

Baird, Amy

From: Baird, Amy
Sent: Tuesday, May 18, 2004 3:03 PM
Subject: 'LTanner@pharmion.com'
Vidaza...Phase 4 commitment

Dr. Temple also slightly revised the phase 4 commitment..see below. Does Pharmion commit to this Phase 4.

We remind you of the postmarketing study commitment made in your submission dated May 11, 2004:

As azacitidine and its metabolites are primarily excreted by the kidneys, you have agreed to conduct a formal pharmacokinetics and safety study in patients with varying degrees of renal impairment. The results of this study will support dosing recommendations for this patient population especially during the first course of therapy. Dose proportionality should be also explored in this study.

You have agreed to the following schedule:

Protocol Submission: by August 2004
Study Start: by November 2004
Final Report Submission: by May 2006

Thanks,
Amy

Baird, Amy

From: LTanner@pharmion.com
Sent: Tuesday, May 18, 2004 3:34 PM
To: Baird, Amy
Subject: Re: Vidaza...Phase 4 commitment

Amy,

The wording below is agreeable to Pharmion. We would like the opportunity to interact with the FDA to finalize the protocol design, methodology, and timing for this Phase IV PK study in renal impaired patients.

Regards,
Linnea Tanner
Director, Regulatory Affairs
Pharmion Corporation
2525 28th Street
Boulder, CO 80301

Telephone: 720-564-9106
Fax: 720-564-9191
e-mail: ltanner@pharmion.com
<http://www.pharmion.com>

"Baird, Amy" <BairdA@cder.fda.gov>

To "LTanner@pharmion.com" <LTanner@pharmion.com>

cc

05/18/2004 01:02 PM

Subject Vidaza...Phase 4 commitment

Dr. Temple also slightly revised the phase 4 commitment..see below. Does Pharmion commit to this Phase 4.

We remind you of the postmarketing study commitment made in your submission dated May 11, 2004:

As azacitidine and its metabolites are primarily excreted by the kidneys, you have agreed to conduct a formal pharmacokinetics and safety study in patients with varying degrees of renal impairment. The results of this study will support dosing recommendations for this patient population especially during the first course of therapy. Dose proportionality should be also explored in this study.

You have agreed to the following schedule:

Protocol Submission: by August 2004
Study Start: by November 2004
Final Report Submission: by May 2006

5/21/2004

Thanks,
Amy

**APPEARS THIS WAY
ON ORIGINAL**

2525 28th Street
Boulder, CO 80301
Telephone: (720) 564-9106
Fax: (720) 564-9191

**PHARMION
CORPORATION**

Fax

To: Amy Baird, CSO
Division of Oncology Drug Products

From: Linnea Tanner, Director of Regulatory
Affairs

Fax: (301) 827-4590

Pages: 2

Phone: (301) 594-5779

Date: 5/11/2004

Re: Vidaza; NDA 50-794
Response to FDA Facsimile Dated 11
May 2004

CC:

Urgent For Review Please Comment Please Reply Please Recycle

● **Comments:**

Dear Amy:

The purpose of this Fax is to respond to the FDA facsimile dated 11 May 2004 regarding the FDA request to conduct a Phase 4 pharmacokinetics and safety study in patients with varying degrees of renal impairment. Pharmion commits to do a Phase 4 pharmacokinetics study in patients with varying degrees of renal impairment. However, Pharmion requests future meetings and/or correspondence with the Division to finalize the timing, protocol design, and methodology for this study. The Pharmion commitment to the FDA recommendation for the Phase 4 PK study is attached. If you have any further questions or requests, do not hesitate to contact me by telephone at 720.564.9106, by cell telephone at 720.201.1197, by facsimile at 720.564.9191, or by e-mail at ltanner@pharmion.com

Regards,



Linnea Tanner

Director, Regulatory Affairs

This facsimile contains confidential information. If you have received this facsimile in error, please mail this document to the attention of Linnea Tanner, Pharmion Corporation, 2525 28th Street, Boulder, CO 80301.

NDA 50-794

Page 2

May 11, 2004

Pharmion Response to FDA facsimile dated May 11, 2004.**FDA Phase 4 Request**

As azacitidine and its metabolites are primarily excreted by the kidneys, we recommend that you conduct a formal pharmacokinetics and safety study in patients with varying degrees of renal impairment. The results of this study will help to make dosing recommendations for this patient population especially during the first course of therapy. In study, you may also address the dose- and time-dependent kinetics of the drug at doses ranging from 25-100 mg/m².

Protocol submission: by August 2004
Study Start: by November 2004
Final Report Submission: by May 2006

Pharmion Commitment:

Pharmion commits to do a Phase 4 pharmacokinetics study in patients with varying degrees of renal impairment. However, Pharmion requests future meetings and/or correspondence with the Division to finalize the timing, protocol design, and methodology for this study.

**APPEARS THIS WAY
ON ORIGINAL**

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 1

Date: May 11, 2004

Re: NDA 50-794 Vidaza. Request for commitment to biopharm phase 4 study.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

The Division requests Pharmion to commit to the following biopharm phase 4 request:

As azacitidine and its metabolites are primarily excreted by the kidneys, we recommend that you conduct a formal pharmacokinetics and safety study in patients with varying degrees of renal impairment. The results of this study will help to make dosing recommendations for this patient population especially during the first course of therapy. In study, you may also address the dose- and time-dependent kinetics of the drug at doses ranging from 25-100 mg/m².

Protocol Submission: by August 2004
Study Start: by November 2004
Final Report Submission: by May 2006

Please provide your commitment in writing via facsimile. Please call should you have any questions.

Thank you,
Amy Baird

151

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 2

Date: April 30, 2004

Re: NDA 50-794 Vidaza. Microbiology deficiencies.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

The microbiology review of your NDA has been completed. Below are a list of comments and deficiencies that we ask Pharmion to commit to responding to as quickly as possible after the upcoming action. Please provide this commitment in writing via facsimile. Please call should you have any questions.

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

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

The _____ scheme for this product includes _____
_____ is minimal. Therefore, these descriptions and data may be provided post-action.

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

The descriptions provided indicate that the container/closure performed adequately during clinical evaluations. Therefore, these data may also be provided post-action.

Thank you,

Amy Baird

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/s/

Amy Baird

4/30/04 03:20:56 PM

CSO

Office of Drug Safety

Memo

To: Richard Pazdur, M.D.
Director, Division of Oncology Drug Products
HFD-150

From: Denise Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support, HFD-420

Through: Carol Holquist, R.Ph.
Deputy Director, Division of Medication Errors and Technical Support, HFD-420

CC: Amy Baird
Project Manager, HFD-150

Date: March 30, 2004

Re: ODS Consult 03-0015-1; Vidaza [Azacitidine for Injection] 100 mg, NDA 50-794

NOTE: This review contains proprietary and confidential information that should not be released to the public.

This memorandum is in response to the March 16, 2004 request from your Division for a re-review of the proprietary name, Vidaza. Additionally, container labels, carton and insert labeling were submitted for review and comment.

A. In our consult, dated March 12, 2003 (ODS consult # 03-0015), DMETS did not have any objections to the use of the proprietary name Vidaza. Since that review, DMETS has identified one additional proprietary name, _____ as having potential sound-alike and look-alike confusion with Vidaza.

Vidaza _____

two names. There are some product characteristics that may help to differentiate the two products: dosage form (powder for injection _____), route of administration (subcutaneous _____) and marketed strengths (100 mg vs. _____). Despite these differences, the two products have overlapping dosing frequencies (*daily*) and a potential for overlapping prescribing doses. During the first course of treatment with Vidaza, the doses may not overlap with _____. However, if a Vidaza patient has reduced Nadir counts, subsequent therapy may result in decreased doses, which could result in an overlap in prescribing doses. For example, a patient with a BSA of 1.6 would initially be prescribed _____ of Vidaza. However, if their Nadir count dropped, the dose could be reduced by 50% _____ during subsequent treatment. This could result

*** Name pending approval. Not FOI releasable.

in an order of Vidaza for seven days. If the route of administration is ambiguous or not clearly communicated, then the order could easily be misinterpreted. Despite the product differences, the orthographic and phonologic similarity, the overlapping dosing frequency, in addition to the potential for overlapping doses, increases the potential for name confusion between Vidaza. Although, DMETS has identified concerns between Vidaza that would prevent the co-existence of both names,

Therefore, additional phonologic or orthographic concerns may also render unacceptable regardless of the status of Vidaza. However, the final acceptability of the name,

Since, the Division of Oncology Drug Products plans to take action on Vidaza first, we recommend that you keep us informed of the status of this NDA so that we can communicate this information to Any delays in the PDUFA timeline (e.g., major amendments, etc) may affect the acceptability of the proprietary name, Vidaza.

B. In the review of the container labels, carton and insert labeling of Vidaza, DMETS focused on safety issues relating to possible medication errors.

1. Container Labels

- a. Increase the size of the established name so that it is at least ½ the size of the proprietary name in accordance with 21 CFR 201.10(g)(2).
- b. 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.
- c. The white lettering on the blue background is difficult to read, we recommend revising the contrasting colors to improve readability.
- d.
- e. Include the statement "Discard unused portion" in conjunction with the statement 'Single-use vials.'

2. Carton and Shipping Labeling

See Comments 1-a through 1-e.

3. 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 recommends deleting these two sections and replacing them with the stability information only. This will provide 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.

In summary, DDMAC had no objections to the use of Vidaza with regards to promotional concerns. DMETS recommends implementation of the label and labeling recommendations outlined above. DMETS has no objections to the use of the proposed proprietary name provided that only one name, Vidaza (NDA 50-794) is

These names should not co-exist in the marketplace due to their similarity. If the approval of the NDA is delayed beyond 90 days from the date of this review, the name and its' associated labels and labeling must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary or established names from this date forward. If you have any questions or need clarification, please contact Sammie Beam at 301-827-2102.

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/s/

Denise Toyer
4/2/04 03:20:24 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
4/2/04 04:41:20 PM
DRUG SAFETY OFFICE REVIEWER

PRE-MEETING MINUTES

MEETING DATE: March 29, 2004 **TIME:** 3:30pm **LOCATION:** B

IND/NDA NDA 50-794

Meeting Request Submission Date: 3-2-04
Briefing Document Submission Date: 3-18-04
Additional Submission Dates:

DRUG: Vidaza

SPONSOR/APPLICANT: Pharmion Corporation

TYPE OF MEETING:

1. NDA review status meeting.
2. **Proposed Indication:** Vidaza is indicated for the treatment of patients with MDS.

FDA PARTICIPANTS:

Ann Farrell, M.D., Clinical Team Leader, DODP
Edvardas Kaminskas, M.D., Clinical Reviewer, DODP
Rajeshwari Sridhara, Ph.D., Act. Statistical Team Leader, DPEI
Yong-Cheng Wang, Ph.D., Statistical Reviewer, DPEI
Amy Baird, Consumer Safety Officer, DODP

MEETING OBJECTIVES:

Discuss sponsor's questions in briefing document dated 3-18-04.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

- 1. What is the current status of the review of NDA 50-794? Are there any significant issues that have been identified? Would any issues raised in the review to date necessitate obtaining additional advice from the Oncologic Drugs Advisory Committee?**

FDA Response:

- The review is proceeding in a timely fashion. We have shared review issues in the past and no unexpected new issues have come to light up to now. We do not plan to present this NDA to the Oncologic Drug Advisory Committee.

- 2. Did Pharmion meet FDA's expectations in completing the additional analyses submitted to the NDA? Are there any additional reviewer questions that Pharmion needs to answer? When should Pharmion expect questions on the CMC and nonclinical sections of the file?**

FDA Response:

- Thank you for the additional analyses. Our analyses indicate that most of the CR and PR responses did not end by the end of the study; therefore, the duration of responses are by necessity underestimated. There are no additional clinical reviewer questions at this time.

- 3. What is the expected timing for clinical investigation site audits and/or manufacturing site pre-approval inspections?**

FDA Response:

The Division has decided that an audit of pivotal study sites is not needed for the following reasons:

- The 3 clinical trials were not conducted by a pharmaceutical company, but by CALGB under NCI auspices. CALGB conducted audits of individual sites.
- CALGB investigators had great interest in satisfying CALGB and NCI criteria for good clinical data management in order to continue participation in CALGB trials, and had no financial gain in falsifying data.

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/s/

Amy Baird
4/6/04 10:07:32 AM

Edvardas Kaminskas
4/7/04 08:06:43 AM

MEMORANDUM

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

DATE: March 17, 2004

TO: NDA 50-794

THROUGH : Ann Farrell, M.D., Clinical Team Leader

FROM: Edvardas Kaminskas, M.D., Clinical Reviewer

SUBJECT: **Justification for not conducting a DSI inspection for the pending NDA 50-794 Vidaza**

The Division of Oncology Drug Products has 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 Cancer and Leukemia Group B (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 multicenter (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 sponsor'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 sponsor's submitted primary trial (9221) are substantiated by similar response rates in other published studies.

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/s/

Amy Baird
3/17/04 09:09:57 AM
CSO

Edvardas Kaminskas
3/23/04 09:57:40 AM
MEDICAL OFFICER

Ann Farrell
3/23/04 10:32:05 AM
MEDICAL OFFICER

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 1

Date: March 16, 2004

Re: NDA 50-794 Vidaza.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Per the request of the biopharmaceutical team, please provide information as to how you analyzed plasma samples data from the Study AZA-2002-BA-002 with concentrations higher than the upper limit of the standard curve. This information is needed as soon as possible. Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
3/16/04 11:11:36 AM
CSO

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 2

Date: March 3, 2004

Re: NDA 50-794 Vidaza. Specifically, your email dated February 20, 2004, request for a meeting to discuss the current status of the FDA review of Vidaza.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

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● **Comments:**

Your request for a meeting has been scheduled as a telephone conference. See the attached. Please call should you have any questions.

Thank you,

Amy Baird

Date: March 31, 2004

Time: 3:00pm EST

FDA Attendees:

Ann Farrell, M.D., Clinical Team Leader, DODP
Edvardas Kaminskas, M.D., Clinical Reviewer, DODP
Hasmukh Patel, Ph.D., Deputy Director, ONDCI
Li-Shan Hsieh, Ph.D., Chemistry Reviewer, ONDCI
John Leighton, Ph.D., Supervisory Pharmacologist, DODP
Shwu-Luan Lee, Ph.D., Pharmacology Reviewer, DODP
Rajeshwari Sridhara, Ph.D., Acting Statistical Team Leader, DODP
Yong-Cheng Wang, Ph.D., Statistical Reviewer, DODP
Atiqur Rahman, Ph.D., Biopharmaceutical Team Leader, DODP
Sophia Abraham, Ph.D., Biopharmaceutical Reviewer, DODP
Amy Baird, Consumer Safety Officer, DODP

Please submit 11 meeting packages as desk copies directly to me NLT March 15, 2004. These desk copies are in addition to the archival copy you should submit to your NDA.

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/s/

Amy Baird

3/5/04 11:42:57 AM

3 pages redacted from this section of
the approval package consisted of draft labeling

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 2

Date: March 3, 2004

Re: NDA 50-794 Vidaza.

Urgent For Review Please Comment Please Reply Please Recycle

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● Comments:

Per the request of the clinical review team, please provide the following exploratory analyses excluding those patients diagnosed as AML. Please call should you have any questions.

1. Please provide a table showing the duration of "improvement" for those patients in the 5-azacytine (as randomized) group and the observation alone (who did not receive 5-azacytidine) group whose best response is classified as improved (defined as improvement, section 11.4.2.2 of the study report). The tables should include descriptive statistics such as mean duration, median, range, etc. If there are any statistically significant differences between groups please provide that information.
2. Please provide a second table using the 2 groups listed in #1 comparing the duration of improvement where the duration of improvement is defined as the time a patient is in a CR, PR or improved (defined as improvement, section 11.4.2.2 of the study report). The tables should include descriptive statistics such as mean duration, median, range, etc. If there are any statistically significant differences between groups please provide that information. Information should be provided separately for each category of patients (those patients whose duration of improvement included CR, those patients whose duration of improvement included PR, and those patients whose duration of improvement was only improvement).
3. Please provide a table comparing the 2 groups listed in #1 for endpoints such as CR, PR, and Hematologic Improvement defined in Cheson, et.al. *Report of an International Working Group to Standardize Response Criteria for Myelodysplastic Syndromes*, Blood 2000 Dec. 1 pp. 3671. Although, the article states that for categorization as having a Hematologic Improvement Response

that the response must be achieved in the absence of cytotoxic therapy, we prefer that the analyses for the 5-azacytidine group (as randomized) include patients both on 5-azacytidine and off 5-azacytidine as long as they are still enrolled in the study. Please report the information for the subgroups of those on 5-azacytidine and off 5-azacytidine separately.

4. Please provide a SAS data set including, for each patient, where available, the baseline transfusion rate (e.g., # of transfusions per month), post-treatment transfusion rate, and post-improvement rate (for those patients who achieved CR, PR or "improvement" by protocol) for both the treatment groups (i.e., 5-azacytidine and observation).

Thank you,



Amy Baird

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/s/

Amy Baird
3/3/04 11:09:28 AM
CSO

MEETING MINUTES

MEETING DATE: April 14, 2003 **TIME:** 3:00 PM **LOCATION:** WOC2/CR G

IND: 64,251(SN022/SN023)

Meeting Request Submission Date: January 20, 2003

Briefing Document Submission Date: March 14, 2003

March 26, 2003

DRUG: Azacitidine

SPONSOR/APPLICANT: Pharmion Corporation

TYPE of MEETING:

1. Pre-NDA Meeting
2. Indication – All Subtypes of Myelodysplastic Syndromes (MDS)

FDA ATTENDEES, TITLES AND OFFICES:

Richard Pazdur, MD, Director, Division of Oncology Drug Products (DODP)
Grant Williams, MD, Deputy Director, DODP
John Johnson, MD, Clinical Team Leader, DODP
Bruce Cheson, MD, ODAC Consultant (pre-meeting only)
Robert White, MD, Medical Officer, DODP
Ann Farrell, MD, Acting Clinical Team Leader, DODP
Robert Kane, MD, Medical Officer, DODP
Stephen Hirschfeld, MD, Medical Officer, DODP (sponsor meeting only)
Atiqur Rahman, PhD, Clinical Pharmacology and Biopharmaceutics Team Leader, DODP
Sophia Abraham, PhD, Clinical Pharmacology and Biopharmaceutics, DODP
Hari Sarker, PhD, Chemistry Reviewer, DODP
Anwar Goheer, PhD, Pharmacology/Toxicology Reviewer, DODP
Raji Sridhara, PhD, Biometrics Reviewer, DODP
Justina Molzon, Pharm, JD, Associate Director for International Affairs, CTD Expert
Gary Gensinger, Office of Information Management, Electronic Submissions
Anthony El Hage, PhD, Office of Medical Policy (OMP), Division of Scientific Investigations (DSI)
Khin M. U, MD, Acting Branch Chief, Good Clinical Practice Branch I, OMP, DSI
Donald Haggerty, MD, Orphan Drug Products (ODP)
Debra Y. Lewis, Director of Grants Program, ODP
John McCormick, MD, Deputy Director, ODP
Brenda Atkins, Project Manager, DODP

INDUSTRY PARTICIPANTS AND TITLES/Pharmion Corporation:

Judith Hemberger, Ph.D., Chief Operating Officer
Gillian Ivers-Read, Vice President, Development & Regulatory Affairs
Jay Backstrom, M.D., Head, North American Medical Affairs and Safety
Joe Como, Vice President of Manufacturing
CL Beach, Pharm.D., Global Team Leader
Linnea Tanner, Director, Regulatory Affairs
Kristi Wyatt, Director, Regulatory Affairs
Chris Mitchell, Manager, Electronic Documentation/Submissions

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—
—
Clinical Experts:

Lewis Silverman, M.D., CALGB Primary Investigator
—
—

MEETING OBJECTIVES:

- Serial Number: 023 - To discuss structure, content and considerations around the timing of submitting the eNDA, which is currently targeted for the end of 2nd quarter 2003.
- Serial Number: 024 - To discuss caveats for Subpart H consideration.

BACKGROUND:

Pharmion acquired the rights to Azacitidine from Pharmacia & Upjohn. On December 19, 2001 the FDA met with Pharmion to discuss this project to confirm previous agreements made with Pharmacia & Upjohn and to discuss the clinical development and chemistry/manufacturing/controls data plans. Pharmion submitted an IND application dated March 7, 2002. Meetings to discuss the development plan for pre-and post-approval studies necessary to characterize the bioavailability and metabolism of Azacitidine and the proposed statistical analysis plan and data collection process of CALGB studies were scheduled to occur on October 8, 2002. Our responses to questions to be addressed at the October 8 meeting were received by Pharmion on October 3, 2002, however, the meeting was cancelled. Instead, an October 2, 2002 teleconference was held, in which Pharmion was reminded that final NDA approval was contingent upon initiating the confirmatory study before submission of the NDA and final review of the data and that the bioavailability study should be completed and submitted in the initial NDA.

Pharmion's December 23, 2002 and January 24, 2003 submissions contained protocol outlines for a confirmatory trial. FDA responded in a March 21, 2003, facsimile the following:

“Please refer to your December 23, 2002 facsimile and submission dated January 24, 2003 (serial number: 019) containing your proposed confirmatory trial design and to our January 24, 2003 facsimile responding to your protocol outline for a confirmatory study of Azacitidine in the treatment of MDS. The FDA has now completed consultations with outside expert consultants. Based on these consultations the FDA has the following comments.

- ◆ Survival should be the primary endpoint. Time to leukemic transformation or a composite of time to leukemic transformation or death are not acceptable primary endpoints, but should be assessed as secondary endpoints. Only a minority of patients has

transformation to acute leukemia prior to death. Most patients die of other causes, such as infection or hemorrhage.

- ◆ The FDA believes rates of transfusion, hemorrhage and infection are important secondary endpoints. These are such important factors in MDS that it would be difficult to assess the effect of a new therapy without this information.
- ◆ The FDA is concerned about the variability introduced into the study by offering three different therapies for patients on the control arm. The FDA suggests reducing the therapies to either low dose Ara-C or Ara-C plus anthracycline. The protocol should specify criteria for which of these two therapies will be used in a particular patient.
- ◆ The FDA agrees that the protocol must have well defined criteria for use of EPO and G-CSF.

“Based on discussions of Accelerated Approval under Subpart H at the Oncology Drugs Advisory Committee on March 12 and 13, 2003, the FDA needs assurance that Phase 4 confirmatory trials can be completed in a timely manner. The FDA is concerned that the proposed confirmatory trial could not be completed and that completion may be more difficult if Azacitidine is approved for marketing prior to assurance of completion of patient accrual on the confirmatory trial.”

We further stated that

“Prior to consideration of Accelerated Approval of Azacitidine under Subpart H, the FDA will require submission of an interim analysis of the Phase 4 confirmatory trial that shows a favorable effect on agreed upon secondary endpoints and that provides assurance of trial completion in an acceptable time frame.”

INDUSTRY QUESTIONS AND DECISIONS REACHED:

After receipt of the March 21, 2003, facsimile the sponsor requested that the majority of time allotted for this meeting focus on the contents of the March 21 facsimile (see above). FDA responses to the sponsor's questions were distributed prior to the commencement of this meeting. The questions are listed below with FDA responses (**bolded**).

QUESTIONS:

The pre-NDA briefing package provides an overview of the structure and content of the eNDA that will support the submission of the eNDA for accelerated approval of azacitidine in the treatment of MDS under 21 CFR Part 314 Subpart H. Pharmion made an initial assessment of response rate from the principal CALGB Study 9221 before the database was locked and closed,

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and compared the results to those reported in the literature. These preliminary results for response rate from the principal CALGB Study 9221 are provided in Section 10.2.2.

Question #1. Does FDA agree the proposed nonclinical, CMC (chemistry, manufacturing, and controls), and clinical data packages provide an adequate basis to submit the eNDA for accelerated approval under 21 CFR Part 314 Subpart H?

FDA Clinical Response(s):

The FDA has previously agreed that the proposed data package centered primarily around CALGB study 9221 might provide an adequate basis for accelerated approval, pending FDA review. The confirmatory study must be initiated prior to submitting the NDA.

However, as new, more detailed, information is provided by you, it has become apparent that the results of study 9221 are poorly documented. Based on the new information provided by you in this meeting package (dated March 14, 2003), the FDA does not believe that your proposed clinical data package is an adequate basis for accelerated approval. It would need to be supported by a successful interim analysis of agreed upon surrogate endpoint(s) from your proposed confirmatory study.

The proposed surrogate endpoint for accelerated approval is tumor response. The new information provided by you indicates there is inadequate documentation of the diagnosis of MDS and inadequate documentation of tumor response in CALGB study 9221. According to page 84 of the meeting package, only one of 16 responders has reviewable slides to document the best response. No reports of CALGB central review of response status beyond baseline could be found. Less than half of the patients (47%) have reviewable baseline slides to confirm the diagnosis of MDS. At a substantial proportion of participating Institutions the Principal Investigator can not be identified.

These serious deficiencies are in addition to the previously identified serious deficiencies, such as failure to collect data in the electronic database to assess protocol specified primary study objectives (transfusion requirements for RBCs, hemorrhage, infection rate, platelet counts and ANC). These are important aspects of MDS. As indicated by you in your submission dated September 10, 2002, Azacitidine dosing is not well documented. Information to calculate baseline BSA is not available for some patients and daily dosing is not well documented. Patients were supposed to record daily dosing in daily diaries along with transfusions, hospitalizations and major medical events, but only 2 institutions used the diaries. You were not able to collect adequate data on baseline infection rates.

Finally, based on discussions of Accelerated Approval under Subpart H at the Oncology Drugs Advisory Committee last month, the FDA needs some assurance that Phase 4 confirmatory trials can be completed in a timely manner. The FDA is concerned that your proposed confirmatory trial can not be completed and that completion may be more difficult if Azacitidine is approved for marketing prior to

assurance of completion of patient accrual and adequate follow-up on the confirmatory trial.

Pharmacology/Toxicology Response:

The proposed nonclinical Pharm/Tox data provide an adequate basis to submit the eNDA.

Clinical Pharmacology and Biopharmaceutics Response:

You should include in the Human PK/BA section of your anticipated eNDA, the following biopharm studies before filing:

- **The BA Study AZA-2002-BA-002**
- **The HPLC assay validation Study Report QKAN-2002-0697-BIO**
- **The *in Vitro* metabolism studies (Studies BA#020049, DXNI1001, and — 023018)**
- **The four research articles by Troetel et al (1972), Israili et al (1976), Rustum and Hoffman (1987), and Rudek et al (2002)**
- **Your proposed dosing adjustment plan for elderly patients and those with renal or hepatic impairment in package insert and provide the rationale for this plan.**
- **Possible drug interactions between Azacitidine and most commonly coadministered drugs in MDS patients.**

Question #2. Does FDA agree preliminary results of response rate observed in the principal CALGB 9221 trial provide adequate evidence of effectiveness to support accelerated approval of azacitidine in the treatment of MDS under 21 CFR Part 314 Subpart H?

FDA Clinical Response:

No. See Clinical Response to Question #1.

Timing of Submissions

The target for submitting all of the eNDA is the end of 2nd quarter 2003, with the exception of the BA (bioavailability) CSR (clinical study report). As previously discussed, the analytical methods for plasma analysis and preparation of plasma samples are technically challenging. Therefore, qualification of the sites is complex and time consuming and must be adequately completed prior to patient enrollment. Due to these challenges, Pharmion would like to discuss the potential option for submitting the eNDA at the end of 2nd quarter 2003 and subsequently submitting the BA CSR in 3rd quarter 2003.

Question #3. Would it be acceptable to submit all of the eNDA, except for the bioavailability report, for eNDA filing and submit the BA CSR as an NDA amendment after initial submission of the eNDA?

FDA Response:

No, this is not acceptable. The BA Study AZA-2002-BA-002 is necessary for filing the eNDA.

Additional Clinical Pharmacology and Biopharmaceutics Comment:

You should characterize the disposition of Azacitidine and determine the plasma levels and activity of major metabolites after subcutaneous administration to MDS patients.

CMC Data and Submission Plan

Pharmion has obtained FDA feedback on the CMC data that should be included in the eNDA. FDA feedback has been taken into consideration for the development of the CMC data package. The content of the submission plans reflect agreements made during FDA/Pharmion interactions (see Section 8.2).

Question #4. Does the Agency concur with Pharmion's proposed CMC data and submission plan?

FDA Response:

This submission does not contain any CMC data except for an outline of the submission. Please request a separate pre-NDA CMC meeting to discuss specific CMC issues.

Environmental Assessment (EA) Categorical Exclusion

In accordance with 21 CFR 25.31(b), Pharmion intends to include a categorical exclusion for the EA in Module 1 of the eNDA. Pharmion will provide justification that the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb.

Question #5. Does FDA agree that inclusion of the EA categorical exclusion in Module 1 is appropriate?

FDA Response:

Yes. It is acceptable to include the EA categorical exclusion in Module 1.

CLINICAL ANALYSIS PLAN

Adjudication of Diagnosis of MDS at Baseline

The site assessment of the bone marrow slides was used to determine the subtypes of MDS at baseline and the response criteria. Although the slides were to be submitted to

the CALGB prior to initiation of therapy, the time for assessment by CALGB of those slides was not defined. To remain consistent with how the study was conducted, we have used the site assessment for MDS subtype at baseline and for determination of response. However, if there were any discrepancies in the diagnosis of MDS vs. AML at baseline in any of the three reviews (ie, at the site, central CALGB, or subsequently by our independent reviewer), the final adjudication for diagnosis will be considered AML and the subject has not met the eligibility criterion of MDS at baseline. Due to insufficient number of response slides for adjudication by the independent reviewer, Pharmion will use the original site assessment to determine whether response criteria has been met.

Question #6. Does FDA agree this is an acceptable plan for the adjudication of diagnosis of MDS and subtypes of MDS at Baseline and for determining response?

FDA Response:

No. See Clinical Response to Question #1. Your proposal is adequate for a supportive study, but a successful interim analysis of agreed upon surrogate endpoint(s) from your proposed confirmatory study will be necessary for accelerated approval.

Clinical Documentation

Pharmion has had several interactions with FDA to obtain feedback on the submission of appropriate clinical documentation. The purpose of the following questions is to obtain further FDA clarification on investigator documentation to be submitted to the eNDA.

Investigator Documentation - Investigator List

Pharmion has attempted to reconstruct a complete list of site principal investigators inclusive of all changes in address, site investigators, etc. However, despite numerous contacts with various branches of the CALGB, the NCI and current site staff, it has not been possible to reconstruct a complete list. FDA did not concur with Pharmion's plan to only provide a list of responsible investigators at the site during the time of data re-collection.

Following ongoing communication, CALGB recently provided Pharmion with some additional information that appears to include the original Principal Investigators for the majority of sites that participated in the 9221, 8921, and 8421 studies. Therefore, we are planning to provide two investigator lists in the eNDA. The first list will identify the original principal investigators who we found for the original trials, and the second will identify the 'responsible physicians' at the time of data re-collection.

Question #7. Does FDA concur with this plan?

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FDA Response:

This is not in compliance with CFR 21 Subpart D 312.50-312.70--Responsibilities of Sponsors and Investigators.

This is a negative factor. It will be considered in the review process along with all other factors.

Please clarify the CALGB policy. If CALGB destroyed the regulatory documentation after 3 years, is the information CALGB recently provided to you valid?

Investigator Qualifications

Pharmion plans to provide the two investigator listings and review these listings against the available disqualification/restricted/assurance lists as well as the debarment list. A search of all available warning letters will also be undertaken to determine if any investigator with responsibility for the conduct of these clinical trials is present on any of these lists or has had any warning letters issued. The results of this search will be fully documented and placed in the appendix of the CSR in lieu of available investigator CVs. Copies of Form 1572 and CVs of the principal investigators who conducted the CALGB studies were originally submitted to the NCI. Thus, Pharmion will provide a letter of cross-reference to NCI's IND to access available investigator information.

Question #8. Does FDA concur with this plan?

FDA RESPONSE:

This is not in compliance with CFR 21 Subpart D 312.50-312.70-- Responsibilities of Sponsors and Investigators. This is suboptimal. It will depend on how complete the lists are. This will be a review issue.

Financial Disclosure

The CALGB cooperative group studies were conducted under an IND sponsored by the NCI (IND # 7574) and funded by NCI and FDA. According to FDA's March 20, 2001, guideline on financial disclosure, "The IND/IDE sponsor is responsible for ensuring that required financial information is collected and is made available to the applicant company, so that the information can be included in the NDA/BLA/PMA submission." Because NCI is a public institution that is not a commercial entity, an investigator would be unable to hold an equity interest, and there are unlikely to be any other financial arrangements to disclose. As the applicant company, Pharmion intends to request appropriate information from NCI and expects to certify on Form FDA 3454 either that there are no financial arrangements to disclose based on information obtained from the IND sponsor (check box 2), or that we have been unable to obtain the information from the IND sponsor (check box 3).

However, although the studies were conducted by NCI, the data recollection efforts for the CALGB studies were undertaken by Pharmion. Pharmion has not paid any investigator in connection with the conduct of this study apart from Dr. Lewis Silverman. Pharmion has paid _____ in consultation fees to Dr Lewis Silverman, the principal investigator for CALGB 9221. Therefore, Pharmion intends to disclose on Form FDA 3455 the "significant payments of other sorts" made by Pharmion to Dr Silverman.

Question #9. Does FDA concur that Pharmion's plan will meet FDA's financial disclosure requirement regarding the CALGB studies?

FDA RESPONSE: Yes.

Administrative and Format Issues

In reviewing the guidance for the format of the CTD, Pharmion was unclear as to where the "Summary of FDA Interactions" should be placed. Therefore, Pharmion proposes to submit a tabular summary of all FDA-Pharmion interactions/agreements similar to what is provided in Section 6. This table will appear in Module 1 of the CTD and will cross-reference the section in the CTD where information and data are provided to address these agreements. Pharmion plans to hyperlink the tabular summary and cross-reference section information with the CTD section in order to aid the reviewer and expedite their review.

Question #10. Does FDA agree that this tabular summary of all FDA-Pharmion interactions/agreements can be provided in Module 1?

FDA RESPONSE: Yes.

eNDA Electronic Submission Issues

All issues pertaining to the submission of an eNDA for Azacitidine are presented in detail in Section 11. The outstanding questions related to the eNDA are presented, below, in Sections 5.7.1 through 5.7.5.

Acceptability of CTD/eNDA Infrastructure

A draft copy of the submission table of contents is provided in Section **Error! Reference source not found.** of this briefing package for the Division's review and agreement. Included in the table of contents are names and locations of the eNDA files and corresponding CTD sections. Additional information regarding the draft table of contents is presented in Section 11.1.

Question #11. Does FDA agree that the proposed CTD/eNDA infrastructure is acceptable?

FDA RESPONSE:

Yes. The proposed format is acceptable.

April 14, 2003

Question #12. Does FDA agree with the proposal wherein critical published literature in Modules 4 and 5 is provided in addition to study reports in the table of contents and organized appropriately?

FDA RESPONSE:

Clinical comment: Yes to the format. No comment on the content.

OIM Comment: The question needs clarification.

Paper Review Copies

The Division has agreed to accept an entirely electronic archive copy and no paper review copies for any documents in the eNDA other than those requiring original, ink signatures (eg, FDA Form 356h), and the CALGB flow sheets (case report forms), which will be provided only in paper.

Question #13. How many copies of CALGB flow sheets will FDA require?

FDA RESPONSE:

Please provide a reviewer and an archival copy.

Question #14. Are there any additional sections of the eNDA for which the Division would like to receive paper review copies?

FDA RESPONSE: No.

SAS Datasets in Lieu of Patient Data Listings and Individual Patient Data Listings

Pharmion proposed in Serial #001 to IND 64,251 that SAS datasets be submitted in lieu of data listings that would, in a paper submission, be included with the CSR as Appendices 16.2 and 16.4. The Agency asked for clarification. A complete explanation of the issues related to the SAS datasets and patient data listings is presented in Section 11.3.

Question #15. Does FDA concur that the proposal to submit SAS datasets is acceptable?

FDA RESPONSE:

Yes. You may submit SAS datasets. Submit a blank annotated CRF. Submit a definition of all Table and Field names and all the codes used.

Question #16. Are laboratory dataset files exceeding 25 MB acceptable to the Division?

FDA RESPONSE:

In general, FDA will accept laboratory dataset files exceeding 25 MB.

Question #17. Are there any additional issues or questions that Pharmion needs to clarify and discuss during the pre-NDA meeting with respect to the SAS datasets?

FDA RESPONSE: Not at this time

Case Report Forms

The case report forms (CRF) for which electronic, PDF renditions will be submitted in this eNDA are identified in Section 11.4.

Question #18. Are there any additional issues or questions that Pharmion needs to clarify and discuss during the pre-NDA meeting with respect to the SAS datasets and/or case report forms?

FDA RESPONSE:

With regard to the CRFs, provide CRFs for the responders and subjects who developed AML by local site assessment, CALGB assessment, _____ assessment, and _____ assessment.

Prototypical Sample Documents with Examples of Proposed Hyperlinks/Bookmarks

A diskette containing sample electronic PDF documents wherein the proposed method of cross-reference is demonstrated was submitted to the IND as Serial #009.

FDA RESPONSE: Not at this time.

Question #19. Was the proposed method of cross-referenced documents demonstrated on the diskette acceptable for the eNDA submission in CTD format?

FDA RESPONSE: Yes.

OTHER

Question #20. Are there any additional issues or questions that Pharmion needs to clarify?

FDA RESPONSE:

For both safety and efficacy, gender, race, and age analyses are required.

In Tables 10-13 involving RBC transfusions; survival; and WBC, ANC, Hb and Platelets, it appears only results for the Azacitidine group are provided and not results for the BSC only group. Results should also be provided for the BSC only group.

OFFICE OF DRUG SAFETY (ODS) Comments:

You are encouraged to evaluate the risk with use of the product and propose ways to manage or reduce these risks. Plans for risk management should be included in Module I of the Common Technical Document for the NDA application.

If the NDA application is not being submitted in the Common Technical Document, plans for risk management should be included in the Clinical Section.

In addition, if you plan risk management activities that include risk communication involving patient education and information (such as a PPI, Medication Guide or other informational/educational products), these materials should be clearly noted as such and included in the risk management plan section.

Additional DMETS Comments:

- 1. We have reviewed the name and found it "Vidaza" acceptable.**
- 2. Labels and Labeling were not submitted and should be submitted.**
- 3. If any information is available on product overdoses or medication errors from the clinical IND or approval outside the US, DMETS requests that it be submitted.**
- 4. Please send copies of the labels and labeling of the diluent as well.**

OTHER FDA COMMENTS:

A. REGULATORY

1. NDA/sNDA Presentations to CDER's Division of Oncology

The Center for Drug Evaluation and Research's Division of Oncology Drug Products implemented an initiative in which we request an NDA/sNDA applicant to present their NDA/sNDA to Division personnel shortly after NDA/sNDA submission and before the expected NDA/sNDA filing date. This initiative allows the applicant to present an overview of the entire NDA/sNDA to the review team and interested Division personnel.

These presentations are generally expected to last one hour followed by a half-hour question and answer session. The applicant, not consultants, should present important information on each technical aspect (i.e., clinical, statistical, CMC, pre-clinical pharmacology and toxicology, and clinical pharmacology and biopharmaceutics) of the NDA/sNDA. In addition to providing an overview of the NDA/sNDA, the applicant should present their reasons for why the Division or the Office of Drug Evaluation I should approve their NDA/sNDA.

Please contact your Project Manager shortly after NDA/sNDA submission to schedule a date for your presentation. Alternatively, you may provide available dates in the cover letter of your NDA/sNDA and we will try to accommodate them.

2. Financial Disclosure Final Rule

We remind you of the requirement to collect the information on all studies that the FDA relies on to establish that the product is effective and any study in which a single investigator makes a significant contribution to demonstration of safety.

Please refer to the March 20, 2001 *"Guidance for Industry: Financial Disclosure By Clinical Investigators"* (posted on the Internet 3/27/2001) at <http://www.fda.gov/oc/guidance/financialdis.html>.

3. Pediatric Final Rule

FDA's Pediatric Rule [at 21 CFR 314.55/21 CFR 601.27] was challenged in court. On October 17, 2002, the court ruled that FDA did not have the authority to issue the Pediatric Rule and has barred FDA from enforcing it. Although the government decided not to pursue an appeal in the courts, it will work with Congress in an effort to enact legislation requiring pharmaceutical manufacturers to conduct appropriate pediatric clinical trials. In addition, third party interveners have decided to appeal the court's decision striking down the rule. Therefore, we encourage you to submit a pediatric plan that describes development of your product in the pediatric population where it may be used. Please be aware that whether or not this pediatric plan and subsequent submission of pediatric data will be required depends upon passage of legislation or the success of the third party appeal. In any event, we hope you will decide to submit a pediatric plan and conduct the appropriate pediatric studies to provide important information on the safe and effective use of this drug in the relevant pediatric populations.

4. Pediatric Exclusivity

The pediatric exclusivity provisions of FDAMA as reauthorized by the Best Pharmaceuticals for Children Act are not affected by the court's ruling. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry on Qualifying for Pediatric Exclusivity (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.

5. DEMOGRAPHICS

In response to a final rule published 2-11-98, the regulations 21 CFR 314.50(d)(5)(v) and 314.50(d)(5)(vi)(a) were amended to require sponsors to present safety and effectiveness data "by gender, age, and racial subgroups" in an NDA. Therefore, as

April 14, 2003

you are gathering your data and compiling your NDA, we request that you include this analysis. To assist you in this regard, the following table is a suggestion for presentation of the numeric patient demographic information. This data, as well as the pertinent analyses, should be provided in the NDA.

Please provide information for each category listed below from the primary safety database excluding PK studies.

Category	Number of Responders to Study	Number of Responders to Study	Number of Responders to Study
Gender	Males	All Females	Females >50
Age:	0-#1 Mo.	>1 Mo.-#2 Year	>2-#12
	12-16	17-64	65
Race	White	Black	Asian
	Other		

ACTION ITEMS:

1. Pharmion should submit the confirmatory trial as a **SPECIAL PROTOCOL ASSESSMENT** request.
2. Pharmion should respond to FDA responses to the above questions in detail.
3. The Division of Scientific Investigations (DSI) would like to receive a list of the investigators by site and include in the list the patients who were responders. *done 5-21-03*
4. Pharmion should not file the NDA until a detailed collection of data has been done. The Agency is interested in the integrity of data collected rather than results.
5. Pharmion must convince FDA that their study(ies) are adequate and well-controlled.

/s/ 5-13-03
Brenda J. Atkins, Project Manger
Minutes Preparer

Concurrence Chair(s): /s/ 5-14-03
Robert White, Medical Officer

Addendum – Slides presented by Pharmion Corporation (16)

**IND 64,251(SN022-SN023)/Azacitidine
ADDENDUM – 16 pages**

**ADDENDUM TO MEETING MINUTES
OVERHEADS PRESENTED BY PHARMION CORPORATION
TOTAL PAGES = 16**

Redacted 16

pages of trade

secret and/or

confidential

commercial

information

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/s/

Robert White

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

2/19/04

FILING COMMUNICATION

NDA 50-794

Pharmion Corporation
Attention: Gillian Ivers-Read
Vice President, Clinical Development and Regulatory
2525 28th Street
Boulder, Colorado 80301

Dear Ms. Ivers-Read:

Please refer to your December 26, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vidaza™ (azacitidine for injectable suspension).

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application will be filed under section 505(b) of the Act on February 27, 2004, in accordance with 21 CFR 314.101(a).

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, M.D.
Director
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Richard Pazdur
2/19/04 11:33:50 AM

Fax



DIVISION OF ONCOLOGY DRUG PRODUCTS

Center for Drug Evaluation and Research, HFD-150

Parklawn Building

5600 Fishers Lane, Rockville, MD 20857

To: Linnea Tanner

From: Amy Baird, CSO

Fax: 720-564-9191

Fax: (301) 827-4590

Phone: 720-564-9106

Phone: (301) 594-5779

Pages (including cover): 1

Date: February 11, 2004

Re: NDA 50-794 Vidaza.

Urgent **For Review** **Please Comment** **Please Reply** **Please Recycle**

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW. If you are not the addressee, or a person authorized to deliver the document to the addressee, you are hereby notified that any review, disclosure, dissemination or other action based on the content of the communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us at the above address by mail. Thank you.

● **Comments:**

Per the request of the pharmacology/toxicology team, please provide the following articles as they are illegible in the electronic submission:

4.2.3.5.3.1: Neoplasma, 23 (1) 53-60, 1976 (for Reproductive toxicity)

4.2.3.3.1.2: Mutation Research, 160 (3): 249-257, 1986 (for Genotoxicity)

"A comparison of mutation spectra detected by the Escherichial di Lac+ reversion assay and the Salmonella typhimurium His+ reversion assay." Mutagenesis 15(4): 317-23, 2000 (pharmtox/pubs/ohata2000.pdf).

Also, per the statistical team, please provide the SAS codes of format library if you have those programs in your data analyses.

Please call should you have any questions.

Thank you,

Amy Baird

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/s/

Amy Baird
2/11/04 02:45:31 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 50-794

Pharmion Corporation
Attention: Gillian Ivers-Read
Vice President, Clinical Development and Regulatory
2525 28th Street
Boulder, Colorado 80301

Dear Ms. Ivers-Read:

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

Name of Drug Product: Vidaza™ (Azacitidine for Injectable Suspension)

Review Priority Classification: Priority (P)

Date of Application: December 26, 2003

Date of Receipt: December 29, 2003

Our Reference Number: NDA 50-794

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 27, 2004, in accordance with 21 CFR 314.101(a). If we file the application, the user fee goal date will be June 29, 2004.

We will review this application under the provisions of 21 CFR 314 Subpart H (accelerated approval). Before approval of this application, you must submit copies of all promotional materials, including promotional labeling as well as advertisements, to be used within 120 days after approval.

Under 21 CFR 314.102(c), you may request a meeting with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the ultimate approvability of the application. Alternatively, you may choose to receive a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:

Center for Drug Evaluation and Research
Division of Oncology Drug Products
Attention: Division Document Room, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Oncology Drug Products, HFD-150
Attention: Document Room 3067
1451 Rockville Pike
Rockville, Maryland 20876

If you have any questions, call Amy Baird, Consumer Safety Officer, at (301) 594-5779.

Sincerely,


{See appended electronic signature page}

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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this page is the manifestation of the electronic signature.**

/s/

Amy Baird
2/10/04 02:43:49 PM
for Dotti Pease

PM

MEETING MINUTES

MEETING DATE: Dec. 19, 2001 **TIME:** 1:30 **LOCATION:** C

IND/NDA: pre-IND **Meeting Request Submission Date:** 9-26-01
Briefing Document Submission Date: 11-8-01, 12-7-01

DRUG: azacitidine **INDICATION:** myelodysplastic syndrome (MDS)

SPONSOR: Pharmion Corp. **TYPE of MEETING:** pre-IND/EOP2/pre-IND

FDA PARTICIPANTS:

- Robert Temple, M.D., Dir., ODEI
- Richard Pazdur, M.D., Dir., DODP
- John Johnson, M.D., Medical Team Leader, DODP
- Robert White, M.D., Medical Officer, DODP
- Richard Lostritto, Ph.D., Chem. Team Ldr, DODP (pre-meeting)
- Raj Upoor, Ph.D., Chemistry Reviewer, DODP (pre-meeting)
- John Leighton, Ph.D., Pharm. Team Leader, DODP
- Anwar Goheer, Ph.D., Pharmacologist, DODP (pre-meeting)
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INDUSTRY PARTICIPANTS:

- Judith Hemberger, Ph.D., Chief Oper. Off., Pharmion
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- Kristi Myatt, Dir. Reg. Affairs, Pharmion
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- Lewis Silverman, M.D., CALGB Primary Investigator
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- Bruce Cheson, M.D., Head, Med. Section, CIB, NCI
- Anthony Murgo, M.D., Sen. Invest., NCI

MEETING OBJECTIVES: Discuss adequacy of proposed IND and sponsor's specific questions.

BACKGROUND: FDA had met on June 19, 2000 with Pharmacia to discuss this project, and Pharmion has since acquired the rights to azacitidine from Pharmacia & Upjohn and wanted to meet to confirm previous agreements and discuss the clinical development and chemistry/manufacturing/controls data plans. After our internal meeting on November 27, FDA responses to sponsor's questions were faxed to them on November 29. Sponsor elected to still have the face-to-face meeting on December 19 and responded with comments on December 7. Those comments and subsequent discussion are reflected by italics below.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Since FDA advised Pharmacia & Upjohn that published reports of existing pharmacokinetic studies would not allow for data verification, Pharmion intends to conduct a pharmacokinetic study to elucidate dose proportionality and bioavailability with the S.C. route of

administration. A protocol outline is provided in Section 7.4 of this pre-meeting package. Is the design of the proposed pharmacokinetic study, along with a commitment to obtain population PK data in the confirmatory study, adequate to support the approval of the NDA?

FDA – The proposed studies are adequate to file the NDA. We recommend you perform *in vitro* metabolism studies (see FDA guidance). You will need to submit in the NDA a literature search with a summary on the clinical pharmacology of azaciditine.

Additional comments:

a. Is the sampling time out to 48 hours adequate?

SPONSOR: The sampling time out to 48 hours was established on the basis of literature data (Israili et al, 1976, and Troetel et al, 1972). Based on published data, ¹⁴C-labeled 5 azaciditine has a half-life of 3.4 to 6.2 hr, on average, following I.V. or S.C. injection. Upon examination of the published concentration-time data, it appears that the terminal half-life reached 9 hours in one subject. Assuming that 5-azaciditine has a similar half-life, the sampling time out to 48 hours would be expected to provide pharmacokinetic information during at least 5 half-lives in all subjects.

b. The manufacturing process of the drug substance is being changed (per CMC information). Will this affect the bioavailability of the SC formulation?

SPONSOR:

for the drug product are planned, Pharmion believes that the bioavailability of the S.C. formulation will not be affected.

c. Please justify the POP PK sampling and analysis plan.

SPONSOR: The population PK sampling times were also established on the basis of literature data describing the pharmacokinetics of ¹⁴C-labeled 5-azaciditine following S.C. administration (Troetel et al., 1972). Samples will be collected around the peak concentration and during the disposition phase out to 24 hours. A total of 7 samples are expected to be collected from each of the 147 subjects randomized to the azaciditine arm, for a total of up to 1029 pharmacokinetic samples.

A detailed data analysis plan is not available yet, but such a document will be prepared prior to data availability. Plasma azaciditine concentrations are expected to be fitted to the appropriate population PK model by nonlinear mixed-effects techniques using NONMEM in order to estimate the population PK parameters, and the interindividual and intraindividual variability of these parameters, and to

ascertain if and how patients' demographics and disease status affect the disposition of azacitidine.

- d. **The analysis of the proposed PK study should include a 90% CI comparison of the 75 mg/m² groups.**

SPONSOR: Pharmion agrees with this recommendation.

2. Please confirm the prior agreement with Pharmacia & Upjohn that the NDA may be acceptable for an accelerated approval application under 21 CFR Part 314 Subpart H, and that such approval would be based on response rate data. While the sponsor is required to collect additional data relative to clinical benefit, the sponsor is not expected to demonstrate statistical clinical benefit on transfusion requirements or frequency, rates of infections, antibiotic usage, or hemorrhage rates for accelerated approval.

FDA - Yes, if all the information agreed upon is collected and submitted. If, after satisfactory review of the NDA, the determination of clinical benefit is unclear, 5-azacytidine may be eligible for accelerated approval; a 2nd study would be required to demonstrate clinical benefit. If 5-azacytidine has a negative effect on clinical benefit, no approval would be indicated.

However, in view that the last patient follow-up included in the database for the pivotal study, CALGB #9221, was in February 1999, sufficient time has elapsed to document clinical benefit (e.g., transfusion requirements or frequency, rates of infections, antibiotic usage, or hemorrhage rates) in CALGB Study #9221. Please provide the reason why this clinical data was not collected pursuant to our request of April 10, 2000. According to the protocol, this comprehensive assessment of the impact of treatment upon the patients' lives would be used to determine the efficacy of azacitidine. This is based on the following evidence:

SPONSOR: Pharmion is unable to respond to FDA's question as to why the clinical benefit data were not collected pursuant to FDA's request of February because we only recently acquired rights to azacitidine from Pharmacia in June 2001. However, Pharmion understands these clinical benefit data are required by the FDA and commits to re-collect and analyze this data. Rights to visit the study sites and to re-collect the data were obtained only recently from the CALGB in October 2001. This data will be submitted in the NDA.

- **In the CALGB 9221 protocol, CALGB 8421 and 8921 were described as demonstrating complete elimination (81%) and 50% reduction (17%) in red cell transfusions in responding patients. Responding patients with thrombocytopenia had increases in their platelet counts and 5 of 6 patients who required platelet transfusions prior to entry on CALGB 8421 had this requirement eliminated. 56% and 69% of patients entered on #8421 or 8921,**

respectively with an initial ANC < 500/ul achieved a maximum neutrophil count above 1500/ul.

- The first protocol objective was to determine the effect of Aza-C on “red blood cell transfusion requirements, platelet counts, ANC, rates of infection and hemorrhage and %BM blasts in comparison to an untreated observation group.”
- For entry on study patients with RA or RARS were required to meet at least one of the following criteria:

Symptomatic anemia requiring PRBC transfusions for at least 3 months prior to study entry (document), or

Thrombocytopenia with platelet counts $\leq 50,000$ or significant clinical hemorrhage (e.g., GI, GU, or GYN hemorrhage requiring platelet transfusion: petechiae alone do not constitute sufficient hemorrhage), or

Neutropenia with absolute neutrophil count < 1000 with an infection requiring treatment with antibiotics

- From the protocol, 13.2 Data Analysis:

The primary analyses will compare the two treatment arms in terms of response, red cell transfusion requirements, platelet counts, ANC, rates of infection, percent bone marrow blasts, other toxicities, and quality of life.

To investigate the optimal responders to azacitidine (Objective 2.3), descriptive analyzes will compare the five myelodysplastic subgroups in terms of response rate, length of remission, peripheral blood counts, percent bone marrow blasts, transfusion requirements and rates of infections.

Furthermore, there was no statistically significant effect on survival. Favorable effects on secondary endpoints such as response rate, time to treatment failure and time to transformation to AML were not reflected in a survival improvement. Thus, it is essential to determine whether they are reflected in other objective clinical benefits such as red blood cell transfusion requirements, platelet or WBC transfusion requirements, rates of infection or hemorrhage.

Study #9221 was a study intended to demonstrate clinical benefit. The regulatory requirement to study the drug further, to verify and describe clinical benefit has been met in Study #9221 and should be submitted with the NDA.

SPONSOR: If, upon analysis of the Phase 3 CALGB data, any, some, or all of the

objective clinical endpoints (i.e., transfusion rates, hemorrhage rates, infection rates, use of antibiotics) show statistical significance for clinical benefit, Pharmion believes this single study would demonstrate clinical benefit of treatment of MDS with azacitidine and provide a sufficient basis for an approval through the traditional process with priority review, rather than through Subpart H accelerated approval. If the data are persuasive, another well-controlled confirmatory study would not need to be conducted.

If, on the other hand, it is unclear whether these objective clinical endpoints demonstrate clinical benefit, Pharmion would submit an NDA for accelerated approval under Subpart H based on the positive effect of azacitidine on the surrogate endpoint of response. A confirmatory study would be initiated prior to NDA submission. (See schematic of plan on p 5 of 12-7-01 submission)

Does FDA concur with Pharmion's plans above for evaluating the data and determining whether the NDA will be submitted through the traditional process or through Subpart H accelerated approval?

FDA – Yes. Azacitidine could be approved (accelerated approval) based on response rate (defined as CR + PR). The response rate category of “improvement” may not be claimed in the labeling.

Demonstration of clinical benefit from this study is doubtful because:

- a. Retrospective collection of data (no statistical analysis possible)*
- b. Lack of statistical analysis plan*
- c. Multiplicity of endpoints*
- d. Missing data*

3. If upon collection of the additional data relative to clinical benefit, there are found to be statistically significant objective benefits on the clinical endpoints of transfusions, infections, any antibiotic usage, and/or hemorrhage, can these data be considered adequate for a full rather than an accelerated approval, such that a confirmatory study would not be required?

FDA – Possibly. This would be a review issue; but this was part of the agreement for accelerated approval. Also, part of the agreement was having the 2nd study underway prior to submission of the NDA.

SPONSOR: Pharmion plans to provide a summary of results on the objective clinical endpoints from CALGB Study 9221 in a pre-NDA meeting to obtain FDA feedback prior to NDA submission. If any, some, or all of the objective clinical endpoints (i.e., transfusion rates, hemorrhage rates, infection rates, use of antibiotics) show statistical significance for clinical benefit, Pharmion believes this single study would demonstrate clinical benefit of treatment of MDS with azacitidine and provide a sufficient basis for an approval through the traditional process with priority review, rather than through Subpart H accelerated

approval.

Does FDA concur that if the clinical benefit data are persuasive from CALGB study 9221, another well-controlled study would not need to be conducted to support approval?

FDA – See # 2. Probably not because of bias of retrospective analysis of the various endpoints. Survival benefit on the additional follow-up time might be useful.

4. Pharmion's strategy for collecting additional information for CALGB studies 9221, 8921, and 8421, prior to submission of results to the FDA, is as follows:

Study 9221 is a well-controlled Phase 3 study on which efficacy and safety of azacitidine will be primarily based. Therefore, Pharmion proposes to collect the following additional data:

- Capture efficacy data (transfusion, hemorrhage, infection) not currently contained in the electronic database
- Audit existing data against source documents
- Collect additional adverse event data from source documents.

A CRF (case report form) outline for use in collecting these data is provided under Tab E. Similar activities will be performed for studies CALGB 8421 and 892 1.

Does FDA agree that the proposed additional data collection for these studies is acceptable?

FDA - No. The following additional data should be retrieved and included in the database for analysis:

- **CBCs, platelets, and the number and dates of RBC, platelet, and WBC transfusions should be included in the database. RBC and platelet transfusion requirements and the infection rate for each patient prior to study should be included in the NDA. "Documentation of doses prescribed and patient compliance" should be included in the database.**
- **Submit all BM (aspirates and biopsies) reports (baseline, follow-up, and central review). For central review: all the slides should be reviewed and not just the slides at the time of best response.**
- **One of the objectives in CALGB #9221 was to determine those myelodysplastic syndromes that will respond optimally to subcutaneous 5-azacytidine. The data and analysis should be submitted.**
- **The data and analysis should be submitted for MDS subtypes and AML.**

- **The first post-study treatment received by the patients (e.g., anti-leukemia therapy) should be submitted with the NDA.**
- **A survival analysis without the 21 patients found to have AML on central pathology review. A survival analysis of the 21 patients found to have AML on central pathology review.**
- **The NDA should have a complete safety database, including information about hepatotoxicity.**

SPONSOR: Pharmion plans to collect the following safety data (please refer to p. 46 of the original submission) to complete the safety database:

A comprehensive safety database will be developed to include all adverse events, including causality assessment for all subjects enrolled in the identified protocols. The analysis of adverse event data will include descriptive summaries of adverse event incidences by treatment group, for all adverse events and for treatment-related adverse. No statistical hypothesis testing will be done for adverse event rates.

Pharmion will evaluate the safety and laboratory data for hepatotoxicity.

Also, in section 4.3 of the protocol, there is a list of CALGB forms (e.g., C-101, C-028, C-187, C-102, C-090, C-022). Please provide copies of these forms. Additional information pertinent to the review of the NDA may have been collected on these forms.

SPONSOR: Copies of the CALGB forms requested by FDA are attached to this document.

5. If the product is considered under the Subpart H regulations, please confirm that the CALGB Phase 2 and Phase 3 studies and a commitment by Pharmion to complete an additional well-controlled study confirming clinical benefit constitute a sufficient clinical data package for the NDA.

FDA - Yes, if the request is for accelerated approval.

6. Pharmion's understanding is that the confirmatory study must be initiated prior to the NDA filing. Is this correct?

FDA -yes

7. Based on discussion with clinical experts on the design and results reported for the CALGB 9221 Phase 3 study, it is Pharmion's opinion that it is not feasible to conduct a scientifically acceptable controlled study that would demonstrate benefit of azacitidine on the clinical benefit endpoints of survival and/or transformation to AML.

The comparative arm of the study must be best supportive care, as there is no drug product approved for treatment of MDS. However, clinical experts consider azacitidine to be an effective treatment for MDS. As such, they have indicated to Pharmion that patients, investigators, and IRBs would be unwilling to accept a study that would not allow best supportive care patients to quickly crossover at the time of progression of disease to treatment with azacitidine or some other experimental therapy. Azacitidine patients who have progression of disease very likely will receive other therapies. Data generated for time to death and/or time to transformation most certainly will be confounded by the administration of azacitidine (to best supportive care patients) and/or other experimental therapies.

Therefore, Pharmion is proposing in the confirmatory study protocol that the primary endpoint be time to treatment failure for patients treated with azacitidine plus best supportive care versus those treated with best supportive care alone. Time to treatment failure is defined as any of the following: death, transformation to AML, progression of disease, relapse, or absence of response by 112 days (four cycles) of treatment. Secondary endpoints will include time to death (survival), time to transformation to AML, time to progression/relapse, complete and partial response rates, hematologic improvement (erythroid response, platelet response, neutrophil response), rates of hemorrhage, transfusion requirements, cytogenetic improvement, red cell transfusion requirements, platelet counts, ANC, rates of infection, change from Baseline in percent bone marrow blasts, and quality of life.

Is the primary endpoint proposed by Pharmion for the confirmatory study acceptable?

FDA – No, survival or clinical benefit should be the primary endpoint. We do not agree that a randomized controlled trial with survival as the primary endpoint cannot be conducted. Have your clinical experts considered the alternative trials proposed by the FDA at the June 19, 2000 meeting?

**Topotecan ± 5-azacytidine
Growth factors ± 5-azacytidine**

What was your clinical experts' rationale for not doing one of the proposed studies with survival as the primary endpoint?

Did the clinical experts who consider 5-azacitidine to be an effective treatment for MDS have access to the clinical benefit data (i.e., transfusion requirements or frequency, rates of infections, antibiotic usage, or hemorrhage rates) in CALGB 9221? According to the protocol, this comprehensive assessment of the impact of treatment upon the patients lives would be used to determine the efficacy of azacitidine.

The proposed time to treatment progression endpoint is a composite and prone to multiple biases. For example, stable disease is handled differently on the two arms. 5-Azacitidine patients who are stable after 112 days on study continue on 5-azacytidine.

Best supportive care patients who are stable after 112 days on study may receive 5-azacytidine, declared absence of response, and contribute as an event in time to treatment failure. Delete ' _____ ' from the definition of time to treatment failure.

SPONSOR: Pharmion will consider these recommendations. However, we would like to obtain further comment from FDA as to why they suggested using topotecan or growth factors for the confirmatory trial. We will then develop another protocol design based on FDA comment and consultation with our clinical experts that will meet FDA's requirements and is acceptable to our clinical experts.

Please confirm the prior agreement with Pharmacia & Upjohn that the existing pharmacology/toxicology study package is sufficient to support an NDA filing.

FDA - Yes. No further preclinical studies are necessary to support an NDA for azacitidine for the treatment of patients with MDS.

8. Pharmion has asked _____ for commercial manufacture of the drug substance. These following _____ do not change the _____ and are not anticipated to significantly affect the chemical characteristics or impurity profile of the active ingredient:

- _____
- _____
- _____

and limits that are acceptable per ICH Q3C Guideline on Impurities: "Residual Solvents."

The manufacturing process for the drug product will not change. To establish initial commercial specifications for both drug substance and drug product, Pharmion plans to evaluate the azacitidine drug substance and drug product used in the CALGB clinical investigations with proposed commercial analytical methodology. Specification limits will be representative of product used to establish safety and efficacy in the CALGB clinical investigations.

Does FDA concur this approach is appropriate to demonstrate that the clinical lots and commercial lots are comparable?

FDA - Yes, in general. Any changes that may be necessary _____ should be clearly stated in the NDA to facilitate review.

SPONSOR: As part of the marketing application, Pharmion commits to provide a complete list of changes _____ that occur through _____ of the drug substance manufacturing process.

9. As a part of the analytical bridging studies described in question 1 above, Pharmion will provide bridging data on impurities from drug substance and drug product used in previously conducted clinical studies and the drug substance from the — commercial manufacturing process.

As outlined in ICH Q3A Guideline on Impurities in New Drug Substances and ICH Q313 Guideline on Impurities in New Drug Products, impurities and degradation products present at levels \sim : 0.1% will be identified.

Does FDA concur that this approach is acceptable to qualify the impurity profile for the drug substance?

FDA - Yes. In addition, as suggested previously on April 10, 2000, we recommend that all impurities present in the drug substance and the drug product at levels greater than the limit of quantitation should also be reported and tabulated for a comparative evaluation. We also recommend that the terminology and guidance used in ICH Guidelines Q3A, Q3B and Q3C be used in your evaluation and reporting of impurities. If the recommended approach is not feasible, then, mitigating circumstances should be reported in the application for Agency's consideration.

SPONSOR: Pharmion comments to using terminology and guidance used in ICH Guidelines Q3A, Q3B, and Q3C to evaluate analytical results from the proposed bridging analysis and in establishing commercial specifications for impurities for both drug substance and drug product.

10. The following stability data will be submitted in the NDA:

Drug Substance

- Three-month accelerated and real-time data for the drug substance produced from the — manufacturing process.
- Additional accelerated and real-time 6-month stability data from the — drug substance manufacturing process will be submitted in an NDA amendment.

Drug Product

Primary stability data for the marketing application will consist of four clinical lots used in CALGB studies, with real-time data ranging from —

Does FDA concur that this stability package is sufficient for NDA filing?

FDA - Yes. In addition, we have the following comments.

For Drug Substance: Submission of limited stability data at the time of filing, and additional submission of data during the review of the application will have impact on the "retest" dating period for the drug substance. Available (through your bridging studies, or previously generated data) stability data on previously manufactured representative batches of drug substance (on older smaller scale batches, as well as new larger scale batches) should also be compared and evaluated by you, and submitted in the application.

SPONSOR: Historically, drug substance for use in clinical investigation has been maintained under refrigerated storage conditions at the NCI clinical repository. NCI coordinated initial release testing of the drug substance through — Ben Venue Laboratories conducted re-testing of the drug substance prior to manufacture of each lot of finished drug product intended for clinical use. There were no formal stability studies conducted.

Pharmion believes the following tabular summary of release and re-test data of four lots of azaciditine drug substance supports a minimum re-test date of — when the drug substance is stored under refrigerated conditions in containers which minimize exposure to moisture. (see table p. 12 of 12-7-01 submission). In the NDA, Pharmion will provide a comparison of these analysis results with the testing results of drug substance prepared using the — manufacturing process.

For Drug Product: Your proposal is acceptable for the purposes of filing the NDA application. However, you have not indicated the extent of long term and accelerated stability data that may be submitted in the application (at filing, or during review) on commercial scale (if larger) drug product batches manufactured using drug substance obtained from the —. Submission of such data is recommended in view of the stated instability of azaciditine in aqueous media (see page 73), specially, if changes will be necessary in the overall duration of the lyophilization process for commercial batches. Submission of such data for review, and its comparison to the existing data on primary batches, prior to approval is encouraged.

SPONSOR: It is Pharmion's intent to propose an expiration dating period for the commercial drug product based on the real-time stability data from primary stability lots NCI-95-210, NCI-98-211, NCI-99-206, and NCI-00-204. Drug product from each of these lots was used in clinical investigations to establish the safety and efficacy of azaciditine for the treatment of MDS.

If, during the course of product development, changes to the drug product manufacturing process are required, Pharmion acknowledges that it would be necessary to provide comparative stability data. Pharmion intends to provide during the review of the NDA a minimum of initial and — month real-time and accelerated stability data on a drug product lot(s) prepared with the drug substance from the — process. Pharmion also intends to

include in the NDA a stability protocol for analysis of this lot(s), as well as stability evaluation of the process validation lots.

In addition, we have the following additional comments:

- (a) Will the reconstituted drug product for subcutaneous injection be a suspension (see page 75)? This should be clarified.**

SPONSOR: After discussions with clinical investigators, it is Pharmion's understanding that the product (reconstituted in 4 mL of WFI) that was used for subcutaneous injection was a suspension of azacitidine. Pharmion will be confirming this as part of the analytical bridging studies.

- (b) Appropriate justification should be provided in the application for the amount of overage that will be used in the manufacturing of the drug product. Typically, use of overage is permitted to the extent of documented loss that occurs during the manufacturing process.**

SPONSOR: [

Pharmion believes there is adequate documentation to support — but would appreciate FDA's comments on the appropriateness —

- (c) Level(s) of impurities formed due to the degradation of drug substance during the manufacturing of drug product should be considered while qualifying and**

proposing the acceptance criteria for impurity(ies) through the shelf-life of drug product.

SPONSOR: Pharmion will be evaluating both drug substance and drug product used in clinical investigations in the analytical bridging studies and commits to incorporating impurities formed due to degradation of the drug substance during manufacture of the drug product into acceptance criteria for drug product impurities.

It is noted that the slope of the stability curve for the drug product containing overage was — (see page 77). Your evaluation of that observation is suggested.

SPONSOR: All of the clinical product lots presented in this stability analysis were — As explained in response to FDA's question regarding the manufacturing overage, —

Pharmion will continue to collect data for these product lots and will provide the data in the marketing application as outlined in ICH Guidance Q1A.

- 11. Would the Division of Oncologic Drug Products be willing to accept a marketing application using the CTD (Common Technical Document) format?

FDA – Yes (as of July, 2001). An electronic submission will also be welcome and will greatly facilitate FDA review of the NDA.

SPONSOR: Pharmion plans to submit the application in CTD format. If the Agency would be amenable to an electronic CTD (eCTD), Pharmion will general an eCTD using the specification outlined in the May 2001 ICH guidance and the July 2001 guidance on FDA Regional Information. Considering that many of the supporting legacy document within this application will be available only as paper, there may be certain limitations with regard to electronic formats (e.g., many documents will be scanned images). Pharmion would like to discuss the extent of such limitations with the Agency as soon as possible. Would the Division of Oncology provide the name of its information specialist and/or another contact with whom such technical issues may be discussed?

FDA – Randy Levin, M.D. (301 594-5411)

ACTION ITEMS:

- 1. Sponsor will consider our comments and submit the IND in January 2002.
- 2. Sponsor will propose a design(s) for the Phase 4 confirmatory study and request another meeting.

TS/

1-10-02

Dotti Pease, Project Manager

Concurrence Chair:

TS/

Robert White, M.D., Medical Reviewer

7/1/02