CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21041

CORRESPONDENCE

V. Spillman

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-041

DepoTech Corporation
10450 Science Center Drive
San Diego, CA 92121

DEC 4 1998

Attention: David B. Thomas
Senior Vice President, Quality Assurance & Regulatory Affairs

Dear Mr. Thomas:

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: DepoCyt (cytarabine liposome injection)

Therapeutic Classification: Priority (P)

Date of Application: October 2, 1998

Date of Receipt: October 5, 1998

Our Reference Number: 21-041

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on December 4, 1998 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be April 5, 1999.

We have determined that this application will be reviewed under 21 CFR 314 Subpart H (accelerated approval). We remind you that as required under 21 CFR 314.550, unless otherwise informed by the Agency, you must submit for Agency review before approval of this application copies of all promotional materials, including promotional labeling as well as advertisements, intended for dissemination or publication within 120 days after marketing approval.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

If you have any questions, contact Ann Staten, Project Manager at (301) 594-5770 or Dianne Spillman, Project Manager, at (301) 594-5746.

Sincerely,

/S/ 12-4-98

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

cc:
Archival NDA 21-041
HFD-150/Div. Files
HFD-150/[redacted]
DISTRICT OFFICE

F/T by: dds/12-1-98
filename: a:\21041\reg-ltrs\ack-ltr

ACKNOWLEDGEMENT (AC)

DepoTech

Tel (619) 625 2424 • Fax (619) 625 2430 • www.depotech.com

March 31, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Acceptable
3/31/99

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041: Phase IV Commitment Letter

The sponsor agrees to conduct a Phase IV study (Protocol C0401-010: "A randomized clinical study to determine the patient benefit and safety of DepoCyt (cytarabine liposome injection) for treatment of solid tumor neoplastic and lymphomatous meningitis") and associated Pharmacokinetic study (Protocol C0401-011: A pharmacokinetic study of DepoCyt (cytarabine liposome injection) for treatment of solid tumor neoplastic and lymphomatous meningitis") as specified in the correspondence between the sponsor and FDA documented in NDA 21-041, Amendments 16, 19, & 21.

The estimated dates for the study timeline are as follows:

Start:	September 1999
Interim Analysis:	4th Quarter 2001 (After 50% of events)
Enrollment Completion:	September 2003

We also estimate 6 months for final data analysis and 3 months for study report completion.

Sincerely,

John P. Longenecker, Ph. D.
President and Chief Operating Officer

Terrence G. Chew, MD
Vice President, Clinical Development

005744d.01

DepoTech

Tel (619) 625 2424 • Fax (619) 625 2439 • www.depotech.com

December 4, 1998

Ms. Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

ORIGINAL

ORIG AMENDMENT
(BC)

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 11: Categorical Exclusion from Environmental Assessment Report

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to a request from Dianne Spillman to advise the Division of our decision regarding the Environmental Assessment of DepoCyt.

The sponsor wishes to claim categorical exclusion from filing an Environmental Assessment per 21 CFR 25.31 (b). The sponsor complies with all categorical exclusion criteria as per 21 CFR 25.15 and has no knowledge that extraordinary circumstances exist.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0055375.01

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DepoTech

April 1, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

via FAX: 301-827-4590

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041: Response to FDA Final Comments on Package Insert

The sponsor agrees to all changes to the Package Insert for DepoCyt as outlined in the FDA's Fax to the sponsor dated 4/1/99.

Please contact me by telephone at (619) 625-2414, ext. 3207 or by FAX at (619) 558-6617 if you have any questions, or if I can provide any further information.

Sincerely,

Raymond Lamy,
Associate Director,
Regulatory Affairs

John P. Longenecker, Ph.D.
President and Chief Operating Officer

cc: Original NDA 21-041
Div File
HFD-150 / Astaten
Dspillman

PM note:
No hard copy sent to NDA
Astaten 4/2/99

0057505.01

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DepoTech

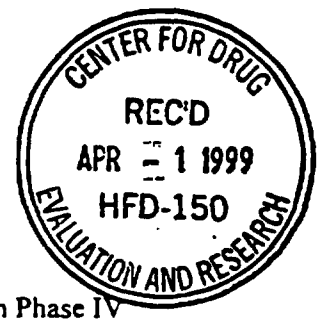
DUPLICATE

NEW CORRESP

NC

March 31, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448



Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 21: Responses to FDA Final Comments on Phase IV Protocol and Phase IV Commitment Letter

This document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter.

The sponsor agrees to all of the changes to the Phase IV study protocol (C0401-010) and associated PK study protocol (C0401-011) as specified in the FDA's FAX to us dated 3/31/99. We will also include the words "solid tumor" before "neoplastic" in the study protocol title per my conversation with Dotti Pease today who confirmed with Dr. Robert Justice that these words were inadvertently left out of the FDA's suggested title in the FAX.

In addition, Dotti Pease also asked why the sentence in the package insert under Lymphoma, page 5, which read "The median overall survival of all treated patients was 82.5 days on the DepoCyt arm and 64 days on the cytarabine arm" was changed to "The median overall survival of all treated patients was 99.5 days on the DepoCyt arm and 63 days on the cytarabine arm" in our revisions to the package insert (Amendment 17, dated 2/19/99). This text describes the intent-to-treat-population, yet the "82.5 days and 64 days" were for the evaluable population. We feel this was an inadvertent error and should be corrected to be consistent with the content of the paragraph and the data presented in the NDA to be "99.5 days and 63 days".

Also, a signed "Phase IV Commitment Letter" containing the information specified by FDA is included in Attachment 1.

Please contact me by telephone at (619) 625-2414, ext. 3207 or by FAX at (619) 558-6617 if you have any questions, or if I can provide any further information.

Sincerely,

Raymond Lamy

Raymond Lamy,
Associate Director,
Regulatory Affairs

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ORIGINAL

February 19, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 17: Revisions to Package Insert

NDA ORIG AMENDMENT
(BL)

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment includes the sponsor's comments and responses to information requests from the FDA's first review of the package insert (FAX dated 2/17/99). The list on the following pages describes each revision, and includes comments on the revision as appropriate.

Please contact me by telephone at (619) 625-2414, ext. 3205 or by FAX at (619) 558-6617 if you have any questions.

Sincerely,

David B. Thomas
Senior Vice President
Quality Assurance and
Regulatory Affairs

ORIGINAL

0056415.01

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DUPLICATE

ORIG AMENDMENT

February 3, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 15: "120-Day" Safety Update

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, §314.50(d)(5)(vi)(b) for the subject NDA, as an integrated summary of all new safety information available to the sponsor as of October 31, 1998, relating to the subject product and which has not previously been submitted in either NDA or the subject NDA (21-041). All information previously submitted in NDA was included by reference in the subject NDA. In addition, safety information has been submitted to the IND for the subject product regularly in the annual report. A signed Form FDA 356h is included following this cover letter.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0055402.01

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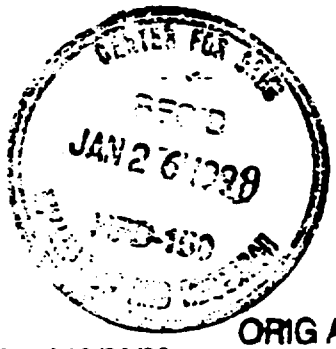
DepoTech

DUPLICAT

January 22, 1999

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448



Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 14: Response to FDA FAX dated 12/30/98

ORIG AMENDMENT
BC

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to the FDA's FAX to us dated 12/30/98, and our response is as follows:

Chemistry Comment #1:

1. The limits of free cytarabine and uracil arabinose in DP should be tightened per NDA

DepoTech Response:

This issue has been previously addressed in NDA Amendment 5, dated 12/9/97 in response to Item 1 of FDA's FAX dated 10/27/98. After discussions between the FDA and sponsor, the sponsor agreed to the FDA's proposed specifications of % Ara-U and % Free Cytarabine as appropriate for the 12 month stability data set under review. It is understood that as additional stability data become available the applicability of this specification will need to be re-examined.

The sponsor's previous response in NDA Amendment 5 is repeated below.

"DepoTech agrees to comply with the above request and will modify the specifications for % Ara-U and % Free Cytarabine of NMT 7% and NMT 6%, respectively, to NMT 5%."

Chemistry Comments #2-5

Further, DepoTech acknowledges that Chemistry Comments #2-5 (actually 2-6 as there are two #4 comments in the FAX) will be incorporated by the FDA into the electronic copy of the package insert. We request though that the phrase "Refrigerate at 2-8°C. Avoid freezing." in comment #4 be revised to read "Refrigerate at 2-8°C. Protect from freezing." for a more proactive approach to conditions for storing the product.

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If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

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DepoTech

DUPLICATE

January 12, 1999

NEW CORRESP

BM

JAN 13 1999
HFD-150
EVALUATION AND RESEARCH

Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 13: Report on Missing Cytopathology Slides

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to Item 1 of FDA's FAX to us dated 11/24/98, following the 11/16/98 ODAC recommendation. Item 1 requests "documentation (letter from IRB, or laboratory director, etc.) stating the reason, for each patient, as to why cytopathology slides are not available for central review". The information included in this submission summarizes the reasons as to why cytopathology slides were not available (or were unevaluable) for review, and Attachments 1-8 provides the supporting documentation.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
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0055668.01

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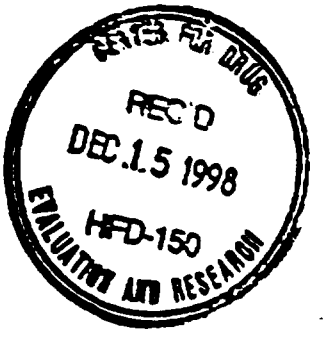
DepoTech

DUPLICATE

December 14, 1998

NEW CORRESP



Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 12: Study Proposal and Meeting Request

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to Item 2 of FDA's FAX to us dated 11/24/98, following the 11/16/98 ODAC recommendation. Item 2 requests a study proposal and draft protocol which would establish the clinical benefit of DepoCyt in lymphomatous meningitis. Item 2 also requests that the sponsor submit a meeting request to FDA to discuss the study proposal and draft protocol. A draft of this amendment was previously submitted by FAX on 12/4/98, for review.

Attachment 1 of this amendment includes the study proposal, and Attachment 2 includes a meeting/teleconference request in accordance with policy and procedure described in MAPP 4512.1.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

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DepoTech

December 3, 1998

Ms. Ann Staten
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

DUPLICATE

ORIG AMENDMENT
(BP)

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 10: Copies of Package Insert Requested References

Dear Ms. Staten,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to your FAX to us dated November 24, 1998 requesting copies of articles referenced in the DepoCyt Package Insert.

The requested references are enclosed herein and identified by numbered tabs corresponding to the Package Insert reference list.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0055359.01

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DepoTech

ORIGINAL

November 6, 1998

Ms. Dianne Spillman
Division of Oncology Drug Products
Office of Drug Evaluation I
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Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

ORIG AMENDMENT
(BM)

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
NOV 0 9 1998
HFD-150

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 9: Response to FDA Clinical Team's B[illegible]

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment includes responses and suggestions for revisions (Attachment 1) to the FDA clinical team's evaluation of cytologic response, duration of response, and patient characteristics, received by FAX, dated 11/2/98.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0054876.01

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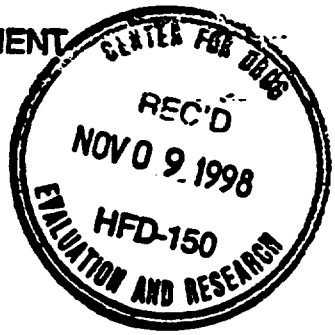
DepoTech

ORIGINAL

November 5, 1998

ORIG AMENDMENT



Ms. Dianne Spillman
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 8: Response to FDA Request for Information (Clinical)

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment includes responses (Attachment 1) to the FDA request for information (clinical) received by FAX, dated 10/30/98.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0054874.01

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DepoTech

October 26, 1998

Ms. Dianne Spillman
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

ORIGINAL

ORIG AMENDMENT
(5M)

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041, Amendment 6

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment is in response to your October 23, 1998 FAX requesting additional clinical information concerning the central cytopathology examinations, and includes information on all patients with — lymphomatous meningitis from the Controlled Trial (the initial 28 patients enrolled in the study and the 5 additional patients, 4 of whom received study drug, whose information was submitted in Amendment 5, dated October 23, 1998 of the NDA), the 2 lymphomatous meningitis patients enrolled in the confirmatory pharmacokinetic (PK) sub-study of the Controlled Trials of DepoCyt, and the 6 lymphomatous meningitis patients enrolled in the phase I intrathecal (IT) study (Protocol LIPO-C).

In this submission, we are providing a listing of all of the lymphomatous meningitis patients included or referenced in the NDA (Attachment I). This listing references the location of the relevant information provided in this NDA or submitted to NDA and cross-referenced to the subject NDA. For your convenience, we have provided patient data listings with CSF cytopathology information (site results and central blinded cytopathologist) for all lymphomatous meningitis patients in the three studies included in the NDA (Attachment II). To assist you in matching the central cytopathologist's report with the sites report from the same sample, we have added the laboratory accession number to the listings. In addition, we have provided copies of all CSF cytopathology reports carried out by the central cytopathologist (Attachment III).

Regarding central review of cytopathology, this method was introduced with the controlled studies (Protocol DTC 92-001) and confirmatory PK sub-study and was not carried out in the phase I IT study. For this latter study, all CSF cytopathology determinations were made at the site by a cytopathologist. For the remaining 35 lymphomatous meningitis patients (31 who received study drug of 33 enrolled in the Controlled Trial and 2 in the confirmatory PK sub-study) central CSF cytopathology reports are available for all but 3 patients who received study

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drug in the controlled trial. The reasons for this lack of central cytopathology confirmation were as follows:

1. Pat: 25-LA-165 All cytopathology slides were requested from the site by the sponsor for central review. The site was able to locate only 1 slide from the middle of the induction period (day 17) for central cytopathology review. According to the study investigator, all other slides are presumed lost.
2. Pat: 04-LN-220 All cytopathology slides were requested from the site by the the sponsor for central review. The site was unable to locate any of the patient's slides and they are presumed lost.
3. Pat: 31-LN-225 All cytopathology slides were requested from the site by the sponsor for central review. The study investigator reported that all cytopathology slides for this patient had been inadvertently destroyed at the site prior to our request.

The inability initial to obtain CSF cytopathology slides for post-study central review in a small proportion of patients was observed in the study of neoplastic meningitis due to solid tumors reported in NDA In that study and in the analyses of the initial 18 lymphomatous meningitis patients all response calculations utilized the central cytopathology results, if available, but reverted to site cytopathology results at any study interval in the absence of central review (NDA Section 8, Appendix 8-3, Appendix 13.9, section 4.2.2.1). This same method was used in the analysis of lymphomatous meningitis results in the current NDA as discussed in the statistical methodology section of the study report (NDA 21-041, Section 8, Appendix 8-1, Appendix 13.1.8, Section 4.2.2.1).

Since the submission of the current NDA, the sponsor has obtained the following additional central CSF cytopathology results which are reflected in this amendment to the NDA. For patient 03-LN-222 (not available for response) central cytopathology results for the follow-up periods from study days 115-407. For patient 04-LN-226 (confirmed complete response), central CSF cytopathology results are now available, confirming the patient's response status.

At this time, the sponsor does not expect additional central CSF cytopathology results beyond the information provided in this amendment will be available for the patients and follow-up periods currently included in this NDA.

If you require additional information regarding this NDA amendment or any other issues, please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

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DoTech

ORIGINAL

ORIG AMENDMENT

BM

October 23, 1998

Ms. Dianne Spillman
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041 Amendment 5

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356h is included following this cover letter. This NDA amendment includes the following documentation for the 5 additional lymphoma patients (not included in the NDA analyses), per your 9/30/98 FAX to us, as being due no later than November 2:

- copies of the local cytology reports (previously submitted as NDA Amendment 2, dated 10/6/98),
- copies of the blinded cytology reports,
- updated case report form pages (It should be noted that these data have not as yet been audited against site documentation).

Also included in this submission are: 1) a summary table of the status of the 5 lymphoma patients; followed by, 2) brief summaries describing the status of the 5 lymphoma patients; and finally 3) the data listings for the 5 lymphoma patients.

An index of the documentation included in this submission is provided following this cover letter and Form FDA 356h. Both an Archive copy and Clinical review copy of the entire submission, including CRFs, (Volumes 6.1-6.4) are provided as well as 2 desk copies of the status summaries, summary table, and data listings only (Volume 6.1).

If you require additional information regarding this NDA amendment please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

for

David B. Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

0054685.01

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DepoTech

October 15, 1998

Ms. Dianne Spillman
Division of Oncology Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
1451 Rockville Pike
Rockville, MD 20852-1448

NDA ORIG AMENDMENT
(BZ)

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041 Amendment 3

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356H is included following this cover letter. This NDA amendment includes NDA Sections 1, 2, 3, 4, 8, and 10, which we committed to providing to you by 10/17/98 in our NDA proposal dated 9/28/98. In addition, we are providing MS Word ('95) versions of both the Study Report on Lymphoma Patients (submitted in the initial NDA application, 10/2/98) and the DRAFT package insert (included in this amendment) as you requested. DepoTech Corporation has scanned the enclosed 3.5" diskettes (Copies 1 & 2) using Cheyenne AntiVirus (Version 3.27) which has found no detectable viruses.

The NDA Index (see Section 1) describes which sections (by volume number) are contained in this submission, which sections were submitted in the initial NDA application (10/2/98), and which sections are crossed referenced to NDA

Attachment 1 to this letter includes replacement Summary Tables 15a & 15b to Appendix 13.3 of the Study Report on Lymphoma Patients submitted in the initial NDA application (Volume 1.5). The reason for these revisions is that in carrying out the calculations of complete response for the intent-to-treat group (Summary Table 15a) and for cytological response for the intent-to-treat group (Summary Table 15b) for the study report submitted, the SAS program for a sub-group of patients which was not the intent-to-treat group (correctly defined as all patients who received study drug) was used. As a result, the denominator used was incorrect, although the effect was small and does not materially effect the conclusions from the study. However, please replace these tables in the study report so that the calculations are correct. In the clinical study summaries in Sections 2 and 8 of this NDA, the corrected rates as shown in these tables for response in the ITT group were used. We regret any inconvenience or confusion that this error may have caused.

Included in this submission is an Archival copy of the entire submission (Volumes 4.1-4.5) and appropriate Technical Review copies, as well as 10 desk copies of Sections 1-3 (Volume 4.1) as requested.

Also, this product qualifies for the orphan drug exception to the user fee under Section 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act. Orphan drug status (#93-733) was granted on June 2, 1993.

DepoTech Corporation • 10450 Science Center Drive • San Diego, California 92121

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October 6, 1998

Ms. Dianne Spillman
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Office of Drug Evaluation I
Center for Drug Evaluation and Research (HFD-150)
Food and Drug Administration
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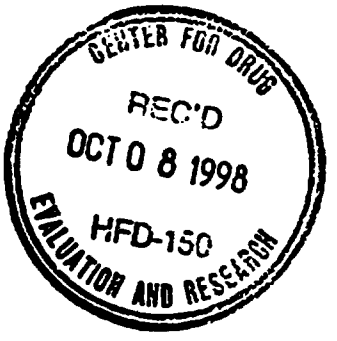
Rockville, MD 20852-1448

NDA ORIG AMENDMENT



Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041 Amendment 2

Dear Ms. Spillman,

The enclosed document is submitted per 21 CFR, Part 314, Subpart B - Applications §314.50. A signed Form FDA 356H is included following this cover letter. This NDA amendment includes the following information which you requested be submitted by 10/9/98 in your FAX to us dated 9/30/98.

Information as to:

- whether the 4 new lymphoma patients are alive or dead (include date of death) as of the last visit.
- whether or not the patient was considered a responder or not based on the local cytopathologist's reading (only).

Attachment 1 includes a summary table of the status of the new lymphomatous meningitis patients not included in the initial NDA 21-041 submission. As stated in Dr. Howell's letter to the FDA dated 9/28/98, 6 additional patients had been accrued since the data cut-off date of 3/1/98 for NDA 21-041. No data exists for 2 of these 6 patients (one patient dropped out before receiving any study drug, and a second was accrued on 9/28/98). The status of the 5 patients (except for the one accrued on 9/28/98) are included in the status summary (Attachment 1). As supportive documentation, copies of the local cytology reports for the 4 of the 5 patients listed in the status summary are included in Attachment 2. Please note that patient 25-LN-230 has no cytology report as she terminated the study after randomization, and never received any study drug.

If you require additional information regarding this NDA submission please contact me by telephone at (619) 625-2414 ext. 3205 or by FAX at (619) 558-6617.

Sincerely,

David Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

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October 5, 1998

Ms. Dianne Spillman
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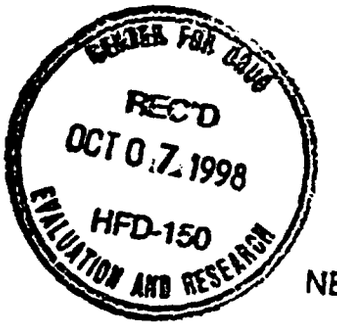

NEW CORRESP

Attention: Document Room

Subject: DepoCyt™ (cytarabine liposome injection), DTC 101
NDA 21-041 Amendment 1 (General Correspondence) - Meeting Request (Teleconference)

Dear Ms. Spillman,

In accordance with policy and procedure described in MAPP 4512.1, DepoTech Corporation requests a meeting (teleconference) with representatives of the reviewing division of the Food and Drug Administration (FDA). The purpose of the meeting is to discuss and reach agreement on the adequacy of the discussion of critical issues in the lymphomatous meningitis study report. In addition, we would like to discuss the process of submitting the remaining sections of the subject NDA as described in the cover letter of the initial submission which was received by FDA's Dockets Management Branch on October 5, 1998. In addition, we would like to discuss the review process for the NDA in light of the short time timeline for an accelerated application. We would like to have this meeting (teleconference) as soon as possible, as we are presently preparing the remaining sections of the NDA and at the same time will need to start preparing materials for an ODAC review of the application.

We are providing, as attachments, the following items relevant to the proposed meeting:

- A proposed agenda and expected times for discussion of each question (Attachment 1).
- A list of proposed participants for the meeting (Attachment 2).
- Schedule and contents of materials to be submitted to the NDA (from as Attachment 3 of NDA 21-041 submission of October 5, 1998).

Thank you for your assistance in setting up this meeting (teleconference). If you have any questions regarding this request or other matters relevant to the NDA, please contact me at (619) 625-2424, or (619) 625-2414, ext. 3205.

Sincerely,

D. B. T.

David Thomas
Senior Vice President,
Quality Assurance and
Regulatory Affairs

Meeting Request Received. Sec FDA fax dated 10/6/98.
ddspillma 10/22/98