CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21041

ADMINISTRATIVE DOCUMENTS

* FROM SPONSOR SUBMISSION DATED 10/15/98 dtapillman

Exclusivity Certification Statement

In accordance with 21 CFR §314.50(j), DepoTech Corporation claims that it is entitled to marketing exclusivity under 21 CFR §108(b) (4) if this New Drug Application (NDA) is approved.

DepoTech Corporation certifies that NDA for cytarabine (lipid-particle injection), DepoCyt™ (DTC 101), contains reports of clinical investigations that are essential to the approval of this NDA as those terms which are defined in 21 CFR §108(a).

DepoTech Corporation certifies that it has conducted a thorough search of the scientific literature. To the best of its knowledge, the list (below) of published studies or publicly available reports of published clinical investigations are relevant to the conditions for which DepoTech Corporation is seeking approval and is complete and accurate. In DepoTech Corporation's opinion, these publicly available reports do not provide a sufficient basis for approval of NDA because cytarabine (lipid-particle injection), DepoCyt™ (DTC 101), is a new product formulation of cytarabine that required proof of safety and efficacy. FDA required an additional controlled clinical study be conducted prior to approval.

The new clinical investigation(s) that are essential to approval were conducted under IND under the sponsorship of DepoTech Corporation.

/S/ 10/15/98

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

Date

1. Kim S, Chatelut E, Kim JC and others. Extended CSF cytarabine exposure following intrathecal administration of DTC 101. J Clin Oncol 1993;11:2186-93.

2. Chamberlain MC, Khatibi S, Kim JC and others. Leptomeningeal metastasis with intraventricular depot ara-C: a phase I study. Arch Neurol 1993;50:261-64.

3. Kim S, Chatelut E, Gim R and others. Comparative pharmacokinetics of DepoFoam-encapsulated cytarabine (DTC 101) following intrathecal versus intraventricular administration. Proc Am Soc Clin Oncol 1993;12:177.

4. Chamberlain MC, Kormanik P, Howell SB and others. Pharmacokinetics of intralumbar DTC-101 for the treatment of leptomeningeal metastases. Arch Neurol 1995;52:912-17.

EXCLUSIVITY SUMMARY FOR NDA # 21-041 SUPPL # 0

Trade Name DepoCyt Generic Name cytarabine liposome injection

Applicant Name DepoTech HFD # 150

Approval Date If Known 4-1-99

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?

YES /X/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /X/

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

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /X/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

APPEARS THIS WAY
ON ORIGINAL

d) Did the applicant request exclusivity?

YES /X/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request? not specified

e) Has pediatric exclusivity been granted for this Active Moiety? No

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IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with

hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

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

NDA# 16-793 Cytosar-U (cytarabine) Ara-C

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

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

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

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

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /✓/

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

_____ _____

_____ _____

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

*Study DTC 92-001 "A randomized clinical study to determine the efficacy and safety of DepoFoam encapsulated ~~cytarabine (DTC101)~~ relative to standard therapy for the treatment of neoplastic meningitis in patients with leukemia, lymphoma or solid tumors."

*Note: The lymphoma and solid tumor portions of this study are considered separate and independent investigations.

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /✓/ ! NO /___/ Explain: _____

! _____

Investigation #2

IND # _____ YES /___/ ! NO /___/ Explain: _____

_____

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

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/ 3-15-99

Signature Date

Title: Project Manager

/S/ 3/31/99

Signature of Office/ Date

Division Director

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21041	**Trade Name:**	DEPOCYT(CYTARABINE LIPOSOME INJ)50MG(10M
Supplement Number:		**Generic Name:**	CYTARABINE LIPOSOME INJ
Supplement Type:		**Dosage Form:**	INJ
Regulatory Action:	PN	**Proposed Indication:**	Depocyt is indicated for the intrathecal treatment of lymphomatous meningitis.

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Does Not Apply
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, ANN STATEN

/S/ 3-17-99

Signature Date

cc: Orig NDA 21-041
Div File
~~HFD-150/Ashok~~

DATED 10/15/98 dispillman

Debarment Certification Statement

In accordance with Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §335a(k)(1), DepoTech Corporation certifies that the applicant did not and will not use in any capacity, the services of any person debarred under sections 306(a) or 306(b), in connection with such application.

D. B. Thomas 11/15/98

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

Date

Chemist's Memo to NDA's file 21-041

NDA Appilicant: DepoTech Corporation,
10450 Science Center Dr.
San Diego, CA 92121

Date: **April 1, 1999**

Biopharm Consult regarding In Vitro Release Specifications was requested for NDA( )The applicant has responded to Biopharm's comments that were reviewed by DR. Atiqur Rahman dated 3/19/99. Biopharm agreed with the applicant's interim specification for *In Vitro* Release Specifications. However, the final *In Vitro* Release Specifications should be established based on *In Vitro* Release test data and stability data that should be reviewed by Biopharm and chemistry reviewers.

/S/ 3/31/99
Chengyi Liang, Ph.D., Review Chemist

/S/ 4/1/99
Liang Zhou, Ph.D.
Chemistry Team Leader

CC:

CC:
Orig. NDA 21-041
HFD-150/Division File
HFD-150/Cliang,LZhou
HFD-860/Mmehta
HFD-860/ARahma
~~HFD-150/Astaten~~ /DSpillman
HFD-810/Director
HFD-150/Director

NDA 20-798

Consult #746 (HFD-150)

DEPOCYT cytarabine liposome injection

There were no look-alike/sound-alike conflicts or misleading aspects found in the proposed proprietary name. However, the Committee was concerned that the "DEPO-" portion of the name implied a traditional depot mechanism of drug release. Some potential for confusion with other depot products might occur with untoward consequences.

Overall, the Committee has no reason to find the proposed proprietary name unacceptable.

/S/ 3/4/97
Chair
CDER Labeling and Nomenclature Committee

cc: NDA
HFD-150 /Div file
/D. Spillman

MEETING MINUTES

MEETING DATE: January 14, 1999 **TIME:** 3pm **LOCATION:** Conference Room G

IND/NDA NDA 21-041 Meeting Request Submission Date: December 14, 1998
Briefing Document Submission Date: December 14, 1998

DRUG: DepoCyt™ (cytarabine liposome injection)

SPONSOR/APPLICANT: DepoTech Corporation

TYPE of MEETING:

1. post-ODAC, confirmatory study design

2. **Proposed Indication:** DepoCyt is indicated for the intrathecal treatment of lymphomatous meningitis.

FDA PARTICIPANTS:
Robert Temple, M.D., Director, Office of Drug Evaluation I (ODEI) (industry only)
Rachel Behrman, M.D., MPH, Deputy Director, ODEI (pre-industry only)
Robert Justice, M.D., Acting Division Director, Oncology Drugs
Julie Beitz, M.D., Acting Deputy Division Director, Oncology Drugs
Grant Williams, M.D., Medical Team Leader
Helgi Van de Velde, M.D., Ph.D., Medical Reviewer
Steve Hirschfeld, M.D., Ph.D., Medical Reviewer
Atiqur Rahman, Ph.D.,Clinical Pharmacology and Biopharmaceutics Team Leader (pre-industry)
Ann Staten, R.D., Project Manager
Kim Margolin, M.D., ODAC Consultant

INDUSTRY PARTICIPANTS:
David Thomas, Senior Vice President, Quality Assurance and Regulatory Affairs
Stephen Howell, M.D., Professor of Medicine, UCSD, Acting Medical Director
Terrence Chew, M.D., Vice President Clinical Department
Raymond Lamy, Associate Director, Regulatory Affairs
Allen Cato, M.D., President, CATO Research
Lynda Sutton, Senior Vice President, Regulatory Affairs and Project Planning, CATO Research
Tom Soeder, Senior Programmer, Statistics, CATO Research, Ltd.

INDUSTRY PARTICIPANTS VIA TELECONFERENCE:
David G. Poplak, M.D., Director, Texas Children's Cancer Center
Sandra Horning, M.D., Stanford University Medical Center
J. Wayne Cowens, M.D., Division Vice President, Product Development, Chiron Technologies
Sandra Patterson, Ph.D., Division Vice President, Regulatory Affairs, Chiron Therapeutics and Vaccines
Greg Baigent, Associate Director, Project Management, Chiron Therapeutics and Vaccines

MEETING OBJECTIVES:

1. To discuss the adequacy of the study proposal for establishing the clinical benefit of DepoCyt in lymphomatous meningitis.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

Is the study proposal for establishing the clinical benefit of DepoCyt in lymphomatous meningitis adequate?

FDA Response:

- The analysis plan described does not fulfill the post marketing requirements in the accelerated approval regulations for the sponsor to "...study the drug further, to verify and describe its clinical benefit..."

- The preferred Phase 4 trial should verify that intrathecal treatment with DepoCyt produces clinical benefit in patients with lymphomatous meningitis.

  Alternatively, the trial could be conducted with neoplastic meningitis from patients with solid tumors, but it would be prudent to include patients with lymphomatous meningitis.

- The preferred design would be a randomized controlled trial designed prospectively to demonstrate that DepoCyt prolongs time to neurological progression or survival in lymphomatous meningitis.

  Time to neurological progression would have to be clearly defined and carefully analyzed.

- Additionally, you should include pharmacokinetic assessment of DepoCyt as an objective of the Phase 4 trial.

DepoTech Response:

- DepoTech believes that their report on European pharmacokinetic study will clarify this point.

ACTION ITEMS:

1. DepoTech will submit their proposed protocol and the time estimate for completing the study as quickly as they can.

2. The Project Manager will clarify the pharmacokinetic assessment request and will communicate back to the sponsor.

3. DepoTech will propose a protocol that may qualify for subpart H for refractory, non-responsive or intolerant solid tumors.

The meeting was concluded at 4:30pm. There were no unresolved issues or discussion points.

/S/ , 1/29/99
Ann Staten Date
Project Manager
Minutes preparer

Concurrence Chair: /S/ , 1/29/99
Steve Hirschfeld, M.D.
Medical Officer

Attachments: DepoTech's facsimile dated 1/12/99 (distributed to FDA team but not reviewed / disussed for meeting)

cc:
Original NDA 21-041
HFD-150/Div File
/JBeitz
/GWillams
/SHirschfeld
/HVandeVelde
/ARahman
/GChen
/LVaccari
/DPease
/AStaten

MEETING MINUTES