

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPLICATION NUMBER: NDA 21041**

**CHEMISTRY REVIEW(S)**

APR - 1 1999

NDA 21-041, Cytarabine liposome injection

Division of Oncologic Drug Products  
Review of Chemistry, Manufacturing and Controls

NDA #: 21-041      CHEM. REVIEW#: 3      REVIEW DATE: March 31, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	10-15-98	10-16-98	10-23-98
BC	12-4-98	12-7-98	12-10-98
BC	1-22-99	1-26-99	1-27-99
NC	2-25-99	3-1-99	3-3-99
Fax	3-30-99	3-30-99	3-30-99

NAME AND ADDRESS OF APPLICANT:      DepoTech Corporation  
10450 Science Center Dr.  
San Diego, CA 92121

DRUG PRODUCT NAMES:

Proprietary:	DepoCyt
Nonproprietary/USAN:	Cytarabine liposome injection
Code Name/#:	CAS DTC-101
Chem. Type/Ther. Class	

PHARMACOL. CATEGORY/INDICATION:      Intrathecal treatment of  
neoplastic meningitis

DOSE FORM/STRENGTHS:      50 mg/5 mL/vial (10mg/mL)

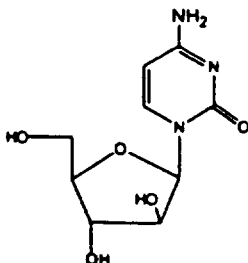
ROUTE OF ADMINISTRATION:      Intrathecal injection

MANUFACTURER:

B. Drug Product  
Depotech Corp  
10450 Science Center Dr.  
San Diego, CA 92121

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Cytosine arabinose, 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone  
C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>, MW = 243.22



**SUPPORTING DOCUMENTS:**

**CONSULTS:**

Consult	Status	Comments
EER		Approved

**REMARK/COMMENTS:**

NDA 21-041 is resubmission of NDA [redacted] from a CMC point of view. All sites in NDA [redacted] which are same sites as those in this NDA 21-041 have been inspected previously. During the review of NDA 21-041, some sites need to be reinspected. The inspection for L-lysine supplier [redacted] is scheduled at 4/26/99 although this site has been inspected previously. We agree the OC's proposal to change this inspection to post-approval inspection and grant recommendation at present. The another testing laboratory [redacted] who performed the [redacted] test and environmental monitoring is withdrawn by the applicant. The applicant states in FAX dated 3/30/99 that [redacted] was only used at one time for testing [redacted]. The applicant is no longer to use this contractor testing laboratory and all the [redacted] tests are performed in house. This information has been reported to OC and inspection for this facility has been cancelled.

Biopharm Consult regarding In Vitro Release Specifications was requested for NDA [redacted]. 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.

**CONCLUSIONS AND RECOMMENDATIONS:**

The approval is recommended.

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

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

- CC:  
Orig. NDA 21-041/003  
HFD-150/Division File  
HFD-150/Cliang, LZhou  
HFD-860/Mmehta, ARahma  
HFD-150/Astaten / Dspillman  
HFD-810/Director

Division of Oncologic Drug Products  
Review of Chemistry, Manufacturing and Controls

NDA #: 21-041      CHEM. REVIEW#: 2      REVIEW DATE: March 13, 1999

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	10-15-98	10-16-98	10-23-98
BC	12-4-98	12-7-98	12-10-98
BC	1-22-99	1-26-99	1-27-99
NC	2-25-99	3-1-99	3-3-99

NAME AND ADDRESS OF APPLICANT:      DepoTech Corporation  
10450 Science Center Dr.  
San Diego, CA 92121

DRUG PRODUCT NAMES:

Proprietary:	DepoCyt
Nonproprietary/USAN:	Cytarabine liposome injection
Code Name/#:	CAS DTC-101
Chem. Type/Ther. Class	

PHARMACOL. CATEGORY/INDICATION:      Intrathecal treatment of  
neoplastic meningitis

DOSAGE FORM/STRENGTHS:      50 mg/5 mL/vial (10mg/mL)

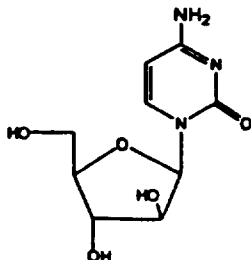
ROUTE OF ADMINISTRATION:      Intrathecal injection

MANUFACTURER:

B. Drug Product  
Depotech Corp  
10450 Science Center Dr.  
San Diego, CA 92121

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:

Cytosine arabinose, 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone  
C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>, MW = 243.22



**SUPPORTING DOCUMENTS:**

**CONSULTS:**

Consult	Status	Comments
EER	Pending	

**REMARK/COMMENTS:**

The applicant accepts the FDA's comments to tighten the impurity limits for free cytarabine and uracil arabinose in DP from NMT 6.0% and NMT 7.0% respectively to both NMT 5.0%. The applicant also accepts the FDA's recommendation to revise the storage temperature as read "refrigerate at 2-8°C. Protect from freezing". The revision will be incorporated into the Package Insert.

The copies of vial/carton label of DepoCyt were provided. The established name "Cytarabine liposome injection" should be printed as regular (non bold and non italic) letter and have a parenthesis as read:

**DepoCyt™**  
(cytarabine liposome injection)

50 mg/5 mL (10 mg/mL)
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The company claimed categorical exclusion per 21 CFR 25.31 (b).

This NDA 21-041 is a resubmission of NDA [redacted]. All the inspection facilities in NDA 21-041 are the same as those in NDA [redacted]. These facilities have been inspected in Dec. 9, 1997 for NDA [redacted] and found to be acceptable from OC. The EER for NDA 21-041 was resubmitted during the review of this NDA resubmission. All the facilities were found to be acceptable by OC dated 3/1/99 except one site [redacted] supplies L-lysine monohydrate which is as one of the inactive ingredients for drug product. This site was also found to be acceptable in Feb. 1997's inspection. The inspection for this site is still pending. The e-mail was sent to OC seeking the special comments for this case based on the following consideration:

1. User Fee Goal Date is close;
2. L-lysine is one of the inactive ingredients for DP;
3. the site is in [redacted] and has been inspected two years ago.

**CONCLUSIONS AND RECOMMENDATIONS:**

The approval is not recommended until the pending issue of last inspection site [redacted] has been solved.

ISI

3/16/99

Chengyi Liang, Ph.D., Review Chemist

ISI

3/14/99

Liang Zhou, Ph.D.  
Chemistry Team Leader

CC:  
Orig. NDA 21-041/002  
HFD-150 Division File  
HFD-150/CLiang  
HFD-150/LZhou  
HFD-150/DSpillman

JEC 30 1998

**Division of Oncologic Drug Products  
Review of Chemistry, Manufacturing and Controls**

**NDA #:** 21-041      **CHEM. REVIEW#:** 1      **REVIEW DATE:** Dec. 20, 1998

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	10-15-98	10-16-98	10-23-98
BC	12-4-98	12-7-98	12-10-98

**NAME AND ADDRESS OF APPLICANT:** DepoTech Corporation  
10450 Science Center Dr.  
San Diego, CA 92121

**DRUG PRODUCT NAMES:**

Proprietary:	DepoCyt
Nonproprietary/USAN:	Cytarabine liposome injection
Code Name/#:	CAS DTC-101
Chem. Type/Ther. Class	

**PHARMACOL. CATEGORY/INDICATION:** Intrathecal treatment of  
neoplastic meningitis

**DOSAGE FORM/STRENGTHS:** 5 ml/vial, 10mg/ml

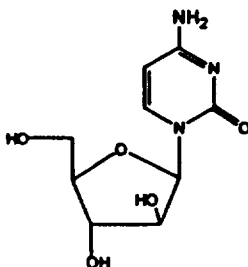
**ROUTE OF ADMINISTRATION:** Intrathecal injection

**MANUFACTURER:**

B. Drug Product  
Depotech Corp  
10450 Science Center Dr.  
San Diego, CA 92121

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR WEIGHT:**

Cytosine arabinose, 4-amino-1-b-D-arabinofuranosyl-2(1H)-pyrimidinone  
C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>, MW = 243.22



**SUPPORTING DOCUMENTS:**

**CONSULTS:**

Consult	Status	Comments
EER	Pending	Resubmitted 12/1/98

**Attachments:**  
NDA

**REMARK/COMMENTS:**

The applicant submitted this NDA for the new indication of the drug Cytarabine liposome injection (NDA) which was reviewed by Dr. Paul Dietze. All the CMC information provided in this NDA is as same as that in NDA. The chemistry comments and recommendations for NDA were sent to the applicant dated 4/17/1998. The applicant's response to these comments was submitted as Amendment 13. Upon the Agency's request, this Amendment is also included in the NDA 21-041:

**FDA question 1:**

The chemical structure for cytarabine depicted in the package insert is the incorrect enantiomer. This needs to be changed to the correct enantiomer.

**Response:**

The reviewer is correct. The drawing in the package insert will be corrected to reflect the drawing presented below.

**Comment:**

The correct structure of DS was provided and found to be acceptable.

**FDA question 2:**

The chemical name for cytarabine should not include a hyphen in the term "2-(1 H)." The correct chemical name is "4-amino-1-D-arabinofuranosyl-2(1 H)-pyrimidone."

**Response:**

The reviewer is correct regarding the hyphen. In fact, the correct chemical name is 4-amino-1-D-arabinofuranosyl-2(1 H)-pyrimidone. The name is correct in Section 3 of the NDA, and will be corrected in the package insert to read as follows:

**DESCRIPTION**



NDA 21-041, Cytarabine liposome injection

DEPOCYT is a sterile, injectable suspension of the antimetabolite cytarabine, encapsulated into multivesicular lipid-based particles (DepoFoam, DepoTech Corporation, San Diego, CA). Chemically, cytarabine is 4-amino-1-β-D-arabinofuranosyl-2(1H)-pyrimidinone, commonly known as cytarabine (C<sub>9</sub>H<sub>13</sub>N<sub>3</sub>O<sub>5</sub>, molecular weight 243.22).

Comment:

The revision of chemical name of cytarabine is acceptable. However, adding company's name and address (DepoFoam, DepoTech Corporation, San Diego, CA) in the Description section is not appropriate.

FDA question 3:

Please address the issue(s) concerning the stability of the drug product that were reported in the IND for this drug product, see IND<sup>1</sup> Amendment Serial No. 052 dated 12/21/97.

Response:

The issues cited in the reviewer comment relate to the relationship between shelf life and storage temperature. Long-term stability data are available for product stored at 4°C (earlier studies) and 8°C (recent studies). Attachment 1 contains updated stability data tables for 1 X scale product (24 months, 2 -8°C) and 10 X scale product (12 months, 6 -10°C). (Note: the manufacturing process proposed for the commercial production of DTC 101 is a 10 X scale up, referred to as 10 X scale, of the process used to manufacture DTC 101 product utilized in the phase III trial and GLP toxicology study, referred to as 1 X scale.) A comparison of these data has shown that the relative rate of degradation, as measured by the concentration of Free Cytarabine, is greater at the higher temperature for trend line plots of Free Cytarabine data in the 1 X and 10 X stability programs). An apparent difference in robustness of product manufactured at the 10 X scale compared to product produced at the 1 X scale can be explained on the basis of the difference in storage temperature alone. An Arrhenius treatment of accelerated degradation data predicts a difference in degradation at these two temperatures which correlates very well with what has been observed. It was concluded that 10 X product stored at a temperature lower than 8°C would behave in a manner similar to that experienced with 1 X product. Actual analyses of product stored for extended periods at 4°C confirmed this conclusion.

A projection of anticipated production of Free Cytarabine in the product stored at 6°C was included in the cited IND amendment, and showed that even a two-degree reduction in storage temperature would produce a significant improvement in product stability.

As a result of the stability analysis, a reduction in claimed shelf life from 18 months to 12 months was made for clinical product. In addition, a request was made to allow a change in storage temperature on the

NDA 21-041, Cytarabine liposome injection

product labeling for clinical supplies to read "Store at 2-6°C".

Based on stability data currently available (8°C storage), the sponsor is proposing to reduce the shelf life being requested for commercial product in this NDA to 12 months, based on data in Attachment 1. At the same time, a request is being made to allow storage labeling of 2-6°C for the commercial product. A stability study has been initiated with 10 X lots of DTC 101, identical to the protocol included in the NDA (pre-Submission of CMC Data, November 22, 1996) except that storage is at 6°C. As data become available, they will be included in regular annual reports to this NDA. When sufficient data are available, appropriate adjustments in the shelf life will be made.

Comment:

The free Cytarabine and Uracil Arabinose in DP specifications (NDA were tightened to NMT 6.0% and NMT 7.5% respectively by the applicant upon the request of FDA. However, these limits in the proposed regulatory specifications for NDA 21-041 are higher than those in NDA (free Cytarabine is NMT 8% and Uracil Arabinose is NMT 10%). These limits should be tightened per NDA

Following FDA's comments, the applicant tested DP at up limit 8°C of storage temperature 2-8°C and found that DP was degraded to increase the free Cytarabine. The extensive studies at different temperature were performed and found that the high temperature promoted the degradation of liposome formulated DP:

Arrhenius Treatment Rate Constants Based on 1X Batch Studies

Measured Values Used for Arrhenius Treatment	
Temperature (°C)	Rate Constant (Slope)
37°	13.694
25°	2.504
20°	1.143
15°	0.507
Extrapolated Rate Constants from Arrhenius Treatment	
Temperature (°C)	Rate Constant (Slope)
8°	0.162
6°	0.115
4°	0.082

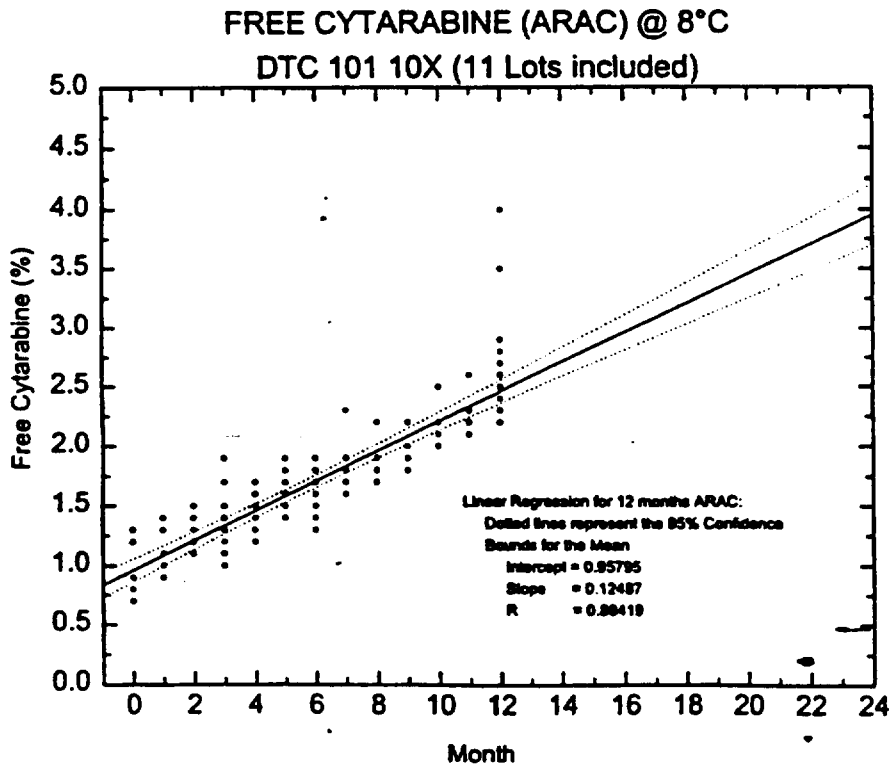
The lower storage temperature such as 4°C and 6°C lower slope of degradation than at 8°C.

% Free Cytarabine for DTC 101 Stability Batches at 8 °C and 4 °C

Lot Number	12 Months, 8 °C	Lot Number	13-14 Months, 4 °C
96-0050, upright	4.0	96-0050, upright	1.6
96-0050, inverted	3.5	96-0050, upright	1.7
		96-0050, upright	1.6
96-0051, upright	2.7	96-0051, upright	1.6
96-0051, inverted	2.8	96-0051, upright	1.7
		96-0051, upright	1.6
96-0052, upright	2.2	96-0052, upright	1.6
96-0052, inverted	2.2	96-0052, upright	1.5
		96-0052, upright	1.5

The degradation of DP under storage temperature 4°C and 8°C was compared. It is obvious that DP stored at 4°C is much more stable than that stored at 8°C.

The real time test data show that 1 x scale DP is stable at 2-8°C for 18 months (free DS 3.3%, 18 M). The eleven 10 x scale DP lots are also stable even at 6-10°C for 12 M (free DS 2.4%, 12 M). Only two DP lots show the significant high level of free DS at 12 M time point when tested at 8°C (free DS reaches 3.5-4.0%). However, these limits are within the specification:



For the safety concern, the applicant proposed to shorten the shelf life of DP from previous 18 months to 12 months and reduce the storage temperature of DP from 2-8°C to 2-6°C. Shorten the shelf life of DP is acceptable, however, change the storage condition from 2-8°C to 2-6°C seems not practical. We recommend the applicant to use USP and FDA recommended storage condition: Store in a refrigerator, 2-8°C (36-46°F).

Item 4:

There are deficiencies that need to be addressed in DMF<sup>1</sup>; The deficiencies have been communicated to the DMF holder.

Response:

The sponsor has been notified by the DMF holder that the deficiencies noted by the Agency have been corrected in an amendment to the DMF. A copy of the notification from the DMF holder is included

Comment:

The amendment to DMF has been reviewed and found to be acceptable.

The Package Insert was also submitted in this NDA. Some deficiencies are found and need to be addressed:

1. The applicant uses two names for drug product: DepoCyt and DepoForm, Only one proprietary name for each drug is appropriate. The applicant should delete DepoForm in the Description section.

2. In How Supplied section, we suggest to write as follow: DepoCyt (cytarabine liposome injection) is supplied as a sterile, white to off-white suspension in 5 ml glass, single use vials.

Each 5 ml preservative-free vial contains 50 mg Cytarabine at a concentration of 10 mg/ml. Discard any unused portion.

Refrigerate at 2-8°C. Avoid freezing.

Available as individual carton containing one ready to use vial. NDC 53905-331-01.

3. Revise the storage temperature to 2°C to 8°C (36°F to 43°F) and delete section in package insert as individual section.

4. Provide the real sample of vial and carton labels.

**CONCLUSIONS AND RECOMMENDATIONS:**

The approval is recommended. However, the following comments should be conveyed to the applicant:

NDA 21-041. Cytarabine liposome injection

1. The limits of free cytarabine and uracil arabinose in DP should be tightened per NDA
2. The storage temperature for DP should follow USP recommendation as read: Store in a refrigerator, 2-8°C (36-46°F).
3. Two names for drug product: DepoCyt and DepoForm are used. Only one for each drug is appropriate. Please delete DepoForm in the Description section of Package Insert.
4. In "How Supplied" section, we suggest you to write as follows:  
DepoCyt (cytarabine liposome injection) is supplied as a sterile, white to off-white suspension in 5 ml glass, single use vials.

Each 5 ml preservative-free vial contains 50 mg Cytarabine at a concentration of 10 mg/ml. Discard any unused portion.

Refrigerate at 2-8°C. Avoid freezing.

Available as individual carton containing one ready to use vial. NDC 53905-331-01.

5. Revise the storage temperature to 2°C to 8°C (36°F to 43°F) and delete section in package insert as individual section.
6. Provide the real sample of vial and carton labels for drug product.

ISI  
12/29/98  
Chengyi Liang, Ph.D., Review Chemist

ISI  
Liang Zhou, Ph.D.  
Chemistry Team Leader  
12/30/98  
Zhou

CC:

Orig. NDA 21-041  
HFD-150 Division File  
HFD-150/CLiang  
HFD-150/LZhou  
HFD-150/DSpillman