

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**50-794**

**Administrative/Correspondence**

**PATENT INFORMATION SUBMITTED WITH THE  
FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance  
(Active Ingredient), Drug Product (Formulation and  
Composition) and/or Method of Use**

NDA NUMBER

21-722 50-794 LOT 12/24/03

NAME OF APPLICANT / NDA HOLDER

Pharmion Corporation

*The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.*

TRADE NAME (OR PROPOSED TRADE NAME)

Vidaza

ACTIVE INGREDIENT(S)

Azacitidine

STRENGTH(S)

100 mg

DOSAGE FORM

Injection, powder, lyophilized, for suspension, for subcutaneous administration

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).

Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

**For hand-written or typewriter versions (only) of this report:** If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

**FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.**

**For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.**

**1. GENERAL**

a. United States Patent Number

b. Issue Date of Patent

c. Expiration Date of Patent

d. Name of Patent Owner

Address (of Patent Owner)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

**For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.**

**2. Drug Substance (Active Ingredient)**

- 2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?  Yes  No
- 2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?  Yes  No
- 2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).  Yes  No
- 2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

- 2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)  Yes  No
- 2.6 Does the patent claim only an intermediate?  Yes  No
- 2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**3. Drug Product (Composition/Formulation)**

- 3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?  Yes  No
- 3.2 Does the patent claim only an intermediate?  Yes  No
- 3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)  Yes  No

**4. Method of Use**

**Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:**

- 4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2 Patent Claim Number (as listed in the patent) Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?  Yes  No
- 4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product Use: (Submit indication or method of use information as identified specifically in the approved labeling)

**5. No Relevant Patents**

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.  Yes

EXCLUSIVITY SUMMARY for NDA # 50-794 SUPPL #

Trade Name Vidaza Generic Name azacitidine

Applicant Name Pharmion Corporation HFD-150  
Approval Date

**PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?**

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA? YES/  / NO /  /

b) Is it an effectiveness supplement? YES /  / NO /  /

If yes, what type (SE1, SE2, etc.)?

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?

7 years (orphan drug status)

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

YES /  / NO /  /

**IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /  / NO /  /

If yes, NDA # \_\_\_\_\_ Drug Name

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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

YES /  / NO /  /

**IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).**

**PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

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

YES /\_\_\_/ NO /✓/

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

NDA #

NDA #

NDA #

2. Combination product.

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

YES /\_\_\_/ NO /✓/

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

NDA #

NDA #

NDA #

**IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.**

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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

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

YES /\_\_\_/ NO /\_\_\_/

**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.**

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.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

- (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 9:**

- (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:

Investigation #1, Study #

Investigation #2, Study #

Investigation #3, Study #

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 /\_\_\_/

Investigation #3 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:

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

(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 /\_\_\_/  
Investigation #3                      YES /\_\_\_/                      NO /\_\_\_/

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

NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #  
NDA # \_\_\_\_\_ Study #

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

Investigation #\_\_, Study #  
Investigation #\_\_, Study #  
Investigation #\_\_, Study #

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:  
!  
!  
!

Investigation #2 !  
!  
IND # \_\_\_\_\_ YES /\_\_\_/ ! NO /\_\_\_/ Explain:  
!  
!  
!  
!

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

Investigation #1 !  
!  
YES /\_\_\_/ 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: \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

\_\_\_\_\_  
Signature of Preparer  
Title:

Date

Signature of Office or Division Director

Date

cc:  
Archival NDA  
HFD- /Division File  
HFD- /RPM  
HFD-610/Mary Ann Holovac  
HFD-104/PEDS/T.Crescenzi

Form OGD-011347  
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

*Orphan - not needed*

NDA/BLA #: 50-794 Supplement Type (e.g. SE5): \_\_\_\_\_ Supplement Number: \_\_\_\_\_

App Date: 12-29-03 Action Date: 6-29-04

HFD -150 Trade and generic names/dosage form: Vidaza (azacitidine for injectable suspension)

Applicant: Pharmion Corporation Therapeutic Class: 1P

Indication(s) previously approved: None.

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

Number of indications for this application(s): 1

Indication #1: treatment of patients with MDS

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

Yes: Please proceed to Section A.

No: Please check all that apply:  Partial Waiver  Deferred  Completed

NOTE: More than one may apply

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

**Section A: Fully Waived Studies**

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Adult studies ready for approval

Formulation needed

Other: \_\_\_\_\_

*If studies are deferred, proceed to Section C If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is*

complete and should be entered into DFS.

**Section C: Deferred Studies**

Age/weight range being deferred:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_  
Max \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ Tanner Stage \_\_\_\_\_

Reason(s) for deferral:

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

Other: \_\_\_\_\_

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min \_\_\_\_\_ kg \_\_\_\_\_ mo. \_\_\_\_\_ yr. \_\_\_\_\_ 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.

This page was completed by:

*{See appended electronic signature page}*

\_\_\_\_\_  
Regulatory Project Manager

cc: NDA 50-794  
HFD-960/ Grace Carmouze

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

(revised 12-22-03)

**Attachment A**

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

Indication #2: \_\_\_\_\_

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: \_\_\_\_\_

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

**Section B: Partially Waived Studies**

Age/weight range being partially waived:

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

Reason(s) for partial waiver:

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

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

**Section C: Deferred Studies**

Age/weight range being deferred:

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

Reason(s) for deferral:

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

Date studies are due (mm/dd/yy): \_\_\_\_\_

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

**Section D: Completed Studies**

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	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}*

\_\_\_\_\_  
Amy Baird  
Consumer Safety Officer

cc: NDA 50-794  
HFD-960/ Grace Carmouze

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

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

/s/

-----  
Amy Baird  
3/16/04 10:30:12 AM

# Demographic Worksheet

Application Information (Enter all identifying information for the submission pertaining to this summary)

NDA Number: 50794      Submission Type: N      Serial Number: SN-000

Populations Included In Application (Please provide information for each category listed below from the primary safety database excluding PK studies)

CATEGORY	NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG		NUMBER EXPOSED TO STUDY DRUG	
	Gender	Males	All Females	Females >50		
		183		87		79
Age:	0-≤1 Mo.	0	>1 Mo.- ≤2Year	0	>2-≤12	
	12-16	0	17-64	100	≥65	170
Race:	White	256	Black	4	Asian	4
	Other	6				

Gender-Based Analyses (Please provide information for each category listed below.)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on gender recommended in the label?  
 If the analysis was completed, who performed the analysis

Was gender-based analysis included in labeling?

YES	No
<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<input checked="" type="checkbox"/> Sponsor	<input type="checkbox"/> FDA

Age-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No	<input type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on age recommended in the label?  
 If the analysis was completed, who performed the analysis

Was age-based analysis included in labeling?

YES	No
<input checked="" type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
<input checked="" type="checkbox"/> Sponsor	<input type="checkbox"/> FDA

Race-Based Analyses (Please provide information for each category listed below)

Category	Was Analysis Performed?			
	If no is checked, indicate which applies or provide comment below			
Efficacy	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent
Safety	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No	<input checked="" type="checkbox"/> Inadequate #'s	<input type="checkbox"/> Disease Absent

Is a dosing modification based on race recommended in the label?  
 If the analysis was completed, who performed the analysis

Was race-based analysis included in labeling?

YES	No
<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<input checked="" type="checkbox"/> Sponsor	<input type="checkbox"/> FDA

In the comment section below, indicate whether an alternate reason (other than "inadequate numbers" or "disease absent") was provided for why a subgroup analysis was NOT performed, and/or if other subgroups were studied for which the metabolism or excretion of the drug might be altered (including if labeling was modified).

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

/s/

-----  
Edvardas Kaminskas  
5/5/04 04:54:35 PM  
MEDICAL OFFICER

Ann Farrell  
5/5/04 05:19:27 PM  
MEDICAL OFFICER

**6. Declaration Certification**

**6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.**

**Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.**

**6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)**

Date Signed

*G. Ivers-Read*

26 December 2003

**NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).**

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Gillian Ivers-Read

Address

2525 28<sup>th</sup> Street

City/State

Boulder/Colorado

ZIP Code

80301

Telephone Number

720.564.9105

FAX Number (if available)

720.564.9191

E-Mail Address (if available)

GIvers-Read@pharmion.com

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Food and Drug Administration  
CDER (HFD-007)  
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Rockville, MD 20857

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**Debarment Certification**

NDA 211-722 50-794 LDT 12/24/03  
Vidaza™ (Azacitidine for Injectable Suspension)  
Original Application

Pharmion Corporation 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.



Gillian Ivers-Read  
Vice President, Clinical Development and Regulatory Affairs  
Pharmion Corporation  
720.564.9105

Date: 26 December 2003

**Applicant:** Pharmion Corporation

**NDA:** 21-722

### Section 1.6.1 Waiver

~~Azacitidine has been designated as an Orphan Drug on 3 December 2001 (designation request #01-1501).~~

- Under section 736(a)(1)(E) of the Food, Drug, and Cosmetic Act, a human drug application is not subject to an application fee if the proposed product is for rare disease or condition designated under section 526 of the FD&C Act (orphan drug designation).

and

- If a product has been granted orphan designation for an indication or indications under section 526 of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. 360bb), submission of pediatric data is not required for applications to market the product for the orphan-designated indications and a waiver is not needed (21 CFR 314.55(d) for NDAs and 601.27(d) for BLAs).

Therefore, Pharmion has not requested any waivers for azacitidine.

**APPEARS THIS WAY  
ON ORIGINAL**

## **Division Director's Memorandum**

Date: May 18, 2004  
NDA: 50-794  
Sponsor: Pharmion Corporation  
Proprietary Name: Vidaza™ (azacitidine, 5-azacytidine)

### **Regulatory History**

Azacitidine was synthesized 40 years ago and has been used for more than 30 years in clinical trials under National Cancer Institute (NCI) auspices, mainly for myelodysplastic syndromes (MDS) and acute myelogenous leukemia (AML), and on compassionate use basis, but has never been approved. The drug had previously been under development by Pharmacia and Upjohn. Pharmion Corporation acquired the rights to azacitidine in June 2001.

Azacitidine received Orphan Drug designation on December 3, 2001.

On December 19, 2001, Pharmion Corporation had a pre-IND/EoP2/pre-NDA meeting with the Agency to discuss possible submission of an NDA using three Cancer and Leukemia Group B (CALGB) studies. At that time, the Division agreed that Pharmion could use response rate (complete response plus partial response) for accelerated approval. During the meeting, Pharmion and the Agency discussed the issues of accelerated versus regular approval. The Division voiced concern as to whether a determination of clinical benefit in the completed CALGB trial 9221 was possible because of the retrospective collection of some study data, lack of a statistical analysis plan, multiplicity of endpoints and concern about missing data.

On March 7, 2002, Pharmion Corporation submitted IND 64,251 for azacitidine.

On April 22, 2003, Pharmion submitted a Special Protocol Assessment for a large, randomized, multi-center trial which might confirm clinical benefit.

On October 10, 2003, the Agency granted Fast Track designation to azacitidine.

On December 26, 2003, Pharmion submitted the current NDA.

The PDUFA goal date for this priority review is June 29, 2004.

### **Proposed Indication**

Vidaza is indicated for treatment of patients with the following myelodysplastic syndrome subtypes: refractory anemia or refractory anemia with ringed sideroblasts (if accompanied by neutropenia and/or thrombocytopenia and requiring transfusions), refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia.

### **MDS**

MDS is an incurable and progressive disease with an estimated 15,000 to 20,000 new cases diagnosed each year in the US. The myelodysplastic syndromes, formerly called pre-

leukemia or “smoldering” leukemia, consist of a group of heterogeneous diseases characterized by ineffective hematopoiesis leading to one or more peripheral cytopenias (neutropenia, anemia, thrombocytopenia), progressive bone marrow failure, and an increased risk of development of AML. Although the disorder can be found in children and adults, the highest prevalence occurs in those over 60 years of age.

Treatment for MDS ranges from supportive care to bone marrow transplantation. Remissions do not occur without treatment. Allogeneic bone marrow transplantation is the only curative therapy. Because of the advanced age of MDS patients, few are candidates for bone marrow transplantation. Most patients receive supportive care including cytokine therapy (erythropoietin, granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor), red blood cell and platelet transfusions, and prophylactic antibiotics.

### **Available Therapies**

There is no approved therapy for this disease.

### **Clinical Review** (see review by Dr. Kaminskis and team leader review by Dr. Farrell)

The clinical section contains results from one randomized controlled trial (9221) and two single-arm studies (8921 and 8421). All three trials were conducted by CALGB and were approved and funded by the NCI. The three trials were conducted sequentially between 1985 and 2003, when the last subject had the last follow-up. These three trials are the largest azacitidine trials, as well as the largest trials of any treatment, in MDS.

Pharmion contracted with \_\_\_\_\_

\_\_\_\_\_ to perform retrospective data collection from the original study sites, and verify and analyze the data. The principal investigator of the randomized controlled CALGB 9221 study assisted in data collection and analyses and in locating and contacting individual investigators. Pharmion stated that 100% of the data was collected at all 53 sites for the 191 patients in the randomized trial, and for the 120 patients in the single-arm trials. The applicant also summarized the published results of seven other non-CALGB trials of azacitidine in MDS.

### **EFFICACY**

Efficacy of azacitidine is demonstrated in CALGB trials 9221, 8921 and 8421.

CALGB 9221 was a phase 3, open-label, multi-center, controlled study enrolling 191 patients. Ninety-nine patients were randomized to treatment with azacitidine (administered subcutaneously [SC] at a dose of 75 mg/m<sup>2</sup>/day for 7 days every 28 days) and 92 subjects were randomly allocated to the observation only. Study subjects included patients with all 5 MDS subtypes (Refractory Anemia [RA], Refractory Anemia with Ringed Sideroblasts [RARS], Refractory Anemia with Excess Blasts [RAEB], Refractory Anemia with Excess Blasts in Transformation [RAEB-T], and Chronic Myelomonocytic Leukemia [CMML]). Randomization criteria included stratification by MDS subtype. Observation only subjects were permitted to cross over to treatment with azacitidine, if they met pre-specified criteria of transfusion dependence, thrombocytopenia or neutropenia after a time period

corresponding to 2 to 4 treatment cycles. Fifty-one subjects in the observation arm (55%) crossed over to azacitidine treatment.

CALGB 8921 enrolled 72 subjects with RAEB, RAEB-T and CMMoL, who were treated with the above regimen of azacitidine administered SC. CALGB 8421 enrolled 48 subjects with RAEB and RAEB-T, who were treated with the above dose of azacitidine, which was administered intravenously (IV). CALGB central laboratory adjudicated the following number of subjects to have AML at study entry: 19 subjects in study 9221 (10 in the azacitidine treatment arm and 9 in the observation only arm), 17 subjects in study 8921, and 1 subject in study 8421.

The primary efficacy endpoint was overall response rate (complete and partial response rates). Complete response was defined as normalization of peripheral blood counts and bone marrow blast percentages for at least 4 weeks. Partial response was defined as  $\geq 50\%$  restoration in deficit from normal levels of baseline blood counts and absence of myeloblasts in peripheral blood, and  $\geq 50\%$  decrease in myeloblasts in marrow from baseline (except in RA and RARS, in which there is no increase in marrow myeloblasts).

In study 9221, the response rates were 15.7% in subjects randomized to azacitidine treatment and 0% in observation only subjects. The difference in response rates between the group randomized to azacitidine and the observation only (without crossover) group was statistically significant ( $p < 0.0001$ ). The response rate was 12.8% in azacitidine after observation crossover subjects. The response rate was 13.9% in study 8921 and 18.8% in study 8421. Response rates were similar in all 5 MDS sub-types. Subjects adjudicated to have AML at study entry had the same response rate as MDS subjects. The response rate to azacitidine in the 3 studies, with or without the subjects adjudicated to have AML at study entry, was 16.2%. See statistical section. The responses were long lasting in most patients. The mean and median durations of clinical responses are depicted in Table 1. The response duration could not be accurately estimated, because over 70% of subjects remained in response status at the time of withdrawal from the trials.

Table 1: Summary of Duration of Azacitidine Responses in MDS

Responses (Complete and Partial)	CALGB 9221 All Azacitidine N=136	CALGB 8921 N=55	CALGB 8421 N=47
Median	>330 days	>430 days	>281 days
Mean	>512 days	>810 days	>389 days

All patients who were transfusion dependent became transfusion independent during complete or partial response. In addition to complete or partial responses, azacitidine treatment resulted in lesser responses, termed "improvement", that occurred in about 19% of subjects in the 3 trials, and consisted of increased blood counts and achievement of transfusion independence. The median duration of improvement was 195 days.

The controlled trial was not powered to detect differences in survival between azacitidine-treated and observation only patients. Moreover, crossover of observation subjects to azacitidine treatment made the two groups not comparable with respect to MDS sub-types. Similarly, risk of progression to AML could not be accurately assessed for the above reasons.

**SAFETY**

Azacitidine appears to be a relatively safe drug for a carcinogenic category D malignant condition such as MDS. The major toxicity of azacitidine was myelosuppression, as manifested by thrombocytopenia (and bleeding), neutropenia (and infections), and anemia. Other common adverse events were gastrointestinal (nausea, vomiting, diarrhea, constipation, anorexia), constitutional (fatigue, weakness, fever, rigors), musculoskeletal (arthralgia, pain in limb), pulmonary (cough, dyspnea), and skin and soft tissue (ecchymoses, rash, erythema). Liver function abnormalities occurred in three patients with previously diagnosed cirrhosis of the liver, and in patients with intercurrent hepatobiliary disorders. Renal failure occurred in five azacitidine-treated patients and in one observation-only patient in settings such as sepsis and hypotension.

**SPECIAL POPULATIONS**

There were no noteworthy gender-related or age-related differences in efficacy or safety. Ethnic/racial differences could not be detected, because >95% of study subjects were White (Caucasian). Pregnancy Category is D.

**Biostatistical Review** (see Dr. Wang's review)

The original protocol of the CALGB 9221 study defined the primary objectives as to determine the response rate to azacitidine and the impact of azacitidine on red cell transfusion requirements, platelet counts, ANC, rates of infection and hemorrhage and % BM blasts, in comparison to an untreated observation group. It also defined the response as either Complete Response (CR), Partial Response (PR), or Improvement. The NDA submission defined the primary endpoint as the overall response (CR+PR).

For the overall response, CALGB 9221 appears to demonstrate a significant benefit of azacitidine compared to observation (1) before crossover to treatment arm in the intent-to-treat (ITT) population ( $p < 0.0001$ ), (2) in the ITT population without acute myelogenous leukemia (AML) ( $p < 0.0001$ ), and (3) in the ITT population without AML or protocol violation ( $p = 0.0007$ ). It also appears to demonstrate a significant benefit of azacitidine compared to observation only group (excluding crossover patients) for ITT population ( $p = 0.0033$ ), ITT population without AML ( $p = 0.010$ ), and ITT population without AML or protocol violation ( $p = 0.0276$ ). However, it failed to demonstrate any significant benefit of azacitidine compared to observation before crossover group as measured by complete response for ITT population without AML and/or protocol violation patients. It also failed to demonstrate any significant benefit of azacitidine compared to observation only group as measured by complete response for ITT population with AML and/or protocol violation patients and ITT population without AML and/or protocol violation patients.

Analysis of Response Rates --- FDA Analyses

	Azacitidine	Observation before Crossover	Azacitidine vs. Obs bf X-over	Observation without Crossover	Azacitidine vs. Obs w/o X-over
All ITT Patients	N = 99	N = 92	p-value <sup>a</sup>	N = 41	p-value
Overall (CR+PR) n (%)	16 (16.2)	0 (0.0)	<0.0001	0 (0.0)	0.0033
Complete (CR) n (%)	6 (6.1)	0 (0.0)	0.0294	0 (0.0)	0.1802
Partial (PR) n (%)	10 (10.1)	0 (0.0)		0 (0.0)	

	Azacitidine	Observation before Crossover	Azacitidine vs. Obs bf X-over	Observation without Crossover	Azacitidine vs. Obs w/o X-over
ITT Patients without AML	N = 89	N = 83	p-value	N = 36	p-value
Overall (CR+PR) n (%)	14 (15.7)	0 (0.0)	<0.0001	0 (0.0)	0.0100
Complete (CR) n (%)	5 (5.6)	0 (0.0)	0.0596	0 (0.0)	0.3202
Partial (PR) n (%)	9 (10.1)	0 (0.0)		0 (0.0)	
ITT Patients without AML or protocol violation	N = 54	N = 48	p-value	N = 22	p-value
Overall (CR+PR) n (%)	11 (20.4)	0 (0.0)	0.0007	0 (0.0)	0.0276
Complete (CR) n (%)	5 (9.3)	0 (0.0)	0.0585	0 (0.0)	0.3133
Partial (PR) n (%)	6 (11.1)	0 (0.0)		0 (0.0)	

<sup>a</sup> P-value from Fisher's exact test by comparing the response rates between the azacitidine group and the observation group.

Obs bf X-over=observation before crossover

Obs w/o X-over=observation without crossover

CR=complete response

PR=partial response

### **Chemistry/Manufacturing and Controls Review** (see Dr. L. Hsieh's review)

Vidaza (azacitidine for injectable suspension) is supplied as a sterile lyophilized form for reconstitution. The reconstituted suspension is for SC injection use only. Vials of Vidaza contain 100 mg of azacitidine (active ingredient) and 100 mg mannitol (excipient). Vidaza is supplied in single-use vials packaged in cartons of 1 vial. It is stored at 25°C (77°F); excursions permitted to 15°- 30°C (59°- 86°F). The primary and supportive stability data supports the proposed expiry dating period of 48 months.

Azacitidine is an analog of cytidine by having nitrogen in the 5 position of the heterocyclic ring. It is a white to off-white solid. It is

Its molecular formula is C<sub>8</sub>H<sub>12</sub>N<sub>4</sub>O<sub>5</sub> and the molecular weight is 244. It is well characterized. Adequate controls are provided to assure its quality. The primary and supportive stability data supports its proposed retest period of 24 months.

Due to the instability of azacitidine in aqueous solution, the reconstituted suspension requires special handling and storage. Vidaza should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. The reconstituted suspension must be administered within 1 hour. The reconstituted product may be kept in the vial or drawn into a syringe. If delayed administration happens, the product must be refrigerated immediately (2°- 8°C, 36°- 46°F) for up to 8 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

### **Nonclinical Review** (see Dr. Lee's review and Dr. Leighton's team leader memo)

Altered methylation of DNA has been shown to affect gene expression. Vidaza (5-azacytidine) is a cytotoxic agent with primary action as an inhibitor of DNA methylation. Hypermethylation of DNA has been implicated in gene silencing; 5-azacytidine alters methylation at critical DNA regulatory regions, resulting in re-expression of silenced genes, thus affecting cellular differentiation. Many of the non-clinical studies were conducted based

on this interest in 5-azacytidine as a laboratory tool for molecular pharmacology, as well as the long history of use of 5-azacitidine as an antineoplastic agent.

The study reports submitted to support the non-clinical pharmacology and toxicology for Vidaza were primarily obtained from the scientific literature. Studies assessing the toxicology of 5-azacytidine include all studies normally requested by the Division, including general toxicology, genetic toxicity, and reproductive toxicity reports. Carcinogenicity studies were also provided, although these were not requested by the Division; these studies were evaluated by CDER's Executive Carcinogenicity Assessment Committee (eCAC).

Pharmacology studies indicate that only cells that are rapidly dividing are sensitive to 5-azacytidine, with the primary pharmacodynamic action related to methyl transferase inhibition. Toxicology studies were generally designed as research studies and, as such, did not follow protocols for toxicology studies usually submitted for regulatory purposes. Nevertheless, Dr. Lee concluded that the studies provided an adequate assessment of appropriate endpoints. 5-Azacytidine was positive in genetic toxicity studies (*in vitro* mutagenicity and clastogenicity), reproductive toxicity (developmental toxicity and/or teratogenesis when administered to either male (prior to mating) or pregnant female mice or rats, in the absence of maternal toxicity), and as a carcinogen. The finding that 5-azacitidine was a multi-site tumorigen in both mice and rats, in both sexes suggest a risk for secondary tumors.

### **Clinical Pharmacology & Biopharmaceutic Review** (see Dr. Abraham's review)

Single-dose pharmacokinetics of azacitidine were determined following SC and IV administrations of 75 mg/m<sup>2</sup> azacitidine to six MDS patients. Azacitidine is rapidly absorbed following SC administration with a mean maximum plasma concentration ( $C_{max}$ ) of 750±403 ng/ml attained in 0.5 hour. Azacitidine is widely distributed throughout the body. Mean volume of distribution is 76 L following IV administration which exceeds the volume of total body water (42 L) suggesting extensive tissue distribution. The protein binding of azacitidine is not known. Azacitidine is rapidly eliminated from the body; plasma concentrations were detectable up to 2 hours after the IV dose and up to 4 hours after the SC dose. The mean half-life after IV administration was 22±1.2 minutes, while that after SC administration was 41±8 minutes. Total clearance after IV administration averaged 146±47 L/hr. Azacitidine may undergo hepatic metabolism. Following IV administration to 5 cancer patients, the cumulative urinary excretion is 85% of the radioactive dose while fecal excretion is only < 1% over three days. Mean excretion of radioactivity in urine following receiving SC administration of <sup>14</sup>C-azacitidine is 50%. The effects of intrinsic factors such as age, gender, race, renal impairment or hepatic impairment on the pharmacokinetics of azacitidine have not been evaluated. No *in vivo* drug-drug interaction studies have been conducted. The inhibition potential for azacitidine on CYP P450 enzymes is not known. Azacitidine is not an inducer of CYP P450 enzymes.

*Post Approval Agreements:* Pharmacokinetic and safety studies in patients with varying degrees of renal impairment.

### **Data Integrity Issues**

The Division of Oncology Drug Products decided that a DSI audit of the pivotal studies submitted in support of the approval of Vidaza for the treatment of patients with MDS is not needed for the following reasons:

- The three clinical trials were not conducted by a sponsor, i.e., a pharmaceutical company, but by CALGB under the auspices of NCI. While the trial was ongoing, CALGB conducted audits of individual sites.
- CALGB investigators would perceive no financial gain falsifying data, while they had great interest in satisfying CALGB and NCI criteria for good clinical data management in order to continue participating in CALGB trials.
- The trial was large, randomized, and multi-center (53). Out of the 99 patients enrolled on the 5-azacytidine arm, there were 16 responders. No site contributed more than one 5-azacytidine responder. Thus, the likelihood that significant data falsification occurred which would invalidate the trial results is remote.
- The response rate for 5-azacytidine in the applicant's submitted primary registration trial (9221) is the same as that reported by CALGB in the published literature.
- Response rates for 5-azacytidine for the treatment of myelodysplasia in the applicant's submitted primary trial (9221) are substantiated by similar response rates in other published studies.

### **Labeling** (see DMETS review)

DMETS reviewed the draft container labels, carton, shipping and insert labeling for Vidaza and focused on safety issues relating to possible medication errors. DMETS recommended the following changes to minimize potential user errors.

1. Container Labels and Carton and Shipping Labeling
  - Increase the size of the established name so that it is at least ½ the size of the proprietary name.
  - Increase the prominence of the strength and relocate the strength of the product so that it appears in conjunction with the proprietary and established names.
  - Revise the contrasting colors (white lettering on blue background) to improve readability.
  - Delete the green oblong circles that appear behind the proprietary and established names because they are distracting and decrease the readability of the names.
  - Include the statement "Discard unused portion" in conjunction with the statement 'Single-use vials.'
2. Package Insert labeling (DOSAGE AND ADMINISTRATION, Preparation for Immediate and Delayed Administration Subsections): The stability information is the most important information provided in these two sections. However, this information is combined with the reconstitution directions, which are repeated, thus making it difficult to determine the stability information. DMETS recommended deleting these two sections and replacing them with the stability information only, thus providing the stability information in a clear and concise format. For example:

- Reconstituted Vidaza is stable at room temperature for one hour. If stored at room temperature Vidaza reconstituted solution must be used within XX hour.
- Reconstituted Vidaza is stable under refrigeration for a maximum of eight hours. Reconstituted Vidaza must be used within XX minutes after removal from the refrigerator.

### **Tradename consultation**

The tradename, Vidaza, is acceptable to DDMAC. DMETS has no objections to the use of the proposed proprietary name with one provision (see DMETS review).

### **Pediatric Considerations**

No pediatric studies are proposed. Although the disorder can be found in children as well as adults, the highest prevalence occurs in those over 60 years of age.

### **Conclusions and Recommendations: Regular Approval**

In MDS complete and/or partial responses occur only with treatment. All three studies submitted in the NDA package demonstrated that patients treated with azacitidine could obtain a CR or PR that translated into clinical remission of MDS. The response rates were similar in the three trials ranging from 14-19%. The randomized controlled trial demonstrated that the red blood cell transfusion-dependent azacitidine patients received greater clinical benefit (transfusion independence) compared with the red blood cell transfusion-dependent observation alone patients. The chief clinical benefit was noted in 26% of the azacitidine treated patients who were transfusion dependent at the trial's initiation became RBC transfusion independent on azacitidine for periods greater than 3 months compared to none of the RBC transfusion dependent patients on the observation arm.

Richard Pazdur, MD  
Director, Division of Oncology Drug Products

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

/s/

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Dianne Spillman  
5/19/04 11:30:38 AM  
CSO

Richard Pazdur  
5/19/04 11:39:04 AM  
MEDICAL OFFICER

Note: This review is final and supersedes previous review dated April 27, 2004.

Division of Oncology Drug Products

Medical Team Leader's Review

NDA: 50794  
Sponsor: Pharmion Corporation  
Drug Product: 5-azacytidine, azacitidine, Vidaza  
Review Date: May 17, 2004

***Recommendation:***

I concur with Dr. Kaminskas' review and recommend regular approval for 5-azacytidine for the treatment of Myelodysplastic Syndrome (MDS). This recommendation is based upon the following facts:

- 1) All three clinical studies (8421, 8921, 9221) submitted in the NDA package demonstrated that patients treated with 5-azacytidine could obtain a complete (CR) or partial response (PR) which translated into a clinical remission of their MDS. The response rates (CR and PR) for patients treated with 5-azacytidine in the randomized multicenter trial (9221) and in the single arm studies (8421, 8921) were similar and ranged from 14-19%.
- 2) In the observation arm of the randomized controlled trial, the only patients who achieved either a CR or PR were those patients who crossed over and received treatment with 5-azacytidine. These patients only achieved the CR or PR after initiating treatment with 5-azacytidine.
- 3) In MDS, complete responses, partial responses and clinical remissions only occur with treatment. Spontaneous remissions do not occur in the absence of treatment.
- 4) The randomized controlled trial demonstrated that the red blood cell transfusion-dependent 5-azacytidine treated patients received greater clinical benefit (transfusion independence) compared with the red blood cell transfusion-dependent observation alone patients. The chief clinical benefit was that 26% of the 5-azacytidine treated patients who were red blood cell transfusion-dependent at the start of the study became red blood cell transfusion independent on 5-azacytidine for periods greater than 3 months (range 100-2400<sup>+</sup> days) compared with 0% of the red blood cell transfusion-dependent patients who remained on the observation arm throughout the study.

- 5) Other clinical investigators have reported similar efficacy of 5-azacytidine in the treatment MDS and Acute Leukemia (AL) have. For MDS and AL patients, the clinical benefit reported has been clinical and/or pathologic remission and a decrease in the need for blood transfusions.<sup>12345678910</sup>

I also concur with Dr. Kaminskas' recommendations for a post-marketing study for use of 5-azacytidine in MDS patients with renal impairment.

***Background:***

On December 29, 2003, Pharmion submitted this New Drug Application (NDA) for 5-azacytidine, a new molecular entity, for the treatment of myelodysplastic syndrome for accelerated approval based on 21 Code of Federal Regulations 314.500 (subpart H).

***MDS***

At the present time, myelodysplasia is an incurable and progressive disease with an estimated 15,000 – 20,000 new cases diagnosed each year in the US. The myelodysplastic syndromes (MDS), formerly called pre-leukemia or "smoldering" leukemia, consist of a group of heterogeneous diseases characterized by ineffective hematopoiesis leading to one or more peripheral cytopenias (neutropenia, anemia, thrombocytopenia) and progressive bone marrow failure. Although the disorder can be found in children as well as adults, the highest prevalence occurs in those over 60 years of age.

Treatment for MDS ranges from supportive care to bone marrow transplantation. Remissions do not occur without treatment. The only hope for a cure is an allogeneic bone marrow transplantation (AlloBMT). Few MDS patients are eligible for an AlloBMT because of the age limitation of this procedure (i.e., less than 65). For patients older than age 65, there are no approved therapies. Most patients receive supportive care which may include cytokine therapy (erythropoietin, granulocyte-colony stimulating factor, granulocyte-macrophage colony stimulating factor), red blood cell and platelet transfusions, and prophylactic antibiotics.

For additional details, please see Dr. Kaminskas' review.

***5-Azacytidine***

Although unapproved, 5-azacytidine has been used as monotherapy and in combination chemotherapy for the treatment of MDS and acute leukemia (AL) and solid tumors. Both single agent and combination therapy have resulted in remissions in AL and MDS. However, 5-Azacytidine's role in the treatment of solid tumors is less certain<sup>11</sup>.

***Current Submission***

The current Pharmion NDA submission consists of 1 randomized controlled trial and 2 single arm studies using 5-azacytidine in MDS patients. The National Cancer Institute (NCI) has had a significant role in the pre-clinical and clinical development. The three clinical studies submitted for review were conducted by the Cancer and Leukemia Group B (CALGB) cooperative group under the auspices of the NCI. The applicant has also provided literature on the use of 5-azacytidine in MDS. The Agency has also performed a review of the literature on the use of 5-azacytidine in MDS.

#### *Regulatory History*

The history of drug development for this agent involves over 40 years of research. Pharmion Corporation acquired the rights to 5-azacytidine in June 2001.

On December 3, 2001, the Agency granted Orphan drug designation status for 5-azacytidine.

On December 19, 2001, Pharmion Corporation had a pre-IND/EoP2/pre-NDA meeting with the Agency to discuss possible submission of an NDA using the 3 CALGB studies. At that time, the Division agreed that Pharmion could use response rate (i.e., complete response plus partial response) for accelerated approval. During the meeting, Pharmion and the Agency discussed the issues of accelerated versus regular approval. The Division voiced concern about whether a determination of clinical benefit in the completed CALGB 9221 trial was possible because of the retrospective collection of some study data, the lack of a detailed statistical analysis plan, the multiplicity of efficacy endpoints and missing data.

On March 2, 2002, Pharmion Corporation submitted IND 64251 for 5-azacytidine.

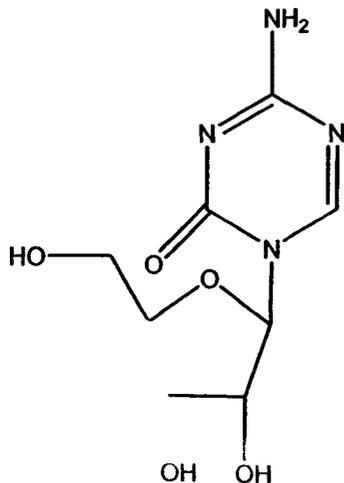
On April 22, 2003, Pharmion submitted a Special Protocol Assessment for a large, randomized, multicenter trial which might confirm clinical benefit.

On October 2, 2003, the Agency granted Fast Track designation to 5-Azacytidine.

#### ***Chemistry:***

##### *Drug Substance*

Vidaza (5-azacytidine) injectable suspension contains 5-azacytidine, a pyrimidine nucleoside analog of cytidine. 5-Azacytidine is 4-amino-1- $\beta$ -D-ribofuranosyl-1,3,5-triazin-2(1H)-one. The structural formula is:



The production of 5-azacytidine is \_\_\_\_\_  
 \_\_\_\_\_ The starting materials used \_\_\_\_\_  
 \_\_\_\_\_ No \_\_\_\_\_ are  
 used in the manufacture \_\_\_\_\_  
 Each of these  
 substances is incorporated as a significant structural fragment into the structure  
 of 5-azacytidine. These  
 \_\_\_\_\_  
 \_\_\_\_\_ manufacturing process. The  
 \_\_\_\_\_  
 manufacturing process

#### *Drug Product*

The finished product is supplied in vials which contain 100 mg of 5-azacytidine (white to off-white solid) and 100 mg mannitol as a sterile lyophilized powder. 5-azacytidine should be reconstituted with 4mL sterile water. The resulting suspension is for subcutaneous injection only.

Due to the rapid degradation of 5-azacytidine in aqueous based solutions, the recommendation for product preparation prior to injection states that the reconstituted suspension formulation be administered to the patient within an hour after preparation. If a delay in administration is anticipated, the suspended formulation may be held in the syringe under refrigerated temperatures (2 to 8°C) for up to 8 hours. After removal from refrigerated conditions, the suspension formulation must be administered within 30 minutes.

For further details, please see Dr. Hsieh 's Chemistry, Manufacturing, and Control (CMC) review of this NDA.

No CMC phase 4 commitment issues have been identified.

**Microbiology:**

The microbiology review identified deficiencies that could be addressed post-approval. The following list is directly copied from that review.

1. The descriptions of and data provided regarding validation are too abbreviated. A thorough description of the test protocol should be provided including, but not limited to:

test results for each of the , the integrity parameters. , and a comparison of the process and validation parameters.

In addition, data obtained with each of the should be provided.

The scheme for this product includes . Therefore, these descriptions and data may be provided post-approval

2. Data generated confirming container/closure integrity using a more "classical" container/closure integrity evaluation should be provided. The sterility test is appropriate for to demonstrate continued container-closure integrity. However, initial evaluation should employ a more stringent test protocol.

**Preclinical Pharmacology and Toxicology Information:**

**Mechanism of Action**

5-Azacytidine's mechanism of action is through hypomethylation and cytotoxicity on abnormal hematopoietic cells in the bone marrow. Hypomethylation may restore normal function to genes (that have been methylated or inactivated through the binding of repressor proteins) that are critical for differentiation and proliferation. The cytotoxic effects of 5-azacytidine cause the death of rapidly dividing cells including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to 5-azacytidine.

Much of the preclinical data on 5-azacytidine is over 25 years old. In 1965, the mutagenic potential of 5-azacytidine was defined. In 1970, the National Cancer Institute conducted the initial single dose toxicity study in rodents. Reproductive toxicity studies performed in the 1970s and 1980s established the potential for embryo/fetal risk. Studies conducted *in vitro* and in rodents have consistently shown that 5-azacytidine is mutagenic, clastogenic, and embryotoxic. Tumorigenicity studies in mice and rats have shown that 5-azacytidine poses a potential carcinogenic risk.

The main nonclinical target organs of toxicity are the bone marrow and gastrointestinal tract.

Over the past 25 years, 5-azacytidine has been administered to approximately 7,500 patients through clinical trials, NCI's Group C Distribution, and the NCI compassionate use "special exception" program. Safety information from these patients constitutes more relevant data than the older nonclinical studies.

For further details, please see the Pharmacology and Toxicology review of this NDA.

#### Office of Pharmacology and Toxicology Phase 4 Commitments

The Agency did not identify a need for pharmacology/toxicology phase 4 commitments.

#### **Human Pharmacology:**

The application lacked some information on the clinical pharmacology of 5-azacytidine.

The only submitted pharmacokinetic study of 5-azacytidine was a multicenter, randomized, open-label, two-treatment, two period, crossover study conducted to determine the pharmacokinetics of subcutaneous (SC) and intravenous (IV) administered 5-azacytidine, using the lyophilized dosage form proposed for marketing, which involved 6 MDS patients who received a single 75 mg/m<sup>2</sup> SC dose and a single 75 mg/m<sup>2</sup> IV dose. The study showed that 5-azacytidine is rapidly absorbed after SC administration with a mean peak plasma azacytidine concentration of 750±403 ng/ml which occurred in 0.5 hour. The bioavailability of azacytidine by the SC route relative to IV dosing was approximately 89% based on area under the curve. Mean volume of distribution following IV dosing was 76 ± 26 L.

Published studies indicate that renal excretion is the primary route of 5-azacytidine elimination. Following IV administration, the cumulative urinary excretion ranged from 73% to 98% of the radioactive dose while fecal excretion was only <1% over three days. The mean excretion of radioactivity in urine following receiving SC administration of <sup>14</sup>C-azacytidine was less than that

following the IV administration (50% versus 85%). The mean elimination half-lives of total radioactivity (5-azacytidine and its metabolites) were comparable after IV and SC administrations (3.5 hours versus 4.2 hours, respectively). No formal Renal Impairment study was conducted.

The applicant has not conducted any formal hepatic Impairment study. The major clinical trial in this NDA restricted the eligibility for patients and did not allow patients with a creatinine > 1.5 times normal nor abnormal liver function tests ((SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase ) > 2 x normal)) or Total bilirubin > 1.5 x normal (unless due to active hemolysis, or ineffective erythropoiesis).

An *in vitro* study of 5-azacytidine incubation in human liver fractions suggested that 5-azacytidine may be metabolized by the liver. Whether 5-azacytidine metabolism may be affected by known microsomal enzyme inhibitors or inducers has not been studied. The potential of 5-azacytidine to inhibit cytochrome P450 (CYP) enzymes is not known. *In vitro* studies with human cultured hepatocytes indicate that 5-azacytidine at concentrations of 0.1 to 100  $\mu$ M does not induce CYP 1A2, 2C19, or 3A4/5.

#### Office of Clinical Pharmacology and Biopharmaceutics Phase 4 Commitments

The Office of Clinical Pharmacology and Biopharmaceutics recommended the following phase 4 commitments:

Safety and pharmacokinetic study of 5-azacytidine in MDS patients with mild-moderate renal impairment

#### **Clinical Studies Summary:**

Please see Dr. Kaminskas' review for details. The National Cancer Institute approved and funded the cooperative group studies submitted. These clinical studies were conducted over a 10-15 year period starting in 1984.

The major trial (CALGB 9221) submitted for the indication was a multicenter, open-label, randomized, placebo-controlled trial enrolling 191 patients with myelodysplastic syndrome classified according to the French, American and British classification system. Pharmion submitted the results from 2 smaller, multicenter, single arm studies which enrolled refractory anemia with excess blasts (RAEB) and RAEBT and CMMoL (chronic myelomonocytic leukemia) patients. Studies submitted for the indication are listed in the table below.

**Table 1: Studies Submitted for the Indication**

CALGB Study Number	Design	Patient Population
8421	Single arm, multicenter trial using intravenous (IV) 5-azacytidine 75 mg /m <sup>2</sup> for 7 days every 28 days for the treatment for MDS	48 MDS patients (RAEB or RAEBT)
8921	Single arm, multicenter trial using subcutaneous (SC) 5-azacytidine 75 mg /m <sup>2</sup> for 7 days every 28 days with best supportive care for the treatment for MDS	72 MDS patients (RAEB,RAEBT,CMMoL)
9221	Randomized, Controlled, multicenter trial comparing 5-azacytidine 75 mg/m <sup>2</sup> SC daily x 7, every 4 weeks versus best supportive care for the treatment for MDS	191 MDS patients (all subtypes) randomized to treatment with 5-azacytidine or best supportive care (observation alone)

Reviewer's Table

Since the major efficacy results are from CALGB 9221, this review will primarily concentrate on 9221.

### CALGB 9221

This study was initially designed and executed by the CALGB cooperative group. The study randomized patients to treatment with 5-azacytidine or observation alone. The protocol did not permit growth factors or steroids. In the original CALGB protocol, the primary endpoint for analysis was response rate defined as complete response (CR) + partial response (PR) + Improvement. These terms are defined in the table below. The primary endpoint for registration purpose and in the statistical analysis plan submitted by the applicant is response rate defined as CR + PR. Secondary endpoints included: response rate, red cell transfusion requirements, platelet counts, absolute neutrophil counts (ANC), rates of infection, percent bone marrow blasts, other toxicities, and quality of life.

**Table 2 – Response criteria**

Response Type	Criteria for Response
Complete (CR)	Normal CBC and absence of myeloblasts in peripheral blood and <5% myeloblasts in the bone marrow for at least 4 weeks.
Partial (PR)	<u>Peripheral blood criteria:</u> ≥50% restoration in the deficit from normal levels of baseline Hgb, WBC, and platelets, and no myeloblasts. For CMMoL, if WBC is elevated at baseline, a 75% reduction in the excess count above ULN. <u>Marrow criterion:</u> for RAEB, RAEB-T & CMMoL, ≥50% decrease in myeloblasts from baseline. For RA & RARS, marrow criterion N/A. Duration of the above responses for at least 4 weeks.
Improvement	≥50% restoration in the deficit from normal in one or more peripheral blood cell lines, but insufficient to meet criteria for PR, or a ≥50% decrease in RBC or platelet transfusion requirements. <u>Note:</u> improvement constituted a remission for the purpose of follow-up.

Reviewer's Table

One major issue with the submission concerns the retrospective data collection performed for the clinical efficacy and safety studies. After Pharmion Corporation obtained the rights to develop and market 5-azacytidine for treatment of myelodysplastic syndromes (MDS) in 2001, Pharmion then contracted with \_\_\_\_\_ to collect data and monitor data collection activities. The data collected for Pharmion were then source-verified, data-entered, and analyzed using a new electronic database. \_\_\_\_\_

\_\_\_\_\_ provided data management and analysis. Assistance was provided for quality control of the final report by \_\_\_\_\_ Pharmion stated that 100% of the data was collected at the 53 sites for the 191 patients including:

- 190/191 (99.5%) patients have baseline local pathology assessments.
- 188/191 (98%) patients have CALGB central review assessments of diagnosis at study entry.
- 95% concordance for the diagnosis of MDS vs. non-MDS (in 173 out of 183 cases) was found between CALGB central pathologist and local hematopathologist at the time of diagnosis.
- 96%-99% of patients in both treatment groups have key hematological (Hgb, WBC, and platelets) laboratory reports available.
- 80% (79/99) of azacitidine-arm patients and 84% (77/92) of observation-arm patients have reports of post-baseline bone marrow blast counts.
- 100% of the 5-azacytidine patients had information available concerning dosing.
- 100% of study patients had information concerning red blood cell and transfusion requirements during the course of the study.

*Reviewer's Comment: The data collection appears acceptable.*

The CALGB protocol required a central pathologic review. Review of pathology suggested that 19 patients (10 in the 5-azacytidine arm, 9 in the observation arm) in the ITT population had AML and not MDS. Results below will be presented including and excluding these patients.

*Reviewer's Comment: AML may arise de novo or in the setting of MDS. In adult patients, most cases of AML arise in the setting of MDS. The French, American and British classification defines RAEB (5-20% blasts), RAEB-T (20%-30% blasts) and AML (> 30% blasts). Thus, the pathologist's diagnosis of diagnosis of MDS or AML may have depended only on the number of blasts counted per field on the microscope slide.*

The study permitted cross-over for those observation only arm patients whose disease worsened or who were transfusion dependent after 4 cycles. During the trial 55% of the patients on the observation arm crossed over to receive treatment with 5-azacytidine. Therefore a strict comparison of response rates

between the as randomized arms no longer makes sense. The table below has a column entitled "Observation before Crossover", in this column are the response rates in the observation arm for patients prior to the time when they crossed over to receive 5-azacytidine. The table below has a column entitled "Observation without Crossover", in this column are the response rates in the observation arm reflect the patients who never crossed over to receive 5-azacytidine.

The response rates are noted in the table below.

**Table 3: Analysis of Response Rates — FDA Analyses**

	Azacitidine	Observation before Crossover	Azacitidine vs. Obs bf X- over	Observation without Crossover	Azacitidine vs. Obs w/o X- over
All ITT Patients	N = 99	N = 92	p-value <sup>a</sup>	N = 41	p-value
Overall (CR+PR) n (%)	16 (16.2)	0 (0.0)	<0.0001	0 (0.0)	0.0033
Complete (CR) n (%)	6 (6.1)	0 (0.0)	0.0294	0 (0.0)	0.1802
Partial (PR) n (%)	10 (10.1)	0 (0.0)		0 (0.0)	
ITT Patients without AML	N = 89	N = 83	p-value	N = 36	p-value
Overall (CR+PR) n (%)	14 (15.7)	0 (0.0)	<0.0001	0 (0.0)	0.0100
Complete (CR) n (%)	5 (5.6)	0 (0.0)	0.0596	0 (0.0)	0.3202
Partial (PR) n (%)	9 (10.1)	0 (0.0)		0 (0.0)	
ITT Patients without AML or protocol violation	N = 54	N = 48	p-value	N = 22	p-value
Overall (CR+PR) n (%)	11 (20.4)	0 (0.0)	0.0007	0 (0.0)	0.0276
Complete (CR) n (%)	5 (9.3)	0 (0.0)	0.0585	0 (0.0)	0.3133
Partial (PR) n (%)	6 (11.1)	0 (0.0)		0 (0.0)	

<sup>a</sup>P-value from Fisher's exact test by comparing the response rates between the azacitidine group and the observation group.

Obs bf X-over=observation before crossover, Obs w/o X-over=observation without crossover, CR=complete response, PR=partial response, CALGB=Cancer and Leukemia Group B  
From Dr. Wang's statistical review

*Reviewer's Comment: No patients in the observation arm before crossover achieved a response and no patients remaining in the observation arm throughout the study achieved a response. Not shown in the above table, 6 patients who crossed over to 5-azacytidine treatment achieved a response (3 CRs, 3 PRs) only after they had been treated with 5-azacytidine.*

*Reviewer's Comment: Whether patients with a central pathologic diagnosis of AML are included or excluded, the results suggest a statistically significant difference in favor of 5-azacytidine treatment. Similarly whether patients with major protocol violation are included or excluded, the results suggest a statistically significant difference in favor of 5-azacytidine treatment. For a list of major protocol violations, see Dr. Kaminskas' review.*

***Reviewer's Comment: Although adjustments have not been made for the multiple endpoints, it is unlikely that any adjustments applied would invalidate the strong statistically persuasive results in favor of 5-azacytidine.***

For analyses of secondary endpoints, please see Dr. Kaminskas' and Dr. Wang's reviews.

#### **Clinical Benefit - Red Blood Cell Transfusion**

***Reviewer's Comment: As discussed by Drs Kaminskas and Wang in their reviews, the red cell transfusion benefit analyses are complicated by several factors including cross-over and withdrawal from treatment or observation and which may have worked against 5-azacytidine. Greater than 50% of observation alone patients crossed over to receive 5-azacytidine. To be eligible for crossover, observation patients must have developed progressive disease or remained transfusion dependent. These crossover patients did not remain in the control arm for subsequent red blood cell transfusion analyses. Reasons for treatment withdrawal included: 1) for both arms the development of AML (there were more in the observation arm); no response after 4 cycles (more in the observation arm) and 2) for the 5-azacytidine arm, patients who achieved CR were withdrawn from the study after receiving the specified number of treatment cycles after achievement of CR. Pharmion and this reviewer have performed additional analyses below.***

The following study results demonstrate that 5-azacytidine patients who were red blood cell transfusion-dependent at the start of the study became transfusion independent on 5-azacytidine for periods greater than 3 months (range 100-2400<sup>+</sup> days). (The stated range underestimates the duration because some patients who achieved CR or PR or Improvement and completed their study period of observation were transfusion-free.) None of the patients who remained in the observation alone arm throughout their participation in the study became transfusion-free for 3 months or more.

Study 9221 collected information on red blood cell transfusion use for 3 months prior to study entry. The table below shows the patients who were red blood cell transfusion-dependent at study entry and became red blood cell transfusion independent for 3 months or more.

**Table 4: Red Blood Cell Transfusion Independence for 3 months or longer for patients red blood cell transfusion dependent at study entry (excluding AML patients)**

	Randomized to 5-azacytidine (N=89)	Randomized to Observation (N=83) <sup>1</sup>
Red Blood Cell Transfusion Dependent at study entry – Numbers of patients	61	56
Transfusion Independent for 3 months or more during study – Numbers of Patients	16	0
Percent transfusion independent for at least 3 months	26.2%	0%

<sup>1</sup> Data reflect study participation when observation patients were not receiving 5-azacytidine.  
Reviewer's Table

At the request of the clinical team, Pharmion attempted to apply the International Working Group<sup>12</sup> classification for Hematologic Improvement (HI) (see note below concerning ability to apply criteria for CR or PR). The criteria state that patients should be assessed for HI response in the absence of cytotoxic therapy. Since 9221 was not designed to collect information from patients off 5-azacytidine, Pharmion performed the analysis while patients in the 5-azacytidine arm were receiving treatment. The table below shows the results using these criteria.

**Table 5: Hematologic Improvement<sup>1</sup> (excluding patients adjudicated to have AML)**

Response category	Group 1 – 5-Azacytidine as Randomized (N=89)	Observation Only (N=36)
<b>Hematologic Improvement</b>		
Major Response	31 (34.8%)	3 (8.3%)
Minor Response	8 (9%)	4 (11.1%)
<b>Total</b>	<b>39 (43.8%)</b>	<b>7 (19.4%)</b>

<sup>1</sup> 5-Azacytidine patients were on cytotoxics during period of response.  
Reviewer's Table from Applicant's Table

*Reviewer's Comment: These results highlight the importance of a control arm when interpreting efficacy in MDS studies. By this analysis, MDS patients on observation alone were classified as having achieved a major HI response in the absence of intervention, these responses were due to fluctuations in their hemoglobin levels.*

**Reviewer's Comment: Regardless of which analysis is used, patients in the 5-azacytidine arm achieve greater numerical benefit than observation alone patients.**

### Efficacy Results from all 3 studies

The table below shows the response rates in the 3 studies submitted for review. Response rates ranged from 12.7% - 19.1%.

**Table 6: 5-Azacytidine Clinical Efficacy and Safety Studies**

CAI GB Study Number	Design	Patient Population	Results
8421	Single arm, Multicenter trial using intravenous (IV) 5-azacytidine 75 mg /m <sup>2</sup> for 7 days every 28 days for the treatment for MDS	48 MDS patients (RAEB or RAEBT)	Response Rate (CR+PR)-18.8%, 19.1% (excluding patients with AML)
8921	Single arm, Multicenter trial using subcutaneous (SC) 5-azacytidine 75 mg /m <sup>2</sup> for 7 days every 28 days with best supportive care for the treatment for MDS	72 MDS patients (RAEB,RAEBT, CMMoL)	Response Rate (CR+PR)-13.9%, 12.7% (excluding patients with AML)
9221	Randomized, Controlled, Multicenter trial comparing 5-azacytidine 75 mg/m <sup>2</sup> SC daily x 7, every 4 weeks versus best supportive care for the treatment for MDS	191 MDS patients (all subtypes) randomized to treatment with 5-azacytidine or best supportive care	55% of observation patients crossed over, Response Rate (CR+PR)-16.2% (all patients who received 5-azacytidine), 15.7% (excluding adjudicated AML), 0% in the observation alone arm

Reviewer's Table

### Additional Suggestions of Efficacy from Exploratory Analyses

The company and the division explored various exploratory Time-To-Event analyses (e.g., survival, time to AML or death); however, these post-hoc analyses remain confounded by the large crossover effect and the fact that 5-azacytidine as randomized and the observation group that did not crossover differed in MDS subtype distribution which could have affected these results.

### Overall Safety Assessment

Results from clinical trials/studies demonstrate that the major toxicities are: gastrointestinal (nausea, vomiting, diarrhea, constipation, anorexia), constitutional (fatigue, fever, rigors), musculoskeletal/connective tissue (arthralgia, pain in limb, weakness), pulmonary (cough, dyspnea), skin soft tissue (ecchymoses, rash, erythema) and bone marrow (neutropenia, anemia, leukopenia).

Although MDS patients with renal and hepatic impairment were excluded from the studies, some renal and hepatic toxicity occurred. The majority of patients who developed these toxicities had other concurrent medical conditions. Two of the three patients, who developed liver failure, had underlying cirrhosis. In the MDS patients who developed renal dysfunction, other underlying medical conditions such as sepsis, hypotension, diabetes were present.

In a 1976 review of 5-azacytidine, Von Hoff et al. reported that the dose-limiting toxicity in early trials were nausea, vomiting, leukopenia<sup>11</sup>. The published review also reported that hepatotoxicity with 5-azacytidine ranged from elevated liver function tests to frank coma. Frank coma occurred in patients with extensive liver metastases. In the CALGB studies, hepatotoxicity tended to be mild.

The early nonclinical data (supported by the mechanism of action) suggest that 5-azacytidine is mutagenic, embryogenic, and likely carcinogenic. However, for the indication under consideration, this drug still provides a favorable risk/benefit ratio.

#### Other Published Literature

The table below lists additional published literature from single arm studies. These published papers describe responses and hematologic improvements as a result of 5-azacytidine treatment. No other randomized comparator trials have been performed.

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Table 7: Supportive Literature for Use of 5-Azacytidine in MDS

Reference	Study Design	Results
Chitambar C, et. al. <sup>13</sup>	Single arm, Open-Label, Dose escalation study of continuous infusion for 14 days every month in 16 MDS patients, doses studied included 10 mg/m <sup>2</sup> /day – 35 mg/m <sup>2</sup> /day	16 enrolled (11m:2f, 3 unknown), median age 64 years (range 31-76), prior history of malignancy allowed (7 prior chemo/XRT), 1 AML pt., 15 evaluable, response rate 3/15 or 20 %, all PRs, 5/15 (33%) patients became transfusion-free
Gryn J. et. al. <sup>14</sup>	Single arm, Open-Label, study of subcutaneous administration of 75 mg/m <sup>2</sup> 5-azacytidine for 7 days every month in 57 MDS patients	57 enrolled (5 AML, 2 never received rx), 50 evaluable (30 m:18 f, 2 unknown), median age 71 (range 36-88), 18/50 (36%) patients became transfusion-free
Jani CR, et. al. <sup>15</sup>	Case Series of 14 patients treated with subcutaneous administration of 75 mg/m <sup>2</sup> 5-azacytidine for 7 days every month	14 patients (1 t-AML), 13 evaluable, 7/13 (54%) transfusion-free
Rugo H, et. al. <sup>16</sup>	Open-Label, subcutaneous administration of 75 mg/m <sup>2</sup> 5-azacytidine for 7 days for 6 months in 35 MDS patients*	35 enrolled, 26 evaluable (others too early), median age 66 (range 48-81), 38% CR+PR, 19%- improved
Rugo H, et.al. <sup>17</sup>	Open-Label, subcutaneous administration of 75 mg/m <sup>2</sup> 5-azacytidine for 7 days for 6 months in 92 MDS patients*	92 enrolled, 17 not evaluable (3 too early), median age not given, 42% CR+PR. 19%- improved
Litam PP, et. al. <sup>18</sup>	Case Report of 1 MDS patient with RAEBT treated with 5-azacytidine	Improvement in WBC parameters and blast percentages

PR defined as a decrease in monthly transfusion requirements by  $\geq 50\%$ , an increase in hgb by 2 gm/dl above pre-treatment levels, an increase in platelet counts by  $> 30,000/\text{mm}^3$  above pre-treatment platelet count if pretreatment platelet count  $< 100,00/\text{mm}^3$ , a sustained increase in granulocyte count by  $500/\text{mm}^3$  and a sustained decrease in blasts in bone marrow by 50% or more.

Improved- greater than 50% improvement in 1 cell line or an improvement in constitutional symptoms

\* These 2 published reports may contain some of the same patients

Reviewer's Table

### Ongoing Trial

At this time, the sponsor also

### *Oncologic Drugs Advisory Consultant*

We discussed this application with a former Advisory Committee chair who is a hematologist and who had been cleared of any conflict of interest.

The consultant agreed that azacitidine had activity in the treatment of myelodysplastic syndrome; however, the consultant had three areas of concern about this application.

- 1) The trial had large numbers of patients on the observation arm who crossed over to azacitidine. Thus, there may have been bias with respect to the patients who crossed over.

*Reviewer's Comment: The protocol had strict criteria about when patients could crossover to the azacitidine arm. In general, patients had to show worsening of their disease (worsening blood counts, major hemorrhage) or remained transfusion dependent after 4 cycles of observation. Cross-over in this trial should work against the 5-azacitidine arm since only observation arm patients with disease progression were eligible for cross-over.*

- 2) The current criteria for PR are more stringent than the criteria used in the protocol.

*Reviewer's Comment: The trial was designed in 1992 and last patient enrolled in 1997. The current criteria published by Cheson et. al. entitled "Report of an international working group to standardize response criteria for myelodysplastic syndromes" was published in Blood on December 1, 2000. We attempted to retrospectively apply those response criteria (CR, PR) to CALGB 9221 trial. However, because Pharmion did not prospectively collect the all necessary information, we were unable to determine response rates using the new criteria.*

- 3) The trial had an observation alone arm which would not be accepted in the modern era since, EPO + GCSF are the de facto standard therapies for cytopenias in the absence of excess blasts.

*Reviewer's Comment: There is no approved therapy at this time so a comparison to an observation alone arm is reasonable.*

We also requested a patient consultant for this application; however, the patient consultant had at least one conflict and could not be cleared.

### Phase 4 Commitments Under Subpart H

None, This reviewer recommends regular approval.

## Additional Requests

The applicant should collect safety information in a renal impairment study.

## *Conclusions and Recommendations*

### Discussion

The 3 submitted studies demonstrated that the use of 5-azacytidine for the treatment of MDS resulted in reproducible response rates and elimination of the need for red blood cell transfusions. These results were not seen in MDS patients who did not receive 5-azacytidine in trial 9221. The evidence of efficacy and safety for the treatment of MDS is supported by the published MDS literature. In addition, the literature for the treatment of acute leukemia, a related disease, also reports clinical remissions and an improvement in transfusion requirements.

### Conclusion

I recommend regular approval based on the clinical studies submitted for the NDA and published literature. The 5-azacytidine indication should be for the treatment of MDS. The Agency should request that the applicant perform a post-marketing study for use of 5-azacytidine in MDS patients with renal impairment.

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## MEMORANDUM

**Date:** April 28, 2004  
**From:** John K. Leighton, Ph.D., DABT  
Supervisory Pharmacologist, HFD-150  
**To:** File for NDA #50-794  
**Re:** Approvability for Pharmacology and Toxicology  
Vidaza (5-azacytidine)

To support the NDA the Sponsor submitted nonclinical studies that investigated the pharmacologic mechanism of action of 5-azacytidine. Also submitted were studies assessing the toxicology of 5-azacytidine; general toxicology, genetic toxicity, reproductive toxicity, and carcinogenicity. Pharmacokinetic and ADME studies were also provided. Most of the studies cited in the review by Dr. Shwu-Luan Lee are available in the published literature. The studies were conducted based on interest of 5-azacytidine as a laboratory tool to investigate the effects of changes in methylation on gene activity and the resulting phenotypic outcome. Other studies were conducted due to the interest in 5-azacytidine as an antineoplastic agent.

5-Azacytidine, a pyrimidine analogue of cytidine, is a cytotoxic agent with primary pharmacodynamic action as an inhibitor of DNA methylation via the noncompetitive inhibition of DNA methyltransferase 1. As summarized in the review, hypermethylation of DNA has been implicated in gene silencing; 5-azacytidine is thought to function in part by decreasing methylation of critical DNA regulatory regions (CpG islands), resulting in re-expression of silenced genes and subsequent cellular differentiation. Pharmacology studies indicate that only cells that are rapidly dividing are sensitive to 5-azacytidine. The role of DNA methylation in cancer development continues to be under active investigation.

The toxicology studies submitted to the NDA were generally designed as research studies and as such did not follow standard protocols for toxicology studies usually submitted for regulatory purposes. Nevertheless, Dr. Lee concluded that the studies provided an adequate assessment of appropriate endpoints. 5-Azacytidine was positive in genetic toxicity studies (*in vitro* mutagenicity and clastogenicity), reproductive toxicity (developmental toxicity and/or teratogenicity when administered to either male or female mice or rats, in the absence of maternal toxicity), and as a carcinogen. The carcinogenicity studies were not requested by the Division but were conducted by the National Toxicology Program under sponsorship by the NCI, or were research studies available in the scientific literature. The studies were evaluated by the Executive Carcinogenicity Assessment Committee (eCAC). The findings as a multi-site tumorigen in both mice and rats, in both sexes, suggest a risk for secondary tumors. No A comprehensive overview of the pharmacology and toxicology study findings and their implication on clinical use can be found in the Executive Summary of her review.

**Recommendations:** I concur with Dr. Lee's conclusion that pharmacology and toxicology data support the approval of NDA 50-794, Vidaza for myelodysplastic syndrome, and that there are no outstanding nonclinical issues.

**APPEARS THIS WAY  
ON ORIGINAL**

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

-----  
John Leighton  
4/28/04 04:54:17 PM  
PHARMACOLOGIST

NDA ACTION LETTER ROUTING RECORD

NDA#: 50-794

Date Received: May 14, 2004

Drug: Vidaza (azacitidine)

Division: HFD-150

Type of Letter: **AP** AE NA

Drug Classification: 1P

REVIEWER

RECEIPT

ACTION

1. Colleen LoCicero Associate Director for Regulatory Affairs  
 Date 5/14 Initials CL Date 5/14 Initials  
 Financial Disclosure review - p.28 of MOR.

Comments: User fee goal date -

2. Chemistry Review  
 Date \_\_\_\_\_ Initials \_\_\_\_\_ Date \_\_\_\_\_ Initials  
 Comments: signed off on Div. routing record - no written comments.

3. Pharmacology & Toxicology Review  
 Date \_\_\_\_\_ Initials \_\_\_\_\_ Date \_\_\_\_\_ Initials  
 Comments: signed off on Div. routing record - no written comments.

3. R Behrman, M.D. Dep Director, ODEI  
 Date \_\_\_\_\_ Initials \_\_\_\_\_ Date \_\_\_\_\_ Initials  
 Comments:

4. R. Temple, M.D. Director, Office of Drug Evaluation I  
 Date 5/14/04 Initials RT Date 5/17/04 Initials RT  
 Returned to Division for Corrections,  Forwarded  
 Letter Signed

Comments:

(5) Was I supposed to do something with this?  
 I'll be in at about 8<sup>00</sup>

# NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

<b>NDA 50-794</b>	Efficacy Supplement Type <b>SE-</b>	Supplement Number
<b>Drug: Vidaza (azacitidine for injectable suspension)</b>		<b>Applicant: Pharmion Corporation</b>
<b>RPM: Amy Baird</b>	<b>HFD-150</b>	<b>Phone # 594-5779</b>
<b>Application Type: ( <input checked="" type="checkbox"/> ) 505(b)(1) ( ) 505(b)(2)</b>		<b>Reference Listed Drug (NDA #, Drug name):</b>
❖ <b>Application Classifications:</b>		
• Review priority		( ) Standard ( <input checked="" type="checkbox"/> ) Priority
• Chem class (NDAs only)		<b>1</b>
• Other (e.g., orphan, OTC)		<b>Orphan</b>
❖ <b>User Fee Goal Dates</b>		<b>6-29-04</b>
❖ <b>Special programs (indicate all that apply)</b>		( <input checked="" type="checkbox"/> ) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ <b>User Fee Information</b>		
• User Fee		( ) Paid
• User Fee waiver		( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception		( <input checked="" type="checkbox"/> ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ <b>Application Integrity Policy (AIP)</b>		
• Applicant is on the AIP		( ) Yes ( <input checked="" type="checkbox"/> ) No
• This application is on the AIP		( ) Yes ( <input checked="" type="checkbox"/> ) No
• Exception for review (Center Director's memo)		N/A
• OC clearance for approval		N/A
❖ <b>Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification &amp; certifications from foreign applicants are cosigned by US agent.</b>		( <input checked="" type="checkbox"/> ) Verified
❖ <b>Patent</b>		
• Information: Verify that form FDA-3542a was submitted.		( <input checked="" type="checkbox"/> ) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted.		21 CFR 314.50(i)(1)(i)(A) ( ) I ( ) II ( ) III ( ) IV
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).		21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii) <span style="float: right;">N/A</span> ( ) Verified <span style="float: right;">N/A</span>

❖ Exclusivity (approvals only)		
• Exclusivity summary		✓
• Is there an existing orphan drug exclusivity protection for the active moiety for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of sameness for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification!		( ) Yes, Application # _____ (✓) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)		
General Information		
❖ Actions		
• Proposed action		(✓) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)		N/A
• Status of advertising (approvals only)		(✓) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications		
• Press Office notified of action (approval only)		(✓) Yes ( ) Not applicable ( ) None (✓) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
• Indicate what types (if any) of information dissemination are anticipated		
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))		
• Division's proposed labeling (only if generated after latest applicant submission of labeling)		✓
• Most recent applicant-proposed labeling		✓ 4-27-04
• Original applicant-proposed labeling		✓ 12-23-03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)		✓ ODS 4-2-04
• Other relevant labeling (e.g., most recent 3 in class, class labeling)		N/A
❖ Labels (immediate container & carton labels)		
• Division proposed (only if generated after latest applicant submission)		N/A
• Applicant proposed		✓ 12-23-03
• Reviews		See CMC review.
❖ Post-marketing commitments		
• Agency request for post-marketing commitments		
• Documentation of discussions and/or agreements relating to post-marketing commitments		
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)		✓
❖ Memoranda and Telecons		✓ (see outgoing correspondence)
❖ Minutes of Meetings		
• EOP2 meeting (indicate date)		✓12-19-01
• Pre-NDA meeting (indicate date)		✓4-14-03
• Pre-Approval Safety Conference (indicate date; approvals only)		N/A
• Other		

❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
<b>Summary of Approval Status</b>	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	Med-TL:4-27-04 Supv.Pharm/Tox:4-28-04
<b>Clinical Information</b>	
❖ Clinical review(s) (indicate date for each review)	4-26-04
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	From MO rev dated 4-26-04
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	3-16-04
❖ Demographic Worksheet (NME approvals only)	5-5-04
❖ Statistical review(s) (indicate date for each review)	4-27-04
❖ Biopharmaceutical review(s) (indicate date for each review)	4-30-04
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
<b>CMC Information</b>	
❖ CMC review(s) (indicate date for each review)	4-29-04
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	From CMC rev dated 4-29-04
• Review & FONSI (indicate date of review)	N/A
• Review & Environmental Impact Statement (indicate date of each review)	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	4-23-04
❖ Facilities inspection (provide EER report)	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ Methods validation	<input type="checkbox"/> Completed <input checked="" type="checkbox"/> Requested <input type="checkbox"/> Not yet requested
<b>Nonclinical Pharm/Tox Information</b>	
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	4-28-04
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	4-6-04

**NDA REGULATORY FILING REVIEW**  
**(Including Memo of Filing Meeting)**

NDA # **50-794** Supplement # SE1 SE2 SE3 SE4 SE5 SE6 SE7 SE8

Trade Name: **Vidaza**  
Generic Name: **azacitidine**  
Strengths: **100 mg**

Applicant: **Pharmion Corporation**

Date of Application: **12-26-03**  
Date of Receipt: **12-29-03**  
Date clock started after UN: **N/A**  
Date of Filing Meeting: **3-5-04**  
Filing Date: **2-27-04**  
Action Goal Date (optional):

User Fee Goal Date: **6-29-04**

Indication(s) requested: **treatment of patients with MDS**

Type of Original NDA: (b)(1) ✓ (b)(2) \_\_\_\_\_  
OR

Type of Supplement: (b)(1) \_\_\_\_\_ (b)(2) \_\_\_\_\_

NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S \_\_\_\_\_ P ✓  
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A  
Chemical Classification: (1,2,3 etc.) 1  
Other (orphan, OTC, etc.) orphan

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

Form 3397 (User Fee Cover Sheet) submitted: **YES**

User Fee ID # \_\_\_\_\_

Clinical data? YES ✓ NO, Referenced to NDA # \_\_\_\_\_

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application?

If yes, explain: YES NO

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

Is the application affected by the Application Integrity Policy (AIP)?  
If yes, explain.

YES                      NO

If yes, has OC/DMPQ been notified of the submission?

YES                      NO

• Does the submission contain an accurate comprehensive index?                      YES                      NO

• 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:

• If an electronic NDA, does it follow the Guidance?                      N/A                      YES                      NO  
**If an electronic NDA, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

**All disciplinary sections.**

Additional comments:

• If in Common Technical Document format, does it follow the guidance?                      N/A                      YES                      NO

• Is it an electronic CTD?                      N/A                      YES                      NO  
**If an electronic CTD, all certifications must be in paper and require a signature.**  
Which parts of the application were submitted in electronic format?

**All disciplinary sections.**

Additional comments:

• Patent information submitted on form FDA 3542a?                      YES                      NO

• Exclusivity requested?                      YES, 7 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 . . . .”

- Financial Disclosure forms included with authorized signature? YES NO  
(Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES NO

**Refer to 21 CFR 314.101(d) for Filing Requirements**

- PDUFA and Action Goal dates correct in COMIS? YES NO  
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections.  
Yes
- List referenced IND numbers: IND 7574 and IND 64251
- End-of-Phase 2 Meeting(s)? Date(s) not held NO  
If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) 4-14-03 NO  
If yes, distribute minutes before filing meeting.

**Project Management**

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES NO
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES NO
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A YES NO

**If Rx-to-OTC Switch application:**

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

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff?  
N/A 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 Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? YES NO

**If 505(b)(2) application, complete the following section:**

- Name of listed drug(s) and NDA/ANDA #:
- 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”).
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.) YES NO
- Is 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 should be refused for filing under 314.101(d)(9). YES NO
- Is the rate at which the product’s active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9). YES NO
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

\_\_\_\_ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

\_\_\_ 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.

*IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].*

\_\_\_ 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. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

☐

\_\_\_ 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.)

\_\_\_ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

• Did the applicant:

• Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?  
YES                      NO

• Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?  
YES                      NO

• Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?  
N/A                      YES                      NO

• Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv).?  
N/A                      YES                      NO

• If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4):

• Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).  
YES                      NO

• A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.  
YES                      NO

- **EITHER**  
The number of the applicant's IND under which the studies essential to approval were conducted.

OR

	IND # _____	NO
--	-------------	----

A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

N/A	YES	NO
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- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES	NO
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**APPEARS THIS WAY  
ON ORIGINAL**

ATTACHMENT

MEMO OF FILING MEETING

DATE: 2-9-04

BACKGROUND:

IND 64,251 azacitidine was submitted March 8, 2002, to initiate a PK study in MDS and AML patients. Pharmion planned to submit two phase 2 studies and one phase 3 study conducted by CALGB under an IND held by the NCI to support a future new drug application.

ATTENDEES: Dr. Kaminskas, Dr. Mann, Dr. Lee, Dr. Leighton, Dr. Farrell, Dr. Wang, Dr. Pazdur, Dr. Sridhara, Dr. Ibrahim and Dr. Patel.

ASSIGNED REVIEWERS:

<u>Discipline</u>	<u>Reviewer</u>
Medical:	Edvardas Kaminskas, M.D.
Secondary Medical:	Ann Farrell, M.D.
Statistical:	Yong-Cheng Wang
Pharmacology:	Shwu-Luan Lee, Ph.D.
Statistical Pharmacology:	
Chemistry:	Li-Shan Hsieh
Environmental Assessment (if needed):	
Biopharmaceutical:	Sophia Abraham, Ph.D.
Microbiology, sterility:	Paul Stinavage, Ph.D.
Microbiology, clinical (for antimicrobial products only):	
DSI:	N/A
Regulatory Project Management:	
Other Consults:	DDMAC and DMETS

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

CLINICAL FILE  REFUSE TO FILE \_\_\_\_\_

- Clinical site inspection needed: YES NO (see memo to NDA 50-794)
- 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 NA  FILE \_\_\_\_\_ REFUSE TO FILE \_\_\_\_\_

STATISTICS FILE  REFUSE TO FILE \_\_\_\_\_

BIOPHARMACEUTICS FILE  REFUSE TO FILE \_\_\_\_\_

- Biopharm. inspection needed: YES NO

PHARMACOLOGY NA \_\_\_\_\_ FILE  REFUSE TO FILE \_\_\_\_\_

- GLP inspection needed: YES NO

CHEMISTRY FILE  REFUSE TO FILE \_\_\_\_\_

- Establishment(s) ready for inspection? YES NO
- Microbiology YES NO

ELECTRONIC SUBMISSION:  
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

\_\_\_\_\_ 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):

**Review Timelines specified by each discipline:**

**Clinical- May 1 for completion of entire review. However, should only take 1 month to complete portion of review to send to consultants for their input.**

**Statistical- Mid April to complete review.**

**Biopharmaceutical- Mid April to complete review.**

**Pharm/Tox- Mid March.**

**CMC- Mid April.**

\_\_\_\_\_  
Regulatory Project Manager, HFD-