times. Test organisms should include at the minimum, *S. aureus*, *C. albicans*, and a hospital based organism (e.g., *Burkholderia cepacia*). Inocula should be approximately 10^3 organisms per test vial, depending on the vial's volume. Incubation temperature should be 20-25°C and the assessment criterion should be not more than 0.5 log

b(4)

Page 2

increase in viable count after 24 hours. The applicant noted that they will quickly complete the proposed study. The FDA estimated the end of January as the latest target date for submitting the results of the study.

APPEARS THIS WAY ON ORIGINAL

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

/s/

Paul Zimmerman
12/21/2007 01:56:11 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, December 04, 2007 11:17 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - labeling - format

Dear Cynthia,

Regarding the 8-10-07 submission, the following labeling comments are our preliminary comments regarding formatting issues. Additional comments regarding content related issues will be provided as our review continues.

NDA 20-140 Labeling – Initial Formatting comments

Highlights: 201.57(a)

The Highlight section must be in Portrait, not Landscape and must be in 8 point font minimum and only one half page in maximum length. Must be in 2 column format (correct). (201.57(d)(8)

Correct ISO-Vorintm. (ISO-Vorin™)?

The initial US approval date is date that the molecular entity was first approved 201.57(a)(3).

b(4)

The Indications and Usage should include pharmacologic class.

The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

“(Drug/Biologic Product) is a (name of class) indicated for (indication(s)).”

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights. Please refer to the “Draft Guidance for

Industry: Labeling for Human Prescription Drugs — Determining Established Pharmacologic Class for Use in the Highlights of Prescribing Information” available at <http://www.fda.gov/cder/guidance/7472dft.pdf>.

All statements in the Highlights section must be cross-referenced, e.g., Isovorin is indicated for osteosarcoma (1)

Include a DOSAGE FORMS AND STRENGTHS section. (201.57(a)(8).

Adverse Reactions should include incidence rate (201.57(a)(11).

General company websites are not permitted in Adverse Reactions sections

Included the "Revised" at the end of the Highlights section in month/year format (201.57(a)(15).

Include a Separation line between Highlights and Table of Contents (201.57(d)(2).

Table of Contents (TOC):

TOC must be in 8 point font minimum and only one half page in maximum length.

Include warning (only) from box warning in bold (all caps) at the beginning of TOC

Section numbers do not need periods.

Sections titles should be bolded. Subsection are not bolded. 201.57(d)(10).

Include a Separation line between and TOC and FPI

Full Prescribing Information (FPI):

Include the boxed warning. See boxed warning comments from highlights.

See Implementation Guidance <http://www.fda.gov/cder/guidance/6005dft.htm> for proper cross-referencing throughout the FPI, e.g., [*see Warnings and Precautions (5.1)*].

ADVERSE REACTIONS

Do not include the places to report adverse reactions in this section, only in highlights.

Do not refer to adverse reactions as "adverse events."

The ADVERSE REACTIONS section does not follow the guidance and should be rewritten. See the guidance Guidance for Industry Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products — Content and Format at <http://www.fda.gov/cder/guidance/5537fml.htm>

Thanks,
Paul

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

/s/

Paul Zimmerman
12/4/2007 11:31:19 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, November 29, 2007 3:25 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - preliminary labeling

Attachments: LABELING COMMENTS SENT TO FIRM 11-29-07.doc

Dear Cynthia,

Attached are our preliminary labeling comments. Additional labeling comments will be provided as our review continues.

Thanks,
Paul



LABELING
COMMENTS SENT TO F

2 Page(s) Withheld

 Trade Secret / Confidential (b4)

× Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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

/s/

Paul Zimmerman
11/29/2007 03:38:41 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Thursday, November 29, 2007 3:29 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - Clinical request

Dear Cynthia,

We have the following request concerning our clinical review.

Thank you for the summary table of L-leucovorin references in you recent submission, covering the period August 2004 to November 6, 2007. None of these appear to deal with the proposed labeled indication. Please provide a summary table and references citing use of L-leucovorin for "rescue" after high dose methotrexate therapy in osteosarcoma and other indications. This may include earlier years, as well as updated to present, if available. Please provide your literature search strategy, as well.

Thanks,
Paul

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

/s/

Paul Zimmerman
11/29/2007 03:33:27 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, November 28, 2007 12:19 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - Micro

Dear Cynthia,

We have the following regarding the proposed label. Additional comments may be provided as our review continues.

The submitted draft labeling (see Reconstitution Instructions, page 5) states

Please be advised that labeling that recommends post-penetration reconstituted drug product holding periods **beyond 4 hours** must be supported by well defined experimental data that extend beyond the labeled holding period. Therefore, please provide microbiological data supporting the ——— holding period following reconstitution of the drug product. Alternatively, the labeling could be changed to indicate use within 4 hours of reconstitution.

b(4)

Thanks,
Paul

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

/s/

Paul Zimmerman
11/28/2007 12:23:38 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, November 14, 2007 8:47 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin

Dear Cynthia,

We have the following requests regarding this application.

- Is Spectrum currently marketing l-levoleucovorin in any jurisdiction or have they filed an application?
- To help us interpret the European postmarketing safety data, are you able to provide utilization data for any of the time periods/locations (e.g. # of units sold or similar)?
- At the time of submission of the pre-NDA briefing document by Targent in June 2005, they provided tables of published literature from January 1991 through November 2004 as part of the safety update. We request that you provide updated references from published literature for levoleucovorin.

Thanks,
Paul

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

/s/

Paul Zimmerman
11/14/2007 08:50:32 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, October 26, 2007 11:43 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin

Dear Cynthia,

We have the following request and we request a response as soon as possible ***to facilitate our review of the WHO post-marketing safety data.***

We reference section 5.3.6 of your NDA 20-140 for ISO-Vorin.

- In section 1.4 (page 5 of 309) you indicate there were "252 events mentioning calcium levofolate". Please explain why you selected events "of potential concern and potentially related to allergic reaction" from a pool of only 217 "unspecified indication" events," rather than from the entire pool of 252 events. You apparently have excluded events where the indication was "non-cancer" (n=4) and "cancer" (n=31).
- Regarding the 6 "events of potential concern" and the 40 "events-possible allergic reaction", we request that you specify the *number of individual* patients these events represent for each category and the 2 categories combined. How many patients experienced allergic reactions, anaphylactic shock, anaphylactoid reactions, and death?
- Please provide **individual case reports with narratives** so we can evaluate the "events of potential concern" and "possible allergic reaction".
- You have provided a list of I-leucovorin products which are marketed in Europe, which form the basis for the WHO reports. Please clarify if Spectrum is currently marketing I-leucovorin, under which names and which countries.

Thanks,
Paul

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

/s/

Paul Zimmerman
10/26/2007 11:46:53 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, October 24, 2007 2:11 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - CMC Information Request

Attachments: CMC IR 10-14-07.doc

Dear Cynthia,

(Please let me know when you receive this.)

Regarding NDA 20-140 for Isovorin, we have the following information requests and we request a response within 10 days. (The items below should be numbered 1 through 11 but due to a glitch they are not. I have included an identical word file that numbers them correctly.)



CMC IR
-14-07.doc (59 K)

CMC Information Request

1. **§ 3.2.S.1.2 Structure (3.0).** Include the molecular weight for the pentahydrate. Submit corrected information.
2. **§ 3.2.S.1.3 General Properties.** Revise description of chirality. Two of the four possible diastereomers have L-configuration in the amino acid moiety. There are also two that are levorotatory. Submit the revised description. For additional information on nomenclature for folic acid derivatives, see:

<http://www.chem.qmul.ac.uk/iupac/misc/folic.html>

3. **§ 3.2.S.3.2 Impurities.** Revise nomenclature in the entire section in order to avoid using the ambiguous L- and D- designations. Submit the revision. (See Comment 2, above).
4. **§ 3.2.S.4.2 Analytical Procedures.** Amend BTS-CM246, pages 22-32, to include absolute configuration (R or S) at each of the two chiral positions (2- and 4-) in all references to folinates (currently designated with L- and D-). Submit the revision.
5. **§ 3.2.S.5 Reference Standards.** You must have reference standards to use for HPLC determination of stereoisomers in § 3.2.S.4.2 Analytical Procedures [BioScreen (pages 22-32)].
 - Provide COA's for L,D-folate standard, D,D-folate standard, and D,L-folate standard as listed in § 3.2.S.4.2 (page 24).
 - Provide a COA for L,L-folate standard as tabulated in § 3.2.S.4.2, page 29.
 - Since the designations L- and D- are not applicable to folinates, provide alternate names which specify the stereochemistry at the 2- and 4- positions.
 - Identify each folinate standard by its unique IUPAC or CA Index name (including salt form and level of hydration).
3. **§ 3.2.P.1 (1.0) Description of Dosage Form.** The dosage form is a lyophilized powder. Add an appropriate description for the drug product being sure to address the following points: 1) after lyophilization and prior to reconstitution there is no liquid volume; 2) calcium levoleucovorin is calculated in terms of levofolinic acid (xx mg acid equivalent per vial), but the vial contains the _____; 3) include the amount of mannitol per vial; 4) the vial does not contain either _____

b(4)

4. **§ 3.2.P.1 (3.0) Composition Statement.** Your drug product is a lyophilized powder.
 - Submit an additional table of qualitative and quantitative components and composition to show the quantities in each vial. The drug substance must be in terms of the actual species in the vial and may include the equivalent weight of levofolinic acid.
 - Provide directions for reconstitution. Include a list or table of suitable diluents and any precautionary statements that may be necessary.
 - Provide a second table showing qualitative and quantitative components and composition per vial and per unit volume (milliliter) after reconstitution.
3. **§ 3.2.P.3.2 Batch Formula.** Your drug product is a lyophilized powder.
 - **(2.1) Component Composition for L-Leucovorin for Injection.** Revise this table to show the weight of calcium levofolate pentahydrate in each batch. You may also include the equivalent weight in terms of levofolinic acid. Submit the revision.
4. **§ 3.2.P.3.3 Manufacturing Process and Process Controls.**
 - **(1.2.1.1) Compounding.** Revise the formulation composition table to show the mass of calcium levofolate pentahydrate used. In addition, you may express the final concentration in terms of levofolinic acid equivalent, but this must be done in a way that eliminates confusion between the acid form and the calcium salt.
 - **Formulation of Product [Unexecuted Batch Record (see page 42-44 of 91)].** § 2.2 “Weight of anhydrous free Levofolinic acid (*L*-leucovorin) to add:” appears to incorrectly identify Target Conc. of *L*-Leucovorin Calcium (10 g/L) and Theoretical Wt. of *L*-Leucovorin Calcium to Add — In both cases, it appears these are equivalent weights in terms of anhydrous levofolinic acid. The actual (not theoretical) amount of *L*-Leucovorin Calcium needed from Lot A is found by calculation (dividing by the “as is” value). In a similar manner, § 2.3 - 2.7 appear to consistently apply incorrect designations for the calcium salt and acid forms. Make all necessary corrections in text, equations, and section headings in such a way as to eliminate any confusion between the actual form of material being added and the equivalent form; incorporate corrections into SOP’s; and submit a copy of the new unexecuted record. It is expected that these changes will be carried forward into production records.
5. **§ 3.2.P.5. Control of Drug Product**
 - **(1.0-1.2) Specifications.**
 - A. Revise “Assay” for Release and Stability Testing to no wider than: 90.0% - 110.0% of the target content amount (53 mg) rather than the label claim (50 mg). Submit revised specifications.
 - B. Links to BTS CM255 are nonfunctional. Repair and resubmit with corrections.
 - C. Sum of all related substances should include — to give a total of NMT —
Make appropriate corrections in tables.
 - D. Your current analysis for impurities (related substances) is inconsistent with the one used for the drug substance. In § 3.2.S.3.2 Impurities, you identify — yet analyze for only — Revise specifications and analytical protocols accordingly. (Note: This may require additional batch analyses, a revised stability protocol, and stability assessment). Consult the DMF holder in order to update and correlate impurity analyses. Submit revisions.
 - E. Current specifications allow the sum of all related substances (impurities) to be no more than — However, in § 3.2.P.5.6.1.4 Justification of Specifications, you state “*The sum of all impurities has been set not to exceed — to account for the increase in impurities that may be formed during the product shelf-life storage.*” Reconcile this apparent contradiction.
 - **(2.0) Analytical Procedures.** See Comment 2, above, and make all necessary changes in designations of stereoisomers in BioScreen method CM246.R01 (HPLC of Stereoisomers in *L*-

b(4)

b(4)

Leucovorin Calcium Drug Substance and Drug Product). Provide updated material.

11. **§ 3.2.P.6 Reference Standards and Materials**

- Comment 5 (above) also applies to this section. Add information on reference standards for all four folinate stereoisomers.
- Add reference standards as needed for revised analytical methods per comment 10(D), above. Include *l*-leucovorin calcium and *d*-leucovorin calcium.
- Submit copies of COA's or evidence of structure and purity for all reference standards.

Thanks,
Paul

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

/s/

Paul Zimmerman
10/24/2007 02:21:16 PM
CSO

Zimmerman, Paul F

From: Cynthia Letizia [CLetizia@spectrumpharm.com]
Sent: Wednesday, October 17, 2007 4:31 PM
To: Zimmerman, Paul F
Subject: RE: NDA 20-140 for Isovorin -50 missing attachments
Attachments: NDA 20-140 CMC info req 2007.10.10- Spectrum response table.pdf; NDA 20-140 CMC info req 2007.10.10- Spectrum response Att1.pdf; NDA 20-140 CMC info req 2007.10.10- Spectrum response Att2.pdf

Dear Paul,

Reference is made to our teleconference today at 11:30 am with the Chemistry review staff and Spectrum attendees (including John Spoden, Director RA, and Bahman Shimiaei, Associate Director Pharmaceutical Development and I). As Spectrum is not in possession of the 50 missing attachments to the Lederle 1993 Deficiency Response for NDA 20-140, we agree to specifically address each reference (attachment or footnote) provided in that response. Please note that Spectrum has no record of submission by Lederle of this information to the pending NDA 20-140.

A summary tabulation is provided herein with an explanation, cross-reference to previously filed information or new attachment. Future hypertext links are indicated with yellow highlights. .

The attachments to this email will be compiled into an eCTD amendment incorporating hypertext links directly to the target page for ease of navigation. The eCTD software does not permit links to previous sequences on file with FDA. Therefore, we must duplicate those reference documents in the new NDA 20-140 Sequence 0003. Due to the submission volume and extent of cross-referencing, the fully validated and quality-controlled CTD amendment will be sent on CD via FedEx on Monday, October 22.

Further, in response to your email request of 10-Oct-2007, Merck Eprova will provide a letter acknowledging receipt of the file 'Lederle-Response-to-1993-Deficiency-1993-Jan-22' to include date of transmission and/or dated acknowledgement of receipt by Merck Eprova.

Thank you for your guidance in resolving these questions.

Kind regards,

Cynthia

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Wednesday, October 10, 2007 11:23 AM
To: Cynthia Letizia
Subject: NDA 20-140 for Isovorin -50 missing attachments

Dear Cynthia,

Please refer to our communication of 21 SEP 2007, in which we requested copies of fifty (50) documents missing from the pdf file entitled "Lederle-Response-to-1993-Deficiencies" found in Module 1 of your submission with cover letter dated 29 JUN 2007. These items are listed on pages 61-64 of that pdf file. Please also note that the subject of the correspondence in that file, found on page 1, is "Response to FDA Letter for Leucovorin IV Dosage Form."

In your response, dated 27 SEP 2007, you provided another pdf file entitled "Lederle-Response-to-1993-Deficiency-1993-Jan-22" and forty-four (44) pdf files, each containing one of the forty-four (44)

10/18/2007

attachments listed on pages 51-54 of that document. The title of that document, found on page 1 of the pdf file, is "Response to Deficiency Letter Dated January 3, 1992. Leucovorin Tablets, NDA 20-141."

The first eighteen (18) attachments in the two responses are identical. The remaining attachments are specific to either the parenteral or oral dosage form (NDA 20-140 and 20-141, respectively).

The document entitled "Note-to-Reviewer," submitted in the 27 SEP 2007 amendment, contains the following statement:

"Therefore, in order to fully address deficiencies related to the drug substance, a full copy (including all attachments) of Lederle's January 29, 1993 amendment to NDA 20-141 is provided, which includes the missing attachments from Module 1.2 of the NDA 20-140 Amendment Sequence 0000, dated July 10, 2007."

Be advised that this statement is erroneous.

Provide copies of the fifty (50) attachments missing from the pdf file entitled "Lederle-Response-to-1993-Deficiencies" found in Module 1 of your submission with cover letter dated 29 JUN 2007. Your complete response will contain the entire series, beginning with 1. "Scanning Electron Microscopy Analysis of Calcium Leucovorin Isomers" and ending with 50. "USP Preservative Effectiveness Test of l-Leucovorin Parenteral Reconstituted with Bacteriostatic Normal Saline and Stored Under Room Temperature for 7 Days and 4 °C for 28 Days, Formulations Research, Volume 7, November 25, 1992."

Thanks,
Paul

10/18/2007

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

/s/

Paul Zimmerman
10/18/2007 07:28:15 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, October 16, 2007 9:27 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin

Dear Cynthia,

This is a follow-up on our information requests dated 19 and 21 SEP 2007. We requested verification that Merck Eprova has received the pdf file entitled "Lederle-Resonse-to-1993-Deficiencies" found in Module 1 of your NDA 20-140. We also requested this verification include your date of transmission and/or dated acknowledgement of receipt by Merck Eprova.

To date we have not received any information verifying Merck Eprova has received a complete copy of the above mentioned pdf file. Please confirm this at your earliest opportunity. We also remind you that Merck Eprova is responsible for including all pertinent information from that communication in their current DMF.

Thanks,
Paul

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

/s/

Paul Zimmerman
10/16/2007 09:30:10 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, October 10, 2007 2:23 PM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin -50 missing attachments

Dear Cynthia,

Please refer to our communication of 21 SEP 2007, in which we requested copies of fifty (50) documents missing from the pdf file entitled "Lederle-Response-to-1993-Deficiencies" found in Module 1 of your submission with cover letter dated 29 JUN 2007. These items are listed on pages 61-64 of that pdf file. Please also note that the subject of the correspondence in that file, found on page 1, is "Response to FDA Letter for Leucovorin IV Dosage Form."

In your response, dated 27 SEP 2007, you provided another pdf file entitled "Lederle-Response-to-1993-Deficiency-1993-Jan-22" and forty-four (44) pdf files, each containing one of the forty-four (44) attachments listed on pages 51-54 of that document. The title of that document, found on page 1 of the pdf file, is "Response to Deficiency Letter Dated January 3, 1992. Leucovorin Tablets, NDA 20-141."

The first eighteen (18) attachments in the two responses are identical. The remaining attachments are specific to either the parenteral or oral dosage form (NDA 20-140 and 20-141, respectively).

The document entitled "Note-to-Reviewer," submitted in the 27 SEP 2007 amendment, contains the following statement:

"Therefore, in order to fully address deficiencies related to the drug substance, a full copy (including all attachments) of Lederle's January 29, 1993 amendment to NDA 20-141 is provided, which includes the missing attachments from Module 1.2 of the NDA 20-140 Amendment Sequence 0000, dated July 10, 2007."

Be advised that this statement is erroneous.

Provide copies of the fifty (50) attachments missing from the pdf file entitled "Lederle-Response-to-1993-Deficiencies" found in Module 1 of your submission with cover letter dated 29 JUN 2007. Your complete response will contain the entire series, beginning with 1. "Scanning Electron Microscopy Analysis of Calcium Leucovorin Isomers" and ending with 50. "USP Preservative Effectiveness Test of l-Leucovorin Parenteral Reconstituted with Bacteriostatic Normal Saline and Stored Under Room Temperature for 7 Days and 4 °C for 28 Days, Formulations Research, Volume 7, November 25, 1992."

Thanks,

Paul

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

/s/

Paul Zimmerman
10/10/2007 04:20:25 PM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, September 28, 2007 8:24 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - CMC request

Dear Cynthia,

Please respond as soon as possible to the following.

Please refer to the Certificate of Analysis for Calcium Levofolate Pentahydrate found in Batch Record 2100-02, Part 2, pages 54-55 of the pdf file (corresponding to printed page numbers 000615-000616). Provide the equation used to calculate *the quantity of "As is" drug required for compounding purposes only*, as shown in footnote 7 and in tabulated item 17(2). Be sure to include a description of how the equation is used and provide an example of the calculation using values from the COA.

Thanks,
Paul

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

/s/

Paul Zimmerman
9/28/2007 08:26:52 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Friday, September 21, 2007 9:43 AM
To: 'Cynthia Letizia'
Subject: RE: NDA 20-140 for Isovorin - CMC request re module 1

Dear Cynthia,

This is a follow-up on the information request sent on Wednesday, 19 SEP 2007.

Regarding the pdf file entitled "Lederle-Resonse-to-1993-Deficiencies" found in Module 1 of your NDA 20-140:

1. Please verify that you have forwarded the pdf file to Merck Eprova (in addition to other information, as indicated in your response of 19 SEP 2007). Include the date of transmisson and/or acknowledgement of receipt in your verification.
2. Please provide copies of missing documents (50 attachments specified on pages 61-65 of the pdf file).

Thanks
Paul

From: Cynthia Letizia [mailto:CLetizia@spectrumpharm.com]
Sent: Wednesday, September 19, 2007 11:59 AM
To: Zimmerman, Paul F
Subject: RE: NDA 20-140 for Isovorin - CMC request re module 1

Dear Paul,

The information request is acknowledged. Merck Eprova will be contacted through the Pharmaceutical Operations group for response to these questions.

Thank you.

Cynthia

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]
Sent: Wednesday, September 19, 2007 6:45 AM
To: Cynthia Letizia
Subject: NDA 20-140 for Isovorin - CMC request re module 1

Dear Cynthia,

Module 1 of your application includes a 65-page response to CMC deficiencies from Lederle. The letter date is 22 JAN 1993. Missing from the pdf file are fifty attachments listed in tabular form on pages 61-65. The stamp at the top of each page shows that Merck Eprova AG has seen or participated in assembling this document as of 03 JAN 2003. The majority of the questions, responses, and material in (missing) attachments should now be incorporated into Merck Eprova's Type II DMF . for Calcium Levofolinate Pentahydrate.

1. Has Merck Eprova recently received or reviewed a copy of the Lederle responses from 1993 (in conjunction with Spectrum's NDA filing)?
2. Is Merck Eprova aware of the necessity for including the details of these responses (to questions about

9/21/2007

manufacturing the drug substance) within their DMF?

Thanks,
Paul

9/21/2007

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Wednesday, September 19, 2007 9:45 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin - CMC request re module 1

Dear Cynthia,

Module 1 of your application includes a 65-page response to CMC deficiencies from Lederle. The letter date is 22 JAN 1993. Missing from the pdf file are fifty attachments listed in tabular form on pages 61-65. The stamp at the top of each page shows that Merck Eprova AG has seen or participated in assembling this document as of 03 JAN 2003. The majority of the questions, responses, and material in (missing) attachments should now be incorporated into Merck Eprova's Type II DMF for Calcium Levofolate Pentahydrate.

1. Has Merck Eprova recently received or reviewed a copy of the Lederle responses from 1993 (in conjunction with Spectrum's NDA filing)?
2. Is Merck Eprova aware of the necessity for including the details of these responses (to questions about manufacturing the drug substance) within their DMF?

Thanks,
Paul

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

/s/

Paul Zimmerman
9/19/2007 09:49:28 AM
CSO

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

/s/

Paul Zimmerman
9/21/2007 09:45:34 AM
CSO

Zimmerman, Paul F

From: Cynthia Letizia [CLetizia@spectrumpharm.com]

Sent: Monday, September 17, 2007 3:00 PM

To: Zimmerman, Paul F

Subject: RE: NDA 20-140 fro Isovorin - CMC question

Dear Paul,

Only _____ facility was used.

b(4)

Regards,

Cynthia

From: Zimmerman, Paul F [mailto:paul.zimmerman@fda.hhs.gov]

Sent: Monday, September 17, 2007 10:32 AM

To: Cynthia Letizia

Subject: NDA 20-140 fro Isovorin - CMC question

Dear Cynthia,

_____ which (you) Spectrum uses for _____, has two facilities, one in _____ the other in _____ Can you verify that you are using ONLY the facility in _____ for testing? Your list of facilities has the _____ address, but the debarment notification letter includes both sites and registration numbers.

b(4)

Thanks,
Paul

9/18/2007

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

/s/

Paul Zimmerman
9/18/2007 07:47:52 AM
CSO

Zimmerman, Paul F

From: Zimmerman, Paul F
Sent: Tuesday, September 18, 2007 11:02 AM
To: 'Cynthia Letizia'
Subject: NDA 20-140 for Isovorin -CMC request

Dear Cynthia,

We have the following request.

CMC Information Request

1. In accordance with 21 CFR 314.50(d)(1)(iii), please submit an Environmental Impact statement, or if already submitted, specify its location in the application by module, section, and page number.

Thanks,
Paul

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

/s/

Paul Zimmerman
9/18/2007 11:05:42 AM
CSO



SPECTRUM
PHARMACEUTICALS

ORIGINAL

Turning Insights into Hope

CDER/CDR

10 July 2007

JUL 11 2007

Richard Pazdur, MD
Director, Division of Drug Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research, Food and Drug Administration
Central Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266
Attn: Mr. Paul Zimmerman, Project Manager

RECEIVED

ORIG AMENDMENT

N-000-B2

**RE: NDA 20-140 ISO-VorinTM (Levoleucovorin Calcium) for Injection
Rescue after High-Dose Methotrexate Therapy in Osteosarcoma
Resubmission of eCTD Sequence 0000**

RECEIVED

JUL 12 2007

CDER White Oak DR 1

Dear Dr. Pazdur:

The purpose of this eCTD resubmission is to replace the eCTD Sequence 0000 filed on June 29, 2007, due to incomplete submission attribute information. Please disregard both the original Sequence 0000 and the subsequent eCTD Sequence 0001 filed on July 03, 2007. These sequences are replaced by the corrected eCTD submission number 020140 Sequence 0000 contained herein.

Further reference is made to the original NDA 20-140 filed on December 14, 1990 and FDA deficiency letters dated January 3, 1992 and December 13, 1993. Please note that the proposed indication is also subject to orphan application 90-484.

The original NDA sponsor, Lederle Laboratories, responded on January 22, 1993 to the first deficiency letter on January 29, 1993. Ownership of the NDA was transferred from Lederle Laboratories to Merck Eprova, then to Targent, Inc. and finally to Spectrum Pharmaceuticals, Inc. (hereinafter Spectrum). Notification of change of ownership was submitted to CDER/ODE III on April 19, 2006. Further reference is made to the pre-NDA meeting held by teleconference with Targent, Inc. and the Agency on July 15, 2005. These communications, a response to pre-NDA minutes and all outstanding deficiencies are included in Module 1. This submission includes revised product labeling, manufacturing, chemistry and controls for drug product and drug substance and a safety update.

ISO-VorinTM is the proposed proprietary name for levoleucovorin calcium. The rationale for this selection is presented in Module 1.16. Review and acceptance of this proposal is requested.



SPECTRUM
PHARMACEUTICALS

Turning Insights into Hope

The application has been formatted according to the information in the Guidance for Industry on Providing Regulatory Submissions in Electronic Format--Human Pharmaceutical Applications and Related Submissions dated April 2006 and the ICH eCTD Specifications 3.2 dated 04 February 2004. Per regulations (21 CFR 11.2(b)(2)), Spectrum Pharmaceuticals has been given clearance to submit electronic CTD submissions based on the sample eCTD 900315 submission submitted on March 5, 2007. The application is provided as one electronic copy of the submission, presented as one (1) compact disc and a cover letter. Spectrum Pharmaceuticals, Inc. certifies that this submission is virus free as tested by _____

b(4)

If you have any questions regarding the information included within this submission, I may be contacted at 949.788.6700 or by email at cletizia@spectrumpharm.com.

Sincerely,

Cynthia Letizia

I am approving this
document
2007.07.10 08:52:11 -07'00'

Cynthia Letizia, MPH, RAC
Vice President, Regulatory Affairs

FDA Telecon Meeting Minutes

Date of Meeting: February 25, 2008

Subject:

NDA 20-140: FDA Review of Proposed Impurity Shelf-life Specifications

Spectrum Participants

Raj Shrotriya, MD

Ashok Gore, PhD

Cynthia Letizia, MPH, RAC

John Spoden, B.S., RAC

Van Huynh, B.S.

Bahman Shimiaei, B.S.

Chief Executive Officer

Sr. Vice President, Pharmaceutical Operations

Vice President, Regulatory Affairs

Sr. Director, Regulatory Affairs

Associate Director, Pharmaceutical Operations

Associate Director, Pharmaceutical Development

FDA Participants

Hans Rosenfeldt, Ph.D

David McGuinn, Ph.D

Sarah Pope, Ph.D

Ravi Harapanhalli, Ph.D

Paul Zimmerman, R.Ph

Pharmacology Reviewer

Acting Pharmacology Team Leader

Pharmaceutical Assessment Lead

Branch Chief, ONDQA

Project Manager

Purpose of Contact

FDA requested telecon to discuss differences between the proposed release and shelf-life specifications for impurities, and the rationale for proposing the shelf-life specifications.

Items Discussed

- During the review of the application, FDA noted differences in release and shelf-life specifications for impurities in drug product; therefore, the review team was seeking additional information regarding these differences.
- Spectrum indicated the drug product release specifications were based directly on specifications established for related substances in the drug substance. Somewhat generous shelf-life specifications were initially established based on Spectrum's limited drug product manufacturing experience and lack of stability data at the time of specification setting.
- Based on updated 12-month real time stability data, Spectrum proposed updated interim shelf-life specifications for drug product related substances and committed to re-examining and finalizing these specifications upon completion of 24-month real time stability testing of the three registrational drug product lots. The interim specifications proposed were as follows:

Impurity	Current	Proposed
----------	---------	----------

b(4)

- FDA also discussed the ICH guidance Q3B(R2) "Impurities in NewDrug Products" and the recommendation to qualify related substances over — based on the theoretical maximum daily dose specified in the labeling —
- Spectrum indicated that a toxicology assessment was submitted previously as an amendment to the application (attachment 34 of SN0003, Oct. 23, 2007).
- FDA also inquired about the status of identifying compounds — and asked Spectrum to provide a timeline for finalizing the identification of these related substances; FDA suggested 6 to 12 months for generating this information.
- FDA also indicated that an expiry date for the product would be based on the approach recommended in ICH guidance Q1E "Evaluation of Stability Data." In order to determine an expiration date, Spectrum was requested to submit 12-month real-time data and a statistical evaluation (at a 95% confidence interval) of the active ingredient and related substances. Based on an evaluation of the stability data, FDA suggested that either an 18-month or 24-month expiry data will be assigned based on a review of the data in accordance with ICH Q1E.

b(4)

General Comments and Action Items

Final Spectrum Commitments:

- Provide proposed interim shelf-life specifications for related substances in the finished product. Finalize specifications based on 24-month real time stability data from registrational lots.
- Provide explanation of how proposed specifications relate to qualification of the related substances with links to source supportive data.
- Provide updated 12-month real-time stability data and updated accelerated stability data.
- Provide statistical analysis of 12-month stability data examining (at a 95% confidence interval) active ingredient and related substance stability profiles.
- Provide a timeline for completion of identification of compounds —

b(4)

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

/s/

Paul Zimmerman
2/29/2008 05:02:57 PM
CSO

TELECON MINUTES

TELECON DATE: July 15, 2005

NDA: 20-140

Meeting Request Date: May 23, 2005

FDA Response Date: May 25, 2005

TYPE of TELECON: pre-NDA

Briefing Document Date: June 25, 2005

DRUG: Isovorin

SPONSOR: Targent

FDA INTERNAL MEETING PARTICIPANTS:

Robert Justice, M.D., Acting Director
Ann Farrell, M.D., Medical Team Leader (invited)
Nancy Scher, M.D., Medical Officer
Rajeshwari Sridhara, Ph.D., Statistical Team Leader
Brian Booth, Ph.D., Acting Biopharmaceutics Team Leader
Sophia Abraham, Ph.D., Biopharmaceutics Reviewer
Chengyi Liang, Ph.D., Chemistry Reviewer
Nallaperumal Chidambaram, Ph.D., Chemistry Team Leader
Paul Zimmerman, R.Ph., Project Manager

SPONSOR: Pauliana Hall, RAC, Regulatory Advisor, PCH Integrated Regulatory Services, Inc.

MEETING OBJECTIVES: To discuss the NDA resubmission plan and identify the potential NDA approval issues.

BACKGROUND: NDA 20-140 was submitted in December 1990 and not approved in January 1992 citing CMC and labeling deficiencies.

After the internal FDA meeting, draft responses were faxed to the sponsor on July 18, 2005. The applicant then confirmed that the responses were clear and that a face-to-face meeting was not needed.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Is our proposed NDA Amendment (Section 3.1) acceptable to the Division?

FDA response: Yes. Please provide more information on the database of the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

2. Will the submission of a new CMC section (**Appendix 13**) addressing the remaining CMC deficiencies cited in the 1992 and 1993 letters (**Appendices 6 and 7**) for NDA 20-140, a revised labeling (**Appendix 11**) and a safety update be sufficient to address the approval issues relating to ISOVORIN (l-leucovorin calcium) for injection for rescue after high dose methotrexate therapy in osteosarcoma, impaired methotrexate elimination and inadvertent methotrexate overdosage?

FDA response:

Yes, it is acceptable if you address the CMC deficiencies cited in 1992 and 1993 non-approval letters provided there are no changes to manufacturing and controls of drug substance and drug product. If you have made changes to manufacturing and controls, it is our expectation that you will provide a complete CMC package highlighting the changes as well as respond to all the deficiencies listed in the above two non-approval letters. Please note that adequate justification needs to be provided for not addressing deficiencies you may consider irrelevant based on changes you are proposing. In view of the differences in recommended dose, the product must be labeled clearly to avoid confusion with the currently marketed racemic mixture. Please also propose a Risk Management Plan to reduce the potential for dosing errors.

4. Will a clinical report that includes documentation (data listings, tables and statistical analyses, but not case report forms) for the results of the NCCTG Phase 3 trial published by Goldberg et. al (**Appendix 3**) be sufficient as the pivotal clinical data to support this approved racemic leucovorin indication?

FDA response: The proposed documentation appears to be adequate. However, please provide the protocol and all amendments, as well as case report forms for patients who died within 30 days of study or who discontinued study.

b(4)

Chemistry, Manufacturing and Controls

The CMC section of this NDA Amendment will be prepared in CTD format (**Appendix 13**). A Drug Master File will be provided directly to the Agency by Merck Eprova for levoleucovorin drug substance. The submission will contain an authorization letter from Merck Eprova to the Agency to permit review of the DMF for the NDA submission on behalf of Targent. The drug product section will contain:

Composition,
Development pharmaceuticals,
Compatibility with diluents for reconstitution and intravenous infusion,
Description of drug product manufacture, and in-process controls,
Drug product manufacturing validation protocol,
Sterilization validation package,
Control of excipients,
Control of drug product,
Batch analysis data for three registration lots
Container/closure description and control,
Six-month stability data for three registration lots
Market product stability protocol
Executed batch records for two registration lots

6. Will submission of two executed batch records be sufficient?

FDA response: Yes.

7. Will a Master Batch Record be required in the submission?

FDA response: Yes.

8. Will data for one lot of drug product (n=2 individual samples) be sufficient for compatibility studies with individual intravenous diluents?

FDA response: Yes.

General Issues

9. We recognize the trade name ISOVORIN is not final until the NDA is approved. Do we need to resubmit the trade name ISOVORIN for the DMET and ODS for review and approval?

FDA response: Yes

10. Is the content and format of the proposed labeling (**Appendix 11**) acceptable?

FDA response: This will be a review issue.

11. Since the reviews of the other sections of this NDA were completed in 1992, the submission of this NDA Amendment (primarily CMC data) should not require a full NDA User Fee. Do you agree?

FDA response: You have indicated that the indications and dosage and administration have not changed and no new clinical data will be submitted. The submission of a response to the not approval letter would not require a user fee.

Paul Zimmerman/7-19-05
Project Manager

Concurrence: _____
Nancy Scher, M.D.
Medical Officer

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

/s/

Paul Zimmerman
7/19/05 03:28:44 PM

Nancy Scher
7/19/05 05:03:28 PM

NDA 20-140

APPEARS THIS WAY ON ORIGINAL

JAN 3 1992

N [REDACTED]

Lederle Laboratories
N. Middletown Road
Pearl River, New York 10965

Attention: Martine J. George, M.D., M.Sc.
Director
U.S. Registration

Dear Dr. George:

Please refer to your December 14, 1990 new drug applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Isovorin (l-leucovorin calcium for injection and l-leucovorin calcium tablets).

We also acknowledge receipt of your communications dated April 30, June 11, June 20, August 23, and September 20, 1991.

We have completed our review and find the information presented is inadequate under section 505(d) of the Act and 21 CFR 314.125 and the applications are not approvable. The deficiencies are summarized below.

The following deficiencies apply to NDA 20-140 and NDA 20-141.

1. Concerning the description of the drug substance:

- a. Provide SEM micrographs of dl-leucovorin cited in the preformulation for comparison to SEM data for the
- b. Explain the difference between the DSC profile provided for the drug substance in the preformulation report and the DSC profile observed for the reference standard.
- c. Submit the particle size data that are referred to in the preformulation report; include data for more than one lot [see item 6(g)].
- d. It is noted that subtle differences were observed in the morphology of experimentally reprocessed drug substance. You are reminded that, once the NDAs are approved, reprocessing of the drug substance will require prior approval through submission of a supplement. The impact of reprocessing

b(4)

b(4)

_____ bioequivalence, etc.
must be established.

b(4)

2. Concerning the description of potential impurities in the drug substance:

a. Provide UV λ_{max} and E_{max} data for the identified impurities.

b. Provide spectral data : _____

b(4)

c. Describe the basis for identification of _____

d. Describe the structural assignment of _____

b(4)

e. State the nature of the batches for which the purity profiles were established (e.g., batch size and whether the batch sizes were representative of the optimized commercial batch size).

3. Concerning the description of the manufacture of the drug substance:

a. Specify the time required for _____

b(4)

b. Specify the temperature and time required to _____

c. Specify the temperature and time required for _____

b(4)

d. Describe the final _____ step for l-leucovorin calcium.

e. Address the handling of _____ in all appropriate manufacturing steps.

b(4)

4. Report the stated assay specifications for the intermediates, _____

b(4)

_____ The specifications should be reflective of representative observed values.

5. Clarify why no tests are performed to monitor reaction progress or completion in the synthesis of the drug substance; it is recommended that such in-process tests be added.
6. Concerning the specifications for the drug substance:

- a. Specify that the standard IR spectrum should run concurrently with the sample spectrum.
- b. In view of the batch analyses of drug substance and stability studies of the drug substance submitted in the application, it appears that the specifications for both "related compounds", and "other related compounds" should be tightened significantly and the "other related compounds" profile should be specified. Furthermore, all observed impurities should be reported individually along with the observed level of each impurity in the drug substance. Individual specifications should be established for each observed impurity. This may be accomplished by defining the profile of identified and unidentified impurities observed to date in the drug substance and establishing the purity limits for the drug substance by setting individual and cumulative limits for these impurities.
- c. It is noted for the impurity profiles submitted on p. 02-117 that several batches contain unusually high levels of one impurity or another depending on the lot analyzed. The following are examples:

┌

Please explain these discrepancies and the variability in impurity levels. Also, explain and justify the fact that the NDA specifications for related compounds

and individual other related compounds are less stringent relative to the IND.

- d. Specify that the observed level of d-leucovorin be reported even if it is below 0.5%.

b(4)

b(4)

- b(4)

- b. Provide full impurity profiles for the lots of drug substance referred to in table 2 on p. 118, vol. 2.
- c. The samples of drug substance used for stability studies should be stored in the packaging actually used or one which more closely simulates the packaging for the drug substance.
- d. All observed impurities in the drug substance should be individually reported. Modify the protocol accordingly to report this information in the future. Provide these data for the studies submitted in the application.
- e. The level of *d*-leucovorin should be reported even if it falls below 0.5%.
- f. The storage temperature for controlled room temperature conditions should be the upper limit of the USP definition (i.e., 30°C).
- g. Clarify what samples of drug substance will be analyzed according to the submitted stability protocol.
- h. It is noted that the method of manufacture of the drug substance has changed during development and for the drug substance stability studies. Only one batch was manufactured using the procedure described in the application. Please make the necessary corrections.
 - (1) Commit to place the first three production batches of drug substance on stability according to the modified stability protocol.
 - (2) In our opinion, the — retesting schedule is not supported because only one lot of drug substance studied was prepared by the synthetic procedure described in the application, and for that batch, only 3 months of data were reported. Until more experience is accumulated, a retesting interval of — is recommended.

b(4)

NDA 20-140

NDA 20-141

Page 6

9. Clarify whether laboratory testing of drug substance and raw materials, and labeling operations are performed at your Pearl River facility.

b(4)

7 Page(s) Withheld

 x Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

b(4)

The following deficiencies concern the injectable product (NDA 20-140).

18. The following comments are concerned with components, composition and batch formula of the drug product.

- a. In drug product manufacture, the targets for filling vials should be the same as the claimed amounts on the label. The use of an overage of drug is not warranted and will lead to superpotent drug concentration when the vials are reconstituted according to the labeling.
- b. The batch formulas provided (vol. 4, pages 4-6) should be modified in accordance with the changes in production scale proposed in your amendment dated 9/20/91.
- c. Composition and batch formulas should list the actual amounts of 1-leucovorin calcium used, in addition to the free acid equivalents.
- d. The statements of drug product components and composition should be modified to indicate that the proposed drug product will be manufactured with compendial grade (NF) sodium hydroxide and hydrochloric acid (as indicated in your footnote on page 3, volume 4).

e.

b(4)

- f. The specifications for microbial limits for mannitol should include numerical limits for total organisms and the absence of certain organisms.

19. Please provide to the NDA the street address of the manufacturing, packaging and testing facility, rather than a box number.
- 20. The ensuing remarks are with regard to the method of manufacture of the drug product.
 - a. Additional information should be provided concerning lots of drug product used in the clinical studies, to allow evaluation of the batch sizes proposed. This information should include the manufacturing scale, the manufacturing process used, site of manufacture, and stability data (if available) for each clinical lot.
 - b. All equipment used, equipment capacities and the nature of the surfaces which come in contact with drug product should be described for the manufacturing process, including the cryodesiccation and packaging operations.
 - c. In the master formula, it should be clarified who is responsible for determining the actual amount of 1-leucovorin calcium to be used, and how it is calculated.
 - d. The following differences in master formula have been noted between the original NDA and the 9/20/91 amendment for all vial sizes.
 - (1) The top — steps on page 2 of the master formula of the 9/20/91 amendment indicate that temperature should not exceed — whereas in the original NDA it states that it should not exceed — This should be clarified. What does the operator do if the temperature does exceed — and what are the consequences for the drug product? b(4)
 - (2) In the 9/20/91 amendment, step — (page 2) has been added to the procedures. The statement "Cool the batch to — if necessary" should be clarified. When is it necessary? b(4)
 - e. There seems to be a discrepancy between the procedures on page 27, vol. 4 and the clinical trial batch records (e.g., pg. 70, vol. 4) concerning the shelf temperatures used in the

lyophilizer (e.g., _____)

b(4)

_____ This should be clarified.

- f. The filling procedures to be used should also be summarized.
21. The following information should be provided concerning in-process tests and limits for manufacture of the drug product.
- a. In-process tests and specifications for ensuring that the product is — and lyophilization is complete should be provided.
 - b. All in-process controls should be summarized in one place.
 - c. The weight specification for the fill dose during filling of the vials should be provided.
 - d. According to the clinical trial batch records, during filling, the fill dose weight is checked
_____ The
_____ justification for this difference should be provided.
22. In regard to release testing of the drug product, you should describe the sampling plan that will be used to assure that the samples of the drug product obtained for release and stability testing are representative of the batch. The plan should include both the sampling of production batches and the selection of sub-samples for analytical testing.
23. The following comments are concerned with drug product regulatory specifications.
- a. The assay specification should be tightened.
 - b. There should be a quantitative specification for particulates in the constituted solution.
 - c. The proposed specifications for all related compounds and for moisture should be tightened.

b(4)

- d. Supporting data (e.g., pharmacological or toxicological information) should be provided or referenced concerning the safety of related compounds which may be present in the drug, or else details should be provided concerning the levels at which individual related compounds were present in lots for pivotal clinical studies.
 - e. Specifications for "constituted solution", "uniformity" and "sterility" should be spelled out rather than to state that they meet the requirements of the test. The NDA monograph should make reference to USP for the content uniformity test rather than referencing a letter (pg. 123, vol. 4).
 - f. Identification specifications should also indicate approximate wavelength maxima and minima values for the UV procedure, and an approximate retention time for the HPLC method.
 - g. There should be a regulatory specification and method for the d-isomer in the drug product.
 - h. The specification range for pH appears too wide _____ since all data presented (volume 5, pages 137, 141, 145, 187, 193, 197, 238, 242 and 246) show a maximum variation between _____. A range of _____ seems reasonable.
24. The clarifications indicated below should be provided regarding your certificates of analysis for the drug product.
- a. The samples or standards used for the chromatograms provided along with the certificates of analysis should be identified, in order that they may be evaluated.
 - b. Certificates of analysis should be modified to show individual impurities and degradation products for "other related compounds", to be consistent with the specification.
25. The following concern the container-closure system:

b(4)

- f. The detailed protocol for statistical analysis of the stability data should be provided.
- g. At the present time, you should withdraw your proposal to extend the expiration dating period in accordance with 21 CFR 314.70(d)(5) for each container size based on full shelf-life data. The basis for this request is the use of a ————— in your current drug product batches on stability (vol. 4 page 9). This overfill would bias the stability results used to calculate the expiration dating period. b(4)
- h. Since product is to be labeled for storage at controlled room temperature ————— room temperature testing should be conducted at the upper limit of that range (i.e., 30°C). b(4)
- i. Please indicate whether all stability tests are performed at all test intervals (except sterility).
- j. Are stability specifications identical to product specifications (vol.4, pg. 99-104)? This should be detailed in the stability protocol, including any differences.
- k. The wording should be changed from "three initial production batches" (to be placed on stability) to "the first three production batches."
- l. There is to be only one approved stability protocol, therefore the test intervals for "subsequent yearly monitoring batches" should be the same as for the initial three production batches. A modification of this protocol may be proposed after approval of the NDA through a supplemental NDA, based on accumulated stability data on production lots.
- m. Concerning your stability commitment (pg. 30, September 20, 1991 amendment), you are reminded that any change in materials comprising the container-closure for the marketed drug product, in the bulk active ingredient supplier, in product formulation, or any significant change in manufacturing procedures will require prior approval of a supplemental NDA.

- n. It should be clarified if stability testing of the reconstituted drug product as described in your amendment dated 9/20/91 will be routinely performed as part of the stability protocol for marketed drug product (e.g., first three production batches, etc.).
 - o. Please clarify the methodology of the "safety test" in the ongoing stability protocol (e.g., pg. 153, vol. 5) and the meaning of the "test depts" and method numbers. Detailed descriptions of methods should be provided (i.e., the notation USPXXI is not sufficient).
 - p. It should be clarified that "other related compounds" will be reported as individual compounds.
27. The ensuing remarks are in regard to your proposed stability report format.
- a. We recommend that as part of the stability report, the batch number of the drug substance used to make each drug product in the stability study, as well as the manufacturers of the container-closure components be included.
 - b. The date of packaging of the drug product, batch size and test method numbers should also be provided.
 - c. Along with the names of the drug product and drug substance manufacturers, the sites of the facilities where drug product and drug substance were manufactured should be listed.
28. The following comments concern the stability data which you have provided.
- a. The stability data provided do not support a 2-year expiration dating period, nor do they support a labeling statement which specifies storage at _____. You should update the data and provide a statistical analysis in support of the expiration dating period, along with a description of the statistical methods used. In addition, stability specifications should be tightened to be more in accordance with the data from the clinical lots.

b(4)

- b. Stability data provided for "other related compounds" appear to be given as the sum of individual compounds, which are not specifically identified. These data are quite variable and they are difficult to interpret without knowing what is happening to individual impurities and degradation products. Results should be listed by individual impurity and degradation product, and unidentified compounds should at least be listed by relative retention times.
- c. You should indicate the minimum quantifiable amount of d-leucovorin in the drug product, and if less than — the actual data for d-leucovorin should be provided so that any trends may be seen (e.g., is there any detectable increase in d-leucovorin over time in the drug product?).
- d. Reconstitution studies conducted at 23°C for up to 7 days (e.g., vol. 5, pg. 239) do not seem to address the possibility of racemization of l-leucovorin in solution. Data should be provided to assure its stability under such circumstances.
- e. Some stressed stability data (e.g., 40°C/75% relative humidity) should be provided for these samples to assess resistance of container-closure to moisture.
- f. Lots of the drug substance used to make the stability lots of the drug product should be identified.
- g. The sampling plan used for the stability studies underway should be described, demonstrating that samples chosen represent the entire batch.
- h. The suppliers of the container-closure components (used for the stability studies which are reported in the NDA) should be indicated. It should be clarified whether these are identical to the container-closure components intended for marketing (except for the glass vial for the — product, which is modified in your amendment dated 9/20/1991). The Lederle Packaging Code Number for the

b(4)

b(4)

"aluminum flip cap seals" used in manufacture of drug product for the ongoing stability studies should be provided.

- i. You should clarify the meaning of the "bulk drug purity check" numbers (e.g., page 110, vol. 5).
 - j. Stability data for drug product packaged in the new proposed vial _____ 9/20/1991 amendment) should be provided to show that _____ of the vial (pg. 19 of amendment) does not adversely affect product stability.
29. The remarks indicated below are with respect to your report on reconstitution compatibility and stability of the drug product (beginning on page 257, vol. 5).
- a. Appropriate stability data should be provided to support microbiological stability of reconstituted solutions in various media and containers. See additional labeling comments (below).
 - b. It should be clarified where lot 0116-108A was manufactured (this lot was used for the reconstitution compatibility study, pg. 257, vol. 5), and whether the formulation used is identical to that proposed for marketing.
 - c. Analytical methods used for the reconstitution study should be specified.
30. The following preliminary comments are concerned with drug product labeling.
- a. The comments below pertain to the "Dosage and Administration" section of the package insert.

- (1) Evidence of the microbiological stability of drug product reconstituted with _____ for injection should be provided to support the statement that such solutions are _____

Alternatively, such statements should be deleted.

b(4)

b(4)

- (2) A storage temperature should be provided to go with the statement that

b(4)

If the storage temperature includes room temperature, microbiological data should be provided to support this statement.

- (3) The statement concerning further dilution of reconstituted solutions of the drug product with 0.9% sodium chloride injection, USP and 5% dextrose injection, USP, which

b(4)

should be modified as follows. Omit the chemical and physical storage information which may be misleading in view of the possibility that storage times may be much shorter due to microbiological considerations, and in view of chemical changes in the drug product on dilution and storage in I.V. bags and tubing.

- (4) The sentence beginning with

b(4)

should be replaced by recommended storage times and conditions for constitution or dilution with various unpreserved vehicles, based on actual microbiological, physical and chemical data.

- b. Concerning the "How Supplied" section of the package insert, the type of container (e.g., should be included.

b(4)

- c. Labeling should clearly indicate that this product requires only half as much of the labeled active ingredient (by weight) per dose as the currently marketed leucovorin calcium for injection.

- d. Labeling should clearly indicate that the label claim of this drug product is calculated as the

b(4)

- e. We recommend that the description section of the package insert also include the molecular formula for the active ingredient.
- f. You should contact the USAN Council concerning the established name for the active ingredient. The name chosen by USAN (established name) should be used in all labels and labeling and it should be placed in parentheses between the trademark and the dosage form: e.g., Isovorin (levoleucovorin calcium) For Injection.

Additional comments will be provided from our continuing review as soon as they become available, including those concerning the Environmental Assessment.

We reserve further comment on the labeling until the applications are otherwise approvable.

Within 10 days after the date of this letter, you are required to amend the applications, notify us of your intent to file an amendment, or follow one of the other options under 21 CFR 314.120. In the absence of any such action FDA may withdraw the application.

Should you have any questions, please contact:

Paul Zimmerman
Consumer Safety Officer
(301) 443-5197

Sincerely yours,

Gregory Burke, M.D., Ph.D.
Director
Division of Oncology and
Pulmonary Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDAs 20-140
 20-141
HFD-150/ Division Files

NDA 20-140

NDA 20-141

Page 25

HFD-150/ PZimmerman/12-19-91/revised/1-3-92

HFD-83

HFD-632

HFD-730

HFD-100/Dr. Temple

HFD-150/RJustice

/JRJohnson

JDeGeorge

WCoulter

JBlumenstein

ASchroeder

JLeak

GPoochikian

HFD-421/Smallikaarjun

R/D init by:JRJohnson/1-3-92

RGScully/1-2-92/1-3-92

JBlumenstein/1-2-92/1-3-92

GPoochikian/1-3-92

ATaylor for JDeGeorge/1-3-92

JLeak/1-3-92

GBurke/

F/T by:PZimmerman/

NOT APPROVABLE

R Scully
1/3/92

9 Burke

1/3/92

Memorandum

Department of Health and Human Services
Food and Drug Administration
Division of Oncology and Pulmonary Drug Products

Date: August 14, 1991
To: File, NDA ~~20-140~~, 20-241 HFD 150

From: J. DeGeorge, Ph.D.
Supervisory Pharmacologist, HFD 150

Subject: Telecon with Gary Dukart, Dr. Poole (Safety Evaluation), Dr. Johnson (Toxicology), Dr. Villar (Genotoxicity and Reproduction Toxicology)

Background: See Prior Memorandum.

I explained the Division's position as decided with Dr. Burke and Dr. Justice that given the low bioavailability and lack of maternal toxicity in the reproductive studies with d,l leucovorin, we would not accept these studies as evidence of adequate animal reproductive testing. Dr. Johnson stated that in previous discussions with Dr. Richman in 1988 they were told that the testing as proposed at that time would be adequate. Further, that in discussions with Dr. Taylor in 1990 they were told that the issue of stereoisomer using the d,l-LV studies for l-LV was resolved and would be adequate. He stated that it was only after the Advisory committee meeting that they were informed that there was an issue bioavailability and adequacy of testing. I stated that their toxicologists must certainly have been aware of the lack of bioavailability of LV at high oral doses, and that while they could readily achieve toxicity/lethality by the i.v. route the failure to achieve maternal toxicity by the oral route should have been an issue of concern for them. Dr. Johnson stated that the reproduction studies were done by a French subsidiary. I stated that we could accept the submission as is given a category C designation and that the only indications for use were with known teratogenic agents (as is the case). He felt that this would be acceptable.

by 110-2
Joseph J. DeGeorge

cc: HFD150 DeGeorge
/ Coulter
/ Burke
/ Justice
/ Zimmerman

Memorandum

Department of Health and Human Services
Food and Drug Administration
Division of Oncology and Pulmonary Drug Products

Date: August 6, 1991 ¹⁴¹
To: File, NDA 20-140, 20-241 HFD 150
From: J. DeGeorge, Ph.D.
Supervisory Pharmacologist, HFD 150
Subject: NDA Original Amendment, July 29, 1991 submission
Sponsor's Response to FDA Questions on Reproduction studies.

Background: Lederle requested a waiver from conducting segment II reproductive studies with l-leucovorin as studies with d,l leucovorin had previously been conducted. The studies with d,l-LV were conducted by the oral route. It is known that in man oral absorption of LV is saturable, calling into question the bioavailability of LV in the reproductive studies conducted in rodent and rabbit. Moreover, there was no maternal toxicity observed in the animals tested to document by pharmacodynamic parameters adequate exposure. In the absence of data on oral bioavailability, inadequate exposure of the pregnant females to LV is possible and may indicate inadequate reproductive toxicity testing. The sponsor was informed that if adequate oral bioavailability had been achieved in the reproductive studies we would accept the d,l-LV studies.

Submission Review: The sponsor submitted a set of protocols to examine the dose-related availability of orally administered drug in pregnant rats and rabbits at doses comparable to those in the prior reproductive studies. The protocols do not include comparable i.v. doses and do not allow determination of absolute oral bioavailability. The sponsor also submitted two published papers. The first paper examines bioavailability in rodents, the second looks at bioavailability in patients. It is apparent from the animal data that the oral bioavailability at the dose tested is 5-10% for both parent and metabolite (see tables attached). Human single dose i.v. exposure (AUC) normalized for dose on a mg/m² basis was not appreciably different for rat and human subjects.

The sponsor requested that comments on the protocols be provided as soon as possible to allow them to initiate the studies by mid August. I contacted Gary Dukart by phone — and informed him that given the apparent low oral bioavailability (as demonstrated in the published rodent study) and the similarity of the i.v. AUC for LV in human and rat when normalized to mg/m², it seemed unlikely that the exposure in the oral reproductive studies previously performed would be adequate to allow conclusions on the reproductive hazard of l-LV. He indicated that he would inform the rest of their staff and that they would be in contact with me.


Joseph J. DeGeorge

cc: HFD150 DeGeorge/ Coulter/ Justice/ Zimmerman

b(6)

TABLE 3. Plasma Area Under the Concentration Time Curve (AUC) of Leucovorin and 5-CH₃FH₄ After Administration of Leucovorin at Different Doses and Routes of Administration

Rat

Dose of leucovorin (mg/kg)	Plasma AUC (μM × hr)					
	dl-Leucovorin			5-CH ₃ FH ₄		
	Oral every hr ×4 doses	2-Hr infusion	48-Hr infusion	Oral every hr ×4 doses	2-Hr infusion	48-Hr infusion
25	—	70	—	—	11	—
100	10	210	75	5	39	32
400	21	710	252	8	129	115

5-CH₃FH₄: 5-methyltetrahydrofolate.

Table 1. Plasma Pharmacokinetics of Folates Following Administration of 500 mg/m² dl-CF by Two-Hour IV Infusion (Twelve Patients, Fifteen Cycles)

	Mean ± SD			
	Plasma Peak (μmol/L)	Plasma AUC (mmol/L/min)	T _{1/2} (h)	Cl (mL/min)
dl-CF	96 ± 38	71 ± 22	8.0 ± 1.4	22 ± 8
l-CF	24 ± 6	2.7 ± 1.5	0.8 ± 0.1	394 ± 241
5-CH ₃ FH ₄	17 ± 8	14 ± 5	7.1 ± 1.9	ne

Abbreviation: ne, not evaluated.

Table 2. Folates Plasma Pharmacokinetics Following Administration of 500 mg/m²/d dl-CF by Five-Day Continuous IV Infusion (Six Patients, Nine Cycles)

	Steady-State Concentrations (μmol/L)	Plasma AUC (mmol/L/min)	Cl (mL/min)
dl-CF	51 ± 17*	364 ± 123	20 ± 7
l-CF	1.2 ± 0.5	6.0 ± 3.9	1261 ± 803
5-CH ₃ FH ₄	12 ± 5	83 ± 38	ne

Abbreviation: ne, not evaluated.

*Mean ± S.D.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Office of Orphan Products Development (HF-35)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

August 1, 1991

Lederle Laboratories
Attention: Mr. Allan Hitchcock
Assistant Director
Global Regulatory Compliance
Pearl River, NY 10965

Dear Mr. Hitchcock:

Reference is made to your orphan drug application of July 25, 1990, submitted pursuant to section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of L-leucovorin (Isovorin) as an orphan drug (application #90-484). We also refer to your amendment dated July 16, 1991.

We have completed the review of this application and have determined that L-leucovorin (Isovorin) qualifies for orphan designation for use in conjunction with high-dose methotrexate in the treatment of osteosarcoma. Please refer to this letter as official notification of designation.

Prior to marketing approval, sponsors of designated orphan products are requested to submit written notification to this Office of their intention to exercise orphan drug exclusivity if they are the first sponsor to obtain such approval for the drug. This notification will assist FDA in assuring that approval for the marketing of the same drug is not granted to another firm for the statutory period of exclusivity. Also please be advised that if L-leucovorin (Isovorin) were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, in order to avoid discrepancies between the designated orphan indication and the proposed marketing indication, sponsors of designated orphan products have the option to submit data to amend their orphan designation prior to marketing approval.

In addition, please inform this office annually as to the status of the development program. If you need further assistance in the development of your product for marketing, please feel free to contact Dr. John McCormick at (301) 443-4718.

Congratulations on obtaining your orphan drug designation.

Sincerely yours,

Marlene E. Haffner, M.D., M.P.H.
Director

cc:

HFD-85/M.A.Ward

HFD-150/NDA 20-141

HF-35/OP File #90-484

HF-35/J.McCormick

HF-35/chron

HF-35/P.Vaccari 8/1/91 dsg.484

L 8/1/91

ACTION PACKAGE CHECKLIST

Application Information		
BLA # NDA # 20-140	BLA STN# NDA Supplement #	If NDA, Efficacy Supplement Type
Proprietary Name: not determined as of 3-6-08 Established Name: levoleucovorin calcium Dosage Form: for Injection		Applicant: Spectrum Pharmaceuticals, Inc.
RPM: Paul Zimmerman		Division: DDOP Phone # 3017961489
NDAs: NDA Application Type: <input type="checkbox"/> 505(b)(1) <input checked="" type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (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.)		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)): none Provide a brief explanation of how this product is different from the listed drug. <input type="checkbox"/> If no listed drug, check here and explain: no referenced listed drug 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. <input type="checkbox"/> Confirmed <input type="checkbox"/> Corrected Date:
❖ User Fee Goal Date ❖ Action Goal Date (if different)		PRE PDUFA APPLICATION 3-7-08
❖ 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 type="checkbox"/> None Not Approvable January 3, 1992
❖ 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: ☒ Standard ☐ Priority
 Chemical classification (new NDAs only): 5

NDAs, BLAs and Supplements:

- ☐ Fast Track
☐ Rolling Review
☐ CMA Pilot 1
☐ CMA Pilot 2

☒ Orphan drug designation

NDAs: Subpart H

- ☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)

Subpart I

- ☐ Approval based on animal studies

BLAs: Subpart E

- ☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)

Subpart H

- ☐ Approval based on animal studies

NDAs and NDA Supplements:

- ☐ OTC drug

Other:

Other comments: NDA 20-140 is pre User Fee and was submitted 12-14-1990 and a Not Approval letter was issued 1-3-1992. The applicant submitted an activating amendment 7-10-2007.

❖ Application Integrity Policy (AIP)

- Applicant is on the AIP

☐ Yes ☒ No

- This application is on the AIP

☐ Yes ☒ No

- Exception for review (*file Center Director's memo in Administrative Documents section*)
- OC clearance for approval (*file communication in Administrative Documents section*)

☐ Yes ☐ No

☐ Yes ☐ Not an AP action

❖ Public communications (approvals only)

- Office of Executive Programs (OEP) liaison has been notified of action

☐ Yes ☐ No

- Press Office notified of action

☐ Yes ☐ No

- Indicate what types (if any) of information dissemination are anticipated

- ☒ None
☐ FDA Press Release
☐ FDA Talk Paper
☐ CDER Q&As
☐ Other

❖ Exclusivity	
<ul style="list-style-type: none"> NDA: Exclusivity Summary (approvals only) (<i>file Summary in Administrative Documents section</i>) 	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? <ul style="list-style-type: none"> NDA/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic 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. NDA: Is there remaining 5-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.) NDA: 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.) NDA: Is there remaining 6-month pediatric 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.) 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # _____ and date exclusivity expires: <input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA # _____ and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> 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. [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). 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii) <input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> [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 section below (Summary Reviews)). [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. <p>Answer the following questions for each paragraph IV certification:</p> <p>(1) Have 45 days passed since the patent owner's receipt of the applicant's</p>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified <input type="checkbox"/> Yes <input type="checkbox"/> No

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	
❖ Summary Reviews (e.g., Office Director, Division Director) (indicate date for each review)	
❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) (indicate date)	
Labeling	
❖ Package Insert	
<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), if applicable 	
❖ Patient Package Insert	
<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 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	
❖ Medication Guide	
<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 	
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling) 	
❖ Labels (full color carton and immediate-container labels)	
<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 	
❖ Labeling reviews and minutes of any labeling meetings (indicate dates of reviews and meetings)	<input checked="" type="checkbox"/> DMETS <input type="checkbox"/> DSRCS <input type="checkbox"/> DDMAC <input checked="" type="checkbox"/> SEALD <input type="checkbox"/> Other reviews <input type="checkbox"/> Memos of Mtgs

Administrative Documents	
❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting; ADRA) (<i>indicate date of each review</i>)	
❖ 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 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>) 	In letter
<ul style="list-style-type: none"> Incoming submission documenting commitment 	3-4-08
❖ Outgoing correspondence (letters including previous action letters, emails, faxes, telecons)	included
❖ Internal memoranda, telecons, email, etc.	included
❖ Minutes of Meetings	
<ul style="list-style-type: none"> Pre-Approval Safety Conference (<i>indicate date; approvals only</i>) 	
<ul style="list-style-type: none"> Pre-NDA/BLA meeting (<i>indicate date</i>) 	<input type="checkbox"/> No mtg 7-15-2005
<ul style="list-style-type: none"> EOP2 meeting (<i>indicate date</i>) 	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> Other (e.g., EOP2a, CMC pilot programs) 	
❖ Advisory Committee Meeting	<input type="checkbox"/>
<ul style="list-style-type: none"> Date of Meeting 	7-1-1991
<ul style="list-style-type: none"> 48-hour alert or minutes, if available 	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	
CMC/Product Quality Information	
❖ CMC/Product review(s) (<i>indicate date for each review</i>)	3-3-08
❖ Reviews by other disciplines/divisions/Centers requested by CMC/product reviewer (<i>indicate date for each review</i>)	<input 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>) 	
<ul style="list-style-type: none"> <input type="checkbox"/> Review & FONSI (<i>indicate date of review</i>) 	
<ul style="list-style-type: none"> <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>)	2-20-08 <input type="checkbox"/>
❖ Facilities Review/Inspection	
❖ NDAs: Facilities inspections (include EER printout)	Date completed: <input 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>)	2-27-08
❖ 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>)	2-27-08
❖ Financial Disclosure reviews(s) or location/date if addressed in another review	Pre FD requirement
❖ Clinical consult reviews from other review disciplines/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None
❖ Microbiology (efficacy) reviews(s) (<i>indicate date of each review</i>)	<input type="checkbox"/>
❖ 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>)	
❖ Controlled Substance Staff review(s) and recommendation for scheduling (<i>indicate date of each review</i>)	<input 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 	
<ul style="list-style-type: none"> • Bioequivalence Studies 	
<ul style="list-style-type: none"> • Clin Pharm Studies 	
❖ Statistical Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None see Clinical review
❖ Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None 1-3-08

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.