

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**22-273**

**ADMINISTRATIVE and CORRESPONDENCE**  
**DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 22-273

SUPPL #

HFD # 150

Trade Name Fludarabine Phosphate

Generic Name Fludarabine Phosphate

Applicant Name Antisoma

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

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

YES  NO

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

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

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

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

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES  NO

IF THE ANSWER TO QUESTION 2 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  NO

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

NDA#	20-038	Fludarabine Phosphate
NDA#	78-393	Fludarabine Phosphate
NDA#	78-544	Fludarabine Phosphate
	77-790	Fludarabine Phosphate
	76-661	Fludarabine Phosphate
	76-349	Fludarabine Phosphate
	22-137	Fludarabine Phosphate

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

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

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

YES  NO

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

1. Study ME96029
2. Study CLL 101 \_\_\_\_\_
3. Study 303080
4. Study LRF CLL4
5. Study CALGB 9011

**b(4)**

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, 2, 3, 4, and 5

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, 2, 3, 4, and 5

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"):

Investigation #1, 2, 3, 4, and 5

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, 2, 3, 4, and 5

IND # 78,332

YES

!  
! NO

! Explain:

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:

Bayer ?

!

!

! 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:

---

Name of person completing form: James M. Saunders

Title: Regulatory project Manager

Date: December 10, 2008

Name of Office/Division Director signing form: Ann Farrell, M.D.

Title: Deputy Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**PEDIATRIC PAGE**

**(Complete for all filed original applications and efficacy supplements)**

NDA/BLA#: 22273

Supplement Number: \_\_\_\_\_

NDA Supplement Type (e.g. SE5): \_\_\_\_\_

Division Name: DDOP

PDUFA Goal Date:  
December 19, 2008

Stamp Date: November 19, 2007

Proprietary Name: \_\_\_\_\_

Established/Generic Name: fludarabine phosphate tablets for oral use

Dosage Form: film-coated tablet

Applicant/Sponsor: Antisoma

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) \_\_\_\_\_
- (2) \_\_\_\_\_
- (3) \_\_\_\_\_
- (4) \_\_\_\_\_

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

**Indication:** Treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

**Q1:** Is this application in response to a PREA PMR? Yes  Continue

No  Please proceed to Question 2.

If Yes, NDA/BLA#: \_\_\_\_\_

Supplement #: \_\_\_\_\_

PMR #: \_\_\_\_\_

Does the division agree that this is a complete response to the PMR?

Yes. Please proceed to Section D.

No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

**Q2:** Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW  active ingredient(s) (includes new combination);  indication(s);  dosage form;  dosing regimen; or  route of administration?\*

(b)  No. PREA does not apply. **Skip to signature block.**

\* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

**Q3:** Does this indication have orphan designation?

Yes. PREA does not apply. **Skip to signature block.**

No. Please proceed to the next question.

**Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?**

- Yes: (Complete Section A.)
  - No: Please check all that apply:
    - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
    - Deferred for some or all pediatric subpopulations (Complete Sections C)
    - Completed for some or all pediatric subpopulations (Complete Sections D)
    - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
    - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

**Section A: Fully Waived Studies (for all pediatric age groups)**

Reason(s) for full waiver: (check, and attach a brief justification for the reason(s) selected)

- Necessary studies would be impossible or highly impracticable because:
  - Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are fully waived on this ground, this information must be included in the labeling.)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

**Section B: Partially Waived Studies (for selected pediatric subpopulations)**

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):  
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

			Reason (see below for further detail):				
	minimum	maximum	Not feasible <sup>#</sup>	Not meaningful therapeutic benefit <sup>*</sup>	Ineffective or unsafe <sup>†</sup>	Formulation failed <sup>Δ</sup>	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

- Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.
- Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Reason(s) for partial waiver (check reason corresponding to the category checked above, and attach a brief

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.

**Justification):****# Not feasible:**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
  - Too few children with disease/condition to study
  - Other (e.g., patients geographically dispersed): \_\_\_\_\_

**\* Not meaningful therapeutic benefit:**

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

**† Ineffective or unsafe:**

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

**Δ Formulation failed:**

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

 Justification attached.

*For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.*

Appears This Way  
On Original

**Section C: Deferred Studies (for selected pediatric subpopulations).**

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Date studies are due (mm/dd/yy): _____							

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

\* Other Reason: \_\_\_\_\_

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Appears This Way  
On Original

**Section D: Completed Studies (for some or all pediatric subpopulations).**

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):**

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

*If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.*

**Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)**

*Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as*

**IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL ([cderpmhs@fda.hhs.gov](mailto:cderpmhs@fda.hhs.gov)) OR AT 301-796-0700.**

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)?  No;  Yes.

Are the indicated age ranges (above) based on Tanner Stage?  No;  Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Appears This Way  
On Original

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

/s/

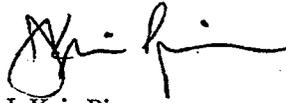
-----  
James Saunders  
12/1/2008 03:57:35 PM

Appears This Way  
On Original

*1.3.3 Debarment Certification*

Xanthus Pharmaceuticals Inc. hereby certifies that it did not or will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application.

Xanthus Pharmaceuticals Inc



J. Kris Piper  
Senior VP of Regulatory Affairs  
and Clinical Operations

Date: 15 Nov 2007

Appears This Way  
On Original

## MEETING MINUTES

**MEETING DATE:** December 15, 2008 **TIME:** 4:00 PM-4: 25 PM **LOCATION:** CR 2201

**NDA:** 22-273

**DRUG:** fludarabine 10mg tablets for oral use

**SPONSOR/APPLICANT:** Antisoma

**TYPE of MEETING:**

1. Pre- Approval Safety Conference
2. Proposed Indication: Treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

**FDA PARTICIPANTS:**

Ann Farrell, M.D., Deputy Division Director  
Martin Cohen, M.D., Clinical Reviewer  
Gene, Williams, Ph.D., Clin Pharm Reviewer, DCPBS  
Corrine Kulick, Safety Evaluator  
Sandra Griffith, OSE Project Manager  
Allen Brinker, M.D. Medical Officer, OSE  
Ann McMahon, OSE-DPV II  
Nancy Carothers, OSE Labeling  
Amna Ibrahim, M.D., Acting Division Director for Safety  
Janet Jamison, Safety Regulatory Project Manager

**BACKGROUND:** The PDUFA date for fludarabine is December 19, 2008. This meeting was scheduled to discuss any new adverse events or other safety issues that have appeared in clinical trials that may be expected to show up in safety reports once the drug is approved.

**DISCUSSION:** The oral formulation of this drug has been in existence for approximately ten years and is approved in many countries. The intravenous formulation of this drug has been marketed in the United States since 1991. During the review of the application for the oral formulation, the adverse events were similar in frequency to those seen with the intravenous formulation. No new adverse events were noted. The label has new information on dose reduction in renal failure.

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

/s/

-----  
Ann Farrell  
12/18/2008 11:34:40 AM

Appears This Way  
On Original

## MEMORANDUM OF TELECON

DATE: December 18, 2008

APPLICATION NUMBER: NDA 22-273, fludarabine phosphate

BETWEEN:

Name: J. Kris Piper  
Phone: (617) 252-6100  
Representing: Antisoma

AND

Name: James M. Saunders  
Division of Drug Oncology Products HFD-150

SUBJECT: Confirmation of sponsor receipt of action letter.

I emailed J. Kris Piper a copy of the official action letter at 4:04P At 4:34 PM, J. Kris Piper called and conformed receipt of the action letter.

---

James M. Saunders  
Senior Regulatory Management Officer

Appears This Way  
On Original

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

/s/

-----  
James Saunders

12/18/2008 04:47:28 PM

CSO

Confirmation of receipt of NDA Approval Letter

Appears This Way  
On Original

**Saunders, James**

---

**From:** Kris Piper [Kris.Piper@antisoma.com]  
**Sent:** Friday, December 12, 2008 7:03 AM  
**To:** Saunders, James  
**Cc:** Stanny BerghsClairmont  
**Subject:** RE: Latest PI with revisions for NDA 22-273

James,

As requested:

For the post-approval clinical study -

The full protocol will be submitted to the Agency by March 31, 2009 and the study start (enrollment of the first patient) will occur by September 30, 2009. Completion of enrollment will occur by March 31, 2012 and completion of the study will occur by September 30, 2013. The final study report including SAS datasets and applicable revised labeling will be submitted to the Agency by June 30, 2014.

Kris

J. Kris Piper  
VP Global Regulatory Affairs  
Antisoma  
617-252-6130  
Xanthus Pharmaceuticals, Inc.: An Antisoma Group Company

---

**From:** Saunders, James [mailto:James.Saunders@fda.hhs.gov]  
**Sent:** Thursday, December 11, 2008 4:11 PM  
**To:** Kris Piper  
**Cc:** Stanny BerghsClairmont  
**Subject:** RE: Latest PI with revisions for NDA 22-273

Thanks Kris; I have passed them on to the reviewers. After checking with my supervisor, I need to ask if the paragraph you sent can be changed to include specific dates for all the milestones in lieu of quarters, etc. Thanks.

**James**  
**FDA/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

---

**From:** Kris Piper [mailto:Kris.Piper@antisoma.com]

12/12/2008

**Sent:** Thursday, December 11, 2008 3:34 PM  
**To:** Saunders, James  
**Cc:** Stanny BerghsClairmont  
**Subject:** RE: Latest PI with revisions for NDA 22-273

Hello James,

Attached are a track changes copy and a clean copy of the revised draft package insert. We have accepted all of the changes made in the draft sent to us yesterday. In addition, we have made a few editorial corrections which are highlighted in the track changes copy. The cover page presented in 2-column format is also attached as requested.

Please let me know if you have any additional comments. Hard copy will be sent to the NDA as an amendment.

Kind regards,  
Kris

J. Kris Piper  
VP Global Regulatory Affairs  
Antisoma  
617-252-6130  
Xanthus Pharmaceuticals, Inc.: An Antisoma Group Company

---

**From:** Saunders, James [mailto:James.Saunders@fda.hhs.gov]  
**Sent:** Wednesday, December 10, 2008 3:06 PM  
**To:** Kris Piper; Stanny BerghsClairmont  
**Subject:** Latest PI with revisions for NDA 22-273

Good afternoon,

Please see the latest label with revisions and comments.

<<03dec2008\_gene-af\_edits\_revised 10dec2008.doc>>

Sincerely,

*James*

James M. Saunders RPh, MS, MBA

Commander, US Public Health Service

Senior Regulatory Management Officer

CDER/OODP/DDOP

10903 New Hampshire Ave.

WO22 Room 2369

12/12/2008

Silver Spring, MD 20993

(301) 796-0621

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, December 03, 2008 6:09 PM  
**To:** 'Kris Piper'; 'Stanny BerghsClairmont'  
**Subject:** NDA 22-273 Efficacy and Safety Analyses

**Follow Up Flag:** Follow up  
**Due By:** Wednesday, December 03, 2008 12:00 AM  
**Flag Status:** Flagged

Hi Kris,

The following request is a result of our continuing review of the geriatric section of the label. We need you to do an efficacy and safety analyses by age comparing the efficacy of oral fludara in those less than 65 and those 65 and older for the label. Approximately 50% of patients in some trials were at least 65 years of age. This would need to be done right away.

Regards,

*James*

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
12/3/2008 06:16:01 PM

Appears This Way  
On Original

## TELECON MINUTES

**TELECON DATE:** December 3, 2008      **TIME:** 12:30 PM – 1:00 PM  
**LOCATION:** CR 2201

**NDA:** 22-273

**DRUG:** fludarabine 10mg tablets for oral use

**SPONSOR/APPLICANT:** Antisoma

**FDA PARTICIPANTS:** Anne Farrell, M.D. Chair  
James M. Saunders, Facilitator

**INDUSTRY PARTICIPANTS:** J. Kris Piper  
Bill Lundberg, M.D.  
Stanny Berghs-Clairmont, Ph.D.

**BACKGROUND:** This meeting was called to discuss the sponsor's request to discuss the indication to be listed on the label, the Agency's comments regarding renal impairment to be added to the label, and DRISK's comments on the PPI.

**ACTION ITEMS:** (Include description, identify person responsible and due date.)

1. After a discussion of DRISK's comments, the sponsor will submit a revised PPI by December 4, 2008 and DRISK will reevaluate
2. The Agency will add information on renal impairment to the latest label and send to the sponsor by December 5, 2008

Appears This Way  
On Original

## REQUEST FOR CONSULTATION

TO (Office/Division): Pediatric and Maternal Health  
ff/IO/OND. Attention MHT Consult  
Coordinator: Tammie Brent, RHPM

FROM (Name, Office/Division, and Phone Number of Requestor): James M. Saunders, RPM, DDOP HFD-150, 301-796-0621

DATE  
August 14, 2008

IND NO.

NDA NO.  
22-273

TYPE OF DOCUMENT  
New Submission

DATE OF DOCUMENT  
August 13, 2008

NAME OF DRUG  
Fludarabine phosphate

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG  
cytotoxic

DESIRED COMPLETION DATE  
August 31, 2008

NAME OF FIRM: Antisoma, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING        |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input checked="" type="checkbox"/> LABELING REVISION  |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE   |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW            |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input type="checkbox"/> OTHER (SPECIFY BELOW):        |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Consult requested for review of pregnancy and nursing mothers section of package insert before approval of NDA 22-273; PDUFA date September 19, 2008. The latest approved labeling is in the EDR. I will also attached the sponsor's original package insert along with the current FDA working copy of the proposed package insert in an email. Please comment/review the proposed package insert with respect to the sections referenced for MHT. The DDOP MO is Marty Cohen, the Pharm Tox reviewer is Doo Lee-Ham if you have questions regarding content. The current plan is to communicate to the sponsor prior to the PDUFA date. Please contact me if you have questions or need additional review time, 6-0621.

SIGNATURE OF REQUESTOR  
James M. Saunders

METHOD OF DELIVERY (Check one)  
 DFS       EMAIL       MAIL       HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER



**DEPARTMENT OF HEALTH & HUMAN SERVICES** Public Health Service

---

Pediatric and Maternal Health Staff  
Office of New Drugs  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Silver Spring, MD 20993  
Tel 301-796-0700  
FAX 301-796-9744

### **Maternal Health Team Label Review**

**Date:** 12-4- 2008 **Date Consulted:** 8-14- 2008

**From:** Leyla Sahin, M.D.  
Medical Officer, Maternal Health Team (MHT)  
Pediatric and Maternal Health Staff

**Through:** Karen Feibus, MD  
Team Leader, Maternal Health Team (MHT)  
Pediatric and Maternal Health Staff

Lisa Mathis, MD  
Associate Director, Pediatric and Maternal Health Staff

**To:** Division of Drug Oncology Products (DDOP)

**Drug:** Oral Fludarabine; NDA 22-273

**Subject:** Pregnancy and Nursing Mothers labeling

**Materials Reviewed:** Pregnancy and Nursing Mothers subsections of Oral Fludarabine-labeling.

**Consult Question:** Please review sections of the proposed label as they relate to pregnancy and lactation.

### **INTRODUCTION**

On November 19, 2007, Antisoma, Inc. submitted a new drug application (NDA) to the Division of DDOP for fludarabine tablets. Fludarabine for injection is marketed by a different sponsor.

Fludarabine is an antineoplastic agent indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen.

On August 14, 2008, the DDOP consulted the Maternal Health Team (MHT) to review the pregnancy and nursing mothers section of the oral fludarabine package insert, and provide comment. The MHT had previously sent labeling recommendations to the Division by e-mail on September 11, 2008 and had participated in the labeling meeting on the same day. This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of labeling for documentation in DFS.

## **BACKGROUND**

The Maternal Health Team (MHT) is working to develop a more consistent and clinically useful approach to the Pregnancy and Nursing Mothers subsections of labeling. This approach complies with current regulations but incorporates "the spirit" of the Proposed Pregnancy and Lactation Labeling Rule (published on May 28, 2008).

As part of the labeling review, the MHT reviewer conducts a literature search to determine if relevant published pregnancy and lactation data are available that would add clinically useful information to the pregnancy and nursing mothers label subsections. In addition, the MHT presents available animal data, in the pregnancy subsection, in an organized, logical format that makes it as clinically relevant as possible for prescribers. This includes expressing animal data in terms of species exposed, timing and route of drug administration, dose expressed in terms of human dose equivalents (with the basis for calculation), and outcomes for dams and offspring. For nursing mothers, when animal data are available, only the presence or absence of drug in milk is considered relevant and presented in the label, not the amount.

This review provides revisions to the sponsor's proposed Pregnancy and Nursing Mothers subsections of oral fludarabine labeling.

## **SUBMITTED MATERIAL**

### **Sponsor's Proposed Pregnancy and Nursing Mothers Labeling**

#### **5 WARNINGS AND PRECAUTIONS**

b(4)

b(4)

**RECOMMENDATIONS**

Provided below are the MHT's recommended revisions to the sponsor's proposed labeling.

**5 WARNINGS AND PRECAUTIONS**

b(4)

b(4)

*Reviewer comment: The Maternal Health Team requests that the Pharmacology review team calculate multiples of human exposures to describe the animal doses. If for some reason this is not possible, then the animal doses may remain in 8.1 Pregnancy, but the labeling subsection should include a statement explaining to the reader that it was not possible to calculate human dose/exposure multiples.*

b(4)

## CONCLUSIONS

While the Proposed Pregnancy and Lactation Labeling Rule, published May 2008, is in the clearance process, the MHT is structuring the Pregnancy and Nursing Mothers label information in a way that is in the spirit of the Proposed Rule while still complying with current regulations. The goal of this restructuring is to make the pregnancy and lactation sections of labeling a more effective communication tool for clinicians.

The MHT's recommended labeling for oral fludarabine is provided on page 3 and 4 of this review.

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

/s/  
-----

Leyla Sahin  
12/9/2008 09:06:40 AM  
MEDICAL OFFICER

Karen Feibus  
12/9/2008 04:18:57 PM  
MEDICAL OFFICER  
I have reviewed and concur with this review

Lisa Mathis  
12/11/2008 02:23:47 PM  
MEDICAL OFFICER

Appears This Way  
On Original



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

Date: November 17, 2008

To: Robert L. Justice, M.D., Director  
**Division of Drug Oncology Products**

Through: Jodi Duckhorn, MA, Team Leader  
**Patient Labeling and Education Team  
Division of Risk Management**

From: Nancy Carothers, RN, BA  
Patient Product Information Specialist  
**Patient Labeling and Education Team  
Division of Risk Management**

Subject: DRISK Review of Patient Labeling (Patient Package Insert

Drug Name(s): Oral Fludarabine Tablets Phosphate Film-Coated tablets

Application Type/Number: NDA 22-273

Applicant/sponsor: Xanthus Pharmaceuticals, Inc.

OSE RCM #: 2008-374

*Appears This Way  
On Original*

## INTRODUCTION

Fludarabine Phosphate Film-Coated tablets is an anti-cancer medicine indicated for the treatment of B-cell chronic lymphocytic leukemia (CLL). It is indicated for patients who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen.

The sponsor submitted a one and-a-half page "Patient Information" leaflet (PPI) on August 11, 2008. The Division of Drug Oncology Products requested that the Patient Labeling and Education Team review the Patient Package Insert (PPI) for the oral dose regimen. This review was written in response to that request.

## MATERIAL REVIEWED

- Fludarabine Tablets Phosphate Film-Coated 10 mg tablets Package Insert (PI) submitted by the Sponsor on August 8, 2008 and further revised by the reviewing division throughout the current review cycle.
- Fludarabine Tablets Phosphate Film-Coated 10 mg tablets Patient Package insert (PPI) submitted by the Sponsor on August 8, 2008 and further revised by the reviewing division throughout the current review cycle.

## DISCUSSION

The purpose of the patient-directed labeling is to enhance appropriate use of and to provide important risk information about medicines. Our recommended changes are consistent with current research to improve risk communication to a broad audience, including those with lower literacy.

The PPI submitted by the sponsor has a Flesch Kinkaid grade level of 8.7, and a Flesch Reading Ease score of 50.7 %. To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60% (60% corresponds to an 8<sup>th</sup> grade reading level). This revised version has a Flesch Kinkaid grade level of 7.8 and a Flesch Reading Ease score of 59.5%. Jodi – new score.

In our review of the PPI, we have:

- simplified wording and clarified concepts where possible,
- made information in the PPI consistent with the PI,
- removed unnecessary and redundant information.
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006).

In 2008, The American Society of Consultant Pharmacists Foundation in collaboration with The American Foundation for the Blind published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. They recommend using fonts such as Arial, Verdana, or APHont to make medical information more accessible for patients with low vision. We have reformatted the PPI document using the font APHont, which was developed by the American Printing House for the Blind specifically for low vision readers.

See the attached document for our recommended revisions to the PPI. Comments to the

review division are ***bolded, underlined, and italicized***.

We are providing to the review division a marked-up and clean copy of the revised PPI.

## CONCLUSIONS AND RECOMMENDATIONS

- The PI contains a Black Box Warning about CNS toxicity, fatal autoimmune hemolytic anemia and fatal pulmonary toxicity. The warning is intended for medical management of the patient. However, if these warnings increase safe use by helping patients assess their response to Fludarabine Tablets, then the warnings should be included in the PPI. Serious and significant risk information should be prominently placed in the PPI in the, “What is the most important information I should know about Fludarabine Tablets?” section.
- The statement to use birth control measures for at least 2 weeks after stopping treatment is in the original PPI, but is not in the PI and should be added to the PI if it will be retained in the PPI. The PI and PPI must be consistent. Also, the PI states, under *Nonclinical Toxicology*, that there are changes in male fertility in animal studies (mice, rats, and dogs). The PI warns women to put off pregnancy. If it is appropriate to warn male patients to put off pregnancy with their partner until well after their treatment has ended or to store sperm for future use, then this should be added to the PI and PPI.
- The instructions for taking a missed dose and the action to take in case of an overdose are not included in the PI. If the patient is under-dosed because of missed doses, the effectiveness of the agent may be impaired. There can be serious CNS toxicity and bone marrow suppression if the product is taken in high doses (Section 10.) Patients should be instructed on how to make up a missed dose and they should know what to do in case of an overdose e.g. contact their healthcare provider or local emergency department right away. If these directions are used in the PPI, then they must be added to the PI. The PI and PPI must be consistent.
- The section, “What should I avoid while taking Fludarabine Tablets?” should include advice on maintaining a safe environment for patients using this drug at home. These patients will be in a medically unsupervised setting and are often unfamiliar with the possible risks associated with handling and using chemotherapeutic/cytotoxic agents. This should include information on handling this drug safely. The PI states in section 16.3 (Handling and Disposal) to avoid skin, eye, inhalation, and mucous membrane exposure with this cytotoxic agent. If this information is used in the PPI, it must be added to the PI under the Patient Counseling Information. The PI and PPI must be consistent.
- This product has the potential to cause serious, even lethal, side effects and patients should be instructed on how to identify them. Most side effects, such as

infection and fatigue, can not be avoided and must be “managed.” This requires patients (and families) to be prompt in reporting side effects. For neutropenic patients, even a low-grade fever can be an indication of a serious infection because of their slower than normal response to infection. Patients should be instructed to check their temperature and if it is 100.5° F, or higher to call their healthcare provider right away. They should be told not to take any fever-reducing medicines until talking to their healthcare provider. This guideline is from the National Cancer Institute’s online advice, *Chemotherapy and You: Support for People with Cancer*. This information is not in the PI or PPI and if it is used in the PPI must be added to the PI for consistency.

- Stomatitis and diarrhea are included in the description of GI symptoms in the PI however; stomatitis is not in Table 2 (which represents the incidence of adverse reactions in Studies 1 and 2.) If stomatitis occurred at a rate comparable to other side effects then it should be included in the PPI. Diarrhea and abdominal and muscle pain did occur, according to Table 2, at similar rates as nausea and should be included as other side effects.
- We added the following statement to the end of the section on side effects.  
“Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.”  
  
This verbatim statement is required for all Medication Guides effective January 2008 (see 21 CFR 208.20 (b)(7)(iii); also see Interim Final Rule, Toll-Free Number for Reporting Adverse events on Labeling for Human Drug Products in Federal Register Vol. 73, No.2, p.402-404, 1/3/2008). Although not required for voluntary PPIs, like [TRADENAME], we recommend adding this language to all FDA-approved patient labeling for consistency.
- Cytotoxic agents are considered a hazardous waste and the guidelines for proper disposal and handling of Fludarabine Tablets should be included in the PPI since this product will be used in the home. Most patients and families will be unfamiliar with safe handling and disposal of these agents. The instructions for “safe handling” are provided in the PI and should be added to the PPI. The sponsor should provide instructions for safe disposal, using specific hazardous waste guidelines. See references 2-6 in the PI. These should be added to the PI and PPI. The PI and PPI must be consistent.

Please let us know if you have any questions.

11   Page(s) Withheld

       Trade Secret / Confidential (b4)

  ✓   Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

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

/s/

-----  
Nancy B Carothers  
11/18/2008 09:36:12 AM  
DRUG SAFETY OFFICE REVIEWER

Jodi Duckhorn  
11/18/2008 09:39:08 AM  
DRUG SAFETY OFFICE REVIEWER

Appears This Way  
On Original



*Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.*

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES  NO   
If yes, explain:

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES  NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO   
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES  NO

- Does the submission contain an accurate comprehensive index? YES  NO   
If no, explain:

- Was form 356h included with an authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. agent must sign.**

- Submission complete as required under 21 CFR 314.50? YES  NO   
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

- 1. This application is a paper NDA YES

- 2. This application is an eNDA or combined paper + eNDA YES   
This application is: All electronic  Combined paper + eNDA   
This application is in: NDA format  CTD format   
Combined NDA and CTD formats

- Does the eNDA, follow the guidance? (http://www.fda.gov/cder/guidance/2353fnl.pdf) YES  NO

**If an eNDA, all forms and certifications must be in paper and require a signature.**

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

- 3. This application is an eCTD NDA. YES

**If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.**

Additional comments:

- Patent information submitted on form FDA 3542a? YES  NO
- Exclusivity requested? YES,   x   Years 3 NO   
*NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.*
- Correctly worded Debarment Certification included with authorized signature? YES  NO   
**If foreign applicant, both the applicant and the U.S. Agent must sign the certification.**  
*NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."*
- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES  NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES  NO
- Is this submission a partial or complete response to a pediatric Written Request? YES  NO   
If yes, contact PMHT in the OND-IO
- Financial Disclosure forms included with authorized signature? YES  NO   
**(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)**  
*NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.*
- Field Copy Certification (that it is a true copy of the CMC technical section) YES  NO
- PDUFA and Action Goal dates correct in tracking system? YES  NO   
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers: IND 78,332 DMF 14924 DMF 20357
- Are the trade, established/proper, and applicant names correct in COMIS? YES  NO   
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s)   pIND meeting July 30, 2007   NO   
If yes, distribute minutes before filing meeting.

- Pre-NDA Meeting(s)? Date(s) \_\_\_\_\_ NO   
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) \_\_\_\_\_ NO   
If yes, distribute letter and/or relevant minutes before filing meeting.

**Project Management**

- If Rx, was electronic Content of Labeling submitted in SPL format? YES  NO   
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:  
Was the PI submitted in PLR format? YES  NO   
  
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES  NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES  NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS?  
N/A  YES  NO
- Risk Management Plan consulted to OSE/IO? N/A  YES  NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA  YES  NO

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

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES  NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES  NO

**Clinical**

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? YES  NO

**Chemistry**

- Did applicant request categorical exclusion for environmental assessment? YES  NO   
If no, did applicant submit a complete environmental assessment? YES  NO   
If EA submitted, consulted to EA officer, OPS? YES  NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES  NO
- If a parenteral product, consulted to Microbiology Team? YES  NO

ATTACHMENT

**MEMO OF FILING MEETING**

DATE: 01/16/08

NDA #: 22-273

DRUG NAMES: fludarabine phosphate

APPLICANT: ~~Xanthus Pharmaceuticals, Inc.~~ Antisoma, Inc. ( June 20, 2008 notification from Sponsor)

BACKGROUND: IV formulation is approved; this is a new dosage form (oral tablet)  
(Provide a brief background of the drug, (e.g., molecular entity is already approved and this NDA is for an extended-release formulation; whether another Division is involved; foreign marketing history; etc.)

ATTENDEES: Robert Justice, Ann Farrell, Gene Williams, Haripada Sarker, Chia-wen (Kiki) Ko, Doo Y Lee Ham, Martin Cohen, Nicholette Hemingway

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	Martin Cohen
Secondary Medical:	
Statistical:	Chia-Wen (Kiki)Ko
Pharmacology:	Doo Y Lee Ham
Statistical Pharmacology:	
Chemistry:	Josephine Jee
Environmental Assessment (if needed):	
Biopharmaceutical:	Gene Williams
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	
OPS:	
Regulatory Project Management:	Hemingway(Saunders 1/11/08)
Other Consults:	

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

CLINICAL FILE x REFUSE TO FILE

- Clinical site audit(s) needed? YES x NO   
If no, explain:
- Advisory Committee Meeting needed? YES, date if known maybe NO

- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

N/A  YES  NO

CLINICAL MICROBIOLOGY N/A  FILE  REFUSE TO FILE

STATISTICS N/A  FILE  REFUSE TO FILE

BIOPHARMACEUTICS FILE  REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES  NO

PHARMACOLOGY/TOX N/A  FILE  REFUSE TO FILE

- GLP audit needed? YES  NO

CHEMISTRY FILE  REFUSE TO FILE

- Establishment(s) ready for inspection? YES  NO

- Sterile product? YES  NO

- If yes, was microbiology consulted for validation of sterilization? YES  NO

**ELECTRONIC SUBMISSION:**

Any comments:

**REGULATORY CONCLUSIONS/DEFICIENCIES:**

**(Refer to 21 CFR 314.101(d) for filing requirements.)**

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
- No filing issues have been identified.
- Filing issues to be communicated by Day 74. List (optional):

**ACTION ITEMS:**

1.  Ensure that the review and chemical classification codes, as well as any other pertinent classification codes (e.g., orphan, OTC) are correctly entered into COMIS.
2.  If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3.  If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4.  If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5.  Convey document filing issues/no filing issues to applicant by Day 74.

James M. Saunders  
Regulatory Project Manager

Appears This Way  
On Original

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

/s/  
-----

James Saunders

10/3/2008 02:11:07 PM

CSO

Revised NDA Regulatory Filing Review (B1 instead of B2;  
Sponsor change; goal date extended)

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, October 01, 2008 10:07 PM  
**To:** 'Kris Piper'; 'Stanny BerghsClairmont'  
**Subject:** NDA 22-273

**Follow Up Flag:** Follow up  
**Due By:** Tuesday, September 30, 2008 12:00 AM  
**Flag Status:** Flagged

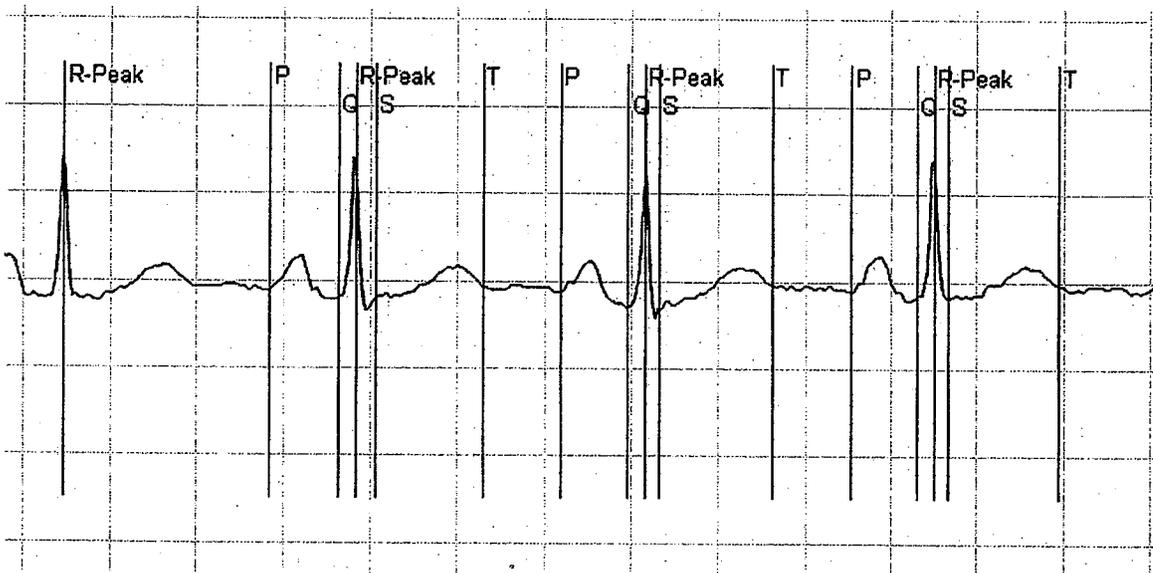
Hi Kris,

Please see the following request from the IRT team:

"For the QT-IRT to review the ECGs related to this application, the T annotations need to be changed in the xml file to T-offset annotations-please see self explanatory email from ECG warehouse below. You can contact Dr. Barry Brown at the ECG warehouse for further assistance."

*From the email:*

You'll notice that the T label is on the right side of the annotation marker drawn by ECG Warehouse. The T label would be drawn on the left side of the marker if it were a T-offset annotation. Unfortunately, this sponsor didn't use onset and offset type annotations for the T-wave. Instead, the sponsor used a "T wave occurs here" type annotation. If you want the ECG Warehouse to compute QT analysis scores for this study, the sponsor will need to change the T annotations to T-offset annotations.



Sincerely,

*James*

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/  
-----

James Saunders

10/2/2008 12:19:10 PM

Additional Information needed to review ECGs

Appears This Way  
On Original

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY ADDENDUM

DATE: September 29, 2008

TO: James Saunders, Regulatory Health Project Manager  
Martin Cohen, M.D., Medical Officer, Clinical Reviewer  
Ann Farrell, M.D., Deputy Director  
Division of Drug Oncology Products

THROUGH: Leslie K. Ball, M.D.  
Division Director  
Division Scientific Investigations

FROM: Tejashri Purohit-Sheth, M.D.  
Branch Chief, Good Clinical Practice Branch II  
Division of Scientific Investigations

SUBJECT: Update on Clinical Inspections

NDA: 22-273

APPLICANT: Antisoma Inc.

DRUG: fludarabine phosphate tablets

SUMMARY:

Fludarabine for injection was approved by the Agency in 1991 for Chronic Lymphocytic Leukemia

\_\_\_\_\_ Xanthus Pharmaceuticals, followed by Antisoma Inc., who submitted NDA 22-273 for the use of oral fludarabine in patients with Chronic Lymphocytic Leukemia. This new application \_\_\_\_\_ includes additional information from QT studies.

No clinical inspections have been requested of DSI in support of NDA 22-273, as there are no new pivotal studies in this current application. However, the Division of Drug Oncology Products requested the original Clinical Inspection Summary completed in 2001 by Dr. U, a then medical officer in DSI, in support of this NDA. DSI requested that the review division check their division files for the final, signed CIS; however, neither the review division nor DSI is able to locate a copy of the signed final version of the CIS.

A copy of the CIS from DSI generated on January 12, 2001 by Dr. Khin U, then a medical officer in DSI, summarizing the inspectional findings is provided below. Dr. U, currently a medical officer in the Division of Cardiovascular and Renal Products, has verified on September 29, 2008 that the CIS attached below is the final version of the 2001 CIS, albeit unsigned. This CIS summarizes inspectional findings from two clinical inspection sites: 1) Professor Sante Tura and 2) Professor Gregor E.G. Verhoef. The final classifications for both of these inspections have been verified in our DSI inspectional database as correct. The CIS attached below concluded that the data from the two sites was considered reliable. Please see the attached CIS for a full summary of inspectional findings.

b(4)

b(4)

5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

-----  
Tejashri Purohit-Sheth  
9/29/2008 05:32:48 PM  
MEDICAL OFFICER

Leslie Ball  
10/2/2008 11:38:26 AM  
MEDICAL OFFICER

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Monday, September 15, 2008 1:16 PM  
**To:** 'Kris Piper'  
**Subject:** Goal Date Extension

**Follow Up Flag:** Follow up  
**Due By:** Sunday, September 14, 2008 12:00 AM  
**Flag Status:** Flagged

**Attachments:** NDA 22273 Goal date extension.pdf

Hi Kris,

Please see the attached file which contains information that the goal date for NDA 22-273 has been extended due to the submission of your QT study. On another note, one of the members of the IRT team who reviews the QTc submission would like to arrange a telecon with you sometime tomorrow (Tuesday) if possible to make sure we're all on the same page. Are there any hours which are preferable to you?



NDA 22273 Goal  
date extension....

*James*

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

**PDUFA GOAL DATE EXTENSION**

NDA 22-273

Antisoma

Attention: J. Kris Piper, Senior Vice President  
Clinical Operations, Regulatory Affairs, and Quality Assurance  
300 Technology Square  
Cambridge, MA 02139

Dear J. Kris Piper:

Please refer to your November 19, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for fludarabine phosphate tablets for oral use.

On August 1, 2008, we received your July 31, 2008, major amendment to this application. The receipt date is within three months of the user fee goal date. Therefore, we are extending the goal date by three months to provide time for a full review of the submission. The extended user fee goal date is December 19, 2008.

If you have questions, call James M. Saunders, Regulatory Project Manager, at (301) 796-0621.

Sincerely,

*{See appended electronic signature page}*

CDR James M. Saunders  
Senior Regulatory Management Officer  
Division of Drug Oncology Products  
Office of Oncology Products  
Center for Drug Evaluation and Research

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
9/15/2008 12:18:21 PM

appears this way  
On Original

**Saunders, James**

---

**From:** Saunders, James  
**Sent:** Tuesday, September 09, 2008 11:44 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22273 / ECG waveforms' annotation correction  
**Follow Up Flag:** Follow up  
**Due By:** Tuesday, September 09, 2008 12:00 AM  
**Flag Status:** Flagged

Hi Kris,

I have another request form the IRT team:

*According to our clinical reviewer, in order to perform our review of ECGs submitted to the warehouse for this study, we would require that the sponsor place labels for annotations of Q/QRS onset and T wave offset in the XML files. Currently there are only peak annotations. Since the markers for the onsets and offsets are present (see the example below), only the labels need to be fixed in the XML file.*

*For further assistance, please have the sponsor contact Barry Brown at Mortara Instrument at: [barry.brown@mortara.com](mailto:barry.brown@mortara.com)*

 cid:image001.jpg@01C90F64.EF11FED0

*James*

9/30/2008

**FDA/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

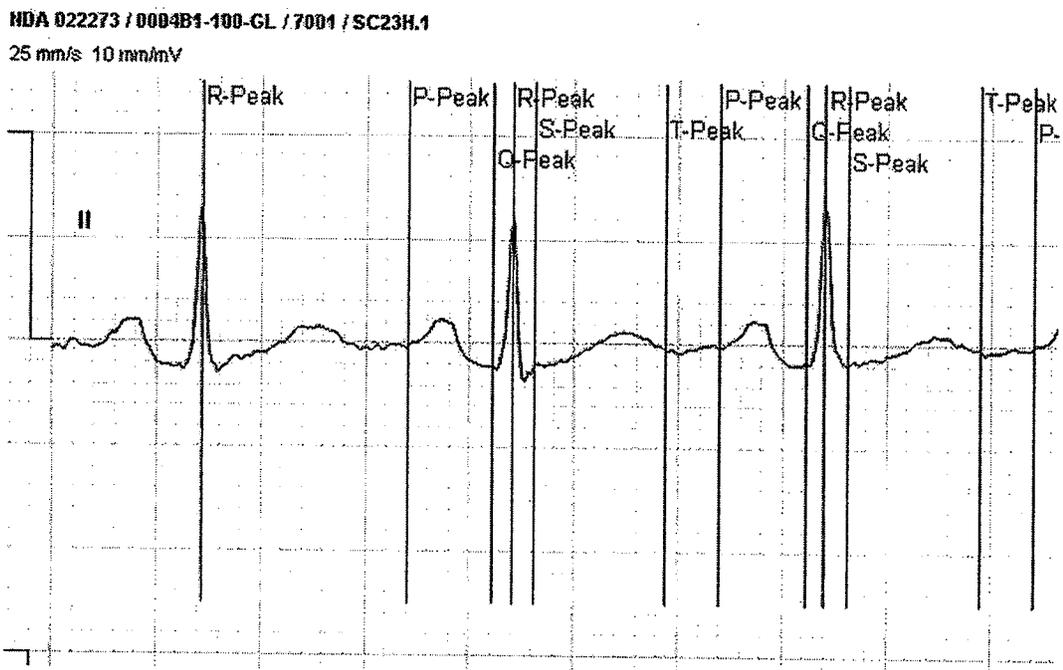
Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Tuesday, September 09, 2008 11:47 PM  
**To:** 'Kris Piper'  
**Subject:** NDA22273 / ECGs

Hi Kris,

*In case you could not see the attached in my previous email*



**James**  
**FDA/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

9/30/2008

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

/s/

-----  
James Saunders  
9/30/2008 03:28:37 PM

Appears This Way  
On Original

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Tuesday, September 09, 2008 11:22 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273

Hi Kris,

I have a request from a member of the IRT Team.

*Please ask the sponsor to submit raw datasets of ECG and pkconc in SAS XPT format.  
ECG: includes intervals of replicates (about 4005 observations) and demographic,  
treatment group, and date/time etc.  
PKCONC: includes PK concentrations of the drug and its metabolites*

Thanks,  
James

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/  
-----

James Saunders  
12/9/2008 08:27:47 PM  
archived email from September 9, 2008

Appears This Way  
On Original

**Saunders, James**

---

**From:** Kris Piper [Kris.Piper@antisoma.com]  
**Sent:** Monday, September 08, 2008 4:40 PM  
**To:** Saunders, James  
**Subject:** RE: NDA 22-273  
**Follow Up Flag:** Follow up  
**Flag Status:** Red  
**Attachments:** 20080908163724.pdf; Phase 4 synopsis for FDA2008Sept08 FINAL.PDF

Hello James,

Our proposal for a post-approval study to convert from accelerated to full approval is attached. Hopefully this addresses all the points raised in your message below. We will submit this as a formal amendment as well.

Kind regards,  
Kris

---

**From:** Saunders, James [mailto:James.Saunders@fda.hhs.gov]  
**Sent:** Wednesday, August 20, 2008 4:57 PM  
**To:** Kris Piper  
**Subject:** NDA 22-273

Hi Kris,

The QT study is considered a major amendment and will extend the regulatory time clock; however the review team will attempt to finish the review quickly.

Please submit your proposal for a study to convert from accelerated to full approval in the form of a protocol synopsis. The proposal should provide details such as study design, endpoints, patient population, date of protocol submission to the FDA, study start date, and study completion date, and date of study submission to the FDA.

Thanks,

*James*

CDR James M. Saunders

Senior Regulatory Management Officer

OND/OODP

Division of Drug Oncology Products

10903 New Hampshire Avenue

12/12/2008

WO-22 Room 2369

Silver Spring, Maryland 20993

(301) 796-0621

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

---

This email has been scanned by the MessageLabs Email Security System.  
For more information please visit <http://www.messagelabs.com/email>

---

Appears This Way  
On Original

**REQUEST FOR STUDY ENDPOINTS CONSULTATION**

**TO: Study Endpoints and Labeling (SEALD)**  
CDER/OND-IO White Oak Bldg 22, Mail Drop 6411  
SEALD.ENDPOINTS@FDA.HHS.GOV

**FROM: Review Division: DDOP**  
Medical Reviewer: Martin Cohen, M.D.  
Project Manager: James M. Saunders, RPM

<b>DATE OF CONSULT REQUEST</b> August 14, 2008	<b>Application# IND/NDA/BLA#</b> NDA 22-273	<b>LETTER # OR SUBMISSION #</b>	<b>TYPE OF DOCUMENT</b> (Meeting; Protocol/SPA; PDUFA Product Review)	<b>REQUESTED SEALD COMPLETION DATE</b> September 12, 2008 PDUFA date: September 19, 2008
---	--	---------------------------------	--	---

<b>DRUG ESTABLISHED NAME</b> Fludarabine Phosphate	<b>DRUG TRADE NAME</b>	<b>NAME OF SPONSOR</b> Antisoma, Inc.	<b>SPONSOR SUBMIT DATE</b> November 19, 2007
---	------------------------	--	---

**DEVELOPMENT PHASE (E.G., pre-IND/NDA/BLA; IND/BB-IND Phase I, II, III; NDA/BLA):**  
**GOAL DATE (if NDA/BLA/SPA):** September 19, 2008  
**ELECTRONIC LINK (if applicable):** ED R  
**BACKGROUND PACKAGE (deliver PAPER to CDER SEALD Endpoints mailbox in Bldg 22, Rm 6411):**

**MEETINGS (IF APPLICABLE) (please send invite to SEALD.ENDPOINTS@FDA.HHS.GOV)**  
 Meeting type (A, B, C):  
 Internal Meeting date:  
 Sponsor/Industry Meeting date:

**PLEASE make certain the background-briefing package IS INCLUDED WITH THIS CONSULT. It should contain the following applicable information needed to start Study Endpoints Review: PROTOCOL OR STUDY ID; ENDPOINT CONCEPT(S); INSTRUMENT(S); INDICATION(S); STUDY POPULATION(S); PRIOR RELATED REVIEWS.**  
**Division PM, please provide the following specific information on this consult form:**

Instrument(s):  
 Indication(s):

Specific Questions/Comments for SEALD: We have had three labeling meetings, and have made CMC, Clinical and Non-Clinical revisions to the current label. We have a consult with Maternal Health to review the Pregnancy/ Nursing mothers section of the label. Our next meeting will have their input as will as Biopharm. I will send you the original label as well as the latest draft FDA label for your review. I will also invite you to the next labeling meetings if appropriate. Should there be any questions, you may call me at (301)796-0621.

Appears This Way  
On Original

Requester  
 James M. Saunders, [James.Saunders@fda.hhs.gov](mailto:James.Saunders@fda.hhs.gov)  
 (301) 796-0621  
 WO 22 Room 2369

Name/Phone number/email address/office location	

Glossary:

**Concept:** The specific goal of a measurement (i.e. the *thing* that is to be measured by a PRO instrument).

**Instrument:** A means to capture data (e.g. questionnaire, diary) plus all the information and documentation that supports its use. Generally, that includes clearly defined methods and instructions for administration or responding, a standard format for data collection, and well-documented methods for scoring, analysis, and interpretation of results.

Appears This Way  
On Original

# 22 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

-----  
Kimberly Shiley  
9/3/2008 04:48:39 PM  
CSO  
SEALD comments sent to review division on 9-3-08.

Jeanne Delasko  
9/3/2008 04:53:39 PM  
CSO

Laurie Burke  
9/4/2008 12:18:29 PM  
INTERDISCIPLINARY

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, August 20, 2008 4:57 PM  
**To:** Kris Piper  
**Subject:** NDA 22-273

**Follow Up Flag:** Follow up  
**Due By:** Wednesday, August 20, 2008 12:00 AM  
**Flag Status:** Red

Hi Kris,

The QT study is considered a major amendment and will extend the regulatory time clock; however the review team will attempt to finish the review quickly.

Please submit your proposal for a study to convert from accelerated to full approval in the form of a protocol synopsis. The proposal should provide details such as study design, endpoints, patient population, date of protocol submission to the FDA, study start date, and study completion date, and date of study submission to the FDA.

Thanks,

*James*

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/20/2008 05:27:29 PM

Appears This Way  
On Original



**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Date:** August 04, 2008

**To:** Robert Justice, MD  
Director, Division of Oncology Products

**Thru:** Linda Kim-Jung, PharmD., Team Leader  
Denise Toyer, PharmD., Deputy Director  
Division of Medication Error Prevention and Analysis

**From:** Walter Fava, R.Ph., Safety Evaluator  
Division of Medication Error Prevention and Analysis and Analysis

**Subject:** Label and Labeling Review

**Drug Name(s):** Fludarabine Phosphate Tablets 10 mg

**Application Type/Number:** NDA: 22-273

**Applicant:** Xanthus Pharmaceuticals, Inc.

**OSE RCM #:** 2008-374

\*\*This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.\*

Appears This Way  
On Original

## CONTENTS

EXECUTIVE SUMMARY .....	1
1 BACKGROUND.....	1
1.1 INTRODUCTION .....	1
1.2 REGULATORY HISTORY .....	1
1.3 PRODUCT INFORMATION .....	2
2 METHODS AND MATERIALS .....	2
2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES .....	3
3 RESULTS.....	3
4 DISCUSSION .....	4
4.1 LABELS AND LABELING RISK ASSESSMENT .....	4
5 CONCLUSIONS .....	4
6 RECOMMENDATIONS .....	5
6.1 COMMENTS TO THE DIVISION .....	5
6.2 COMMENTS TO THE APPLICANT .....	5
7 REFERENCES .....	6
APPENDICES.....	8

Appears This Way  
On Original

## EXECUTIVE SUMMARY

Our analysis of the container labels, carton, and package insert labeling for Fludarabine Phosphate tablets noted several areas of concern with respect to the presentation of important information. Specifically, with respect to the package insert labeling, we recommend that the presentation of the dosing information in Table 1 be changed to increase comprehensibility and minimize confusion. This is particularly important due to the difference in the usual recommended dose of the oral tablets (40 mg/m<sup>2</sup>), and the intravenous dosage formulation (25 mg/m<sup>2</sup>). In conjunction with these changes, we recommend that the Applicant implement an educational plan to explain to practitioners the dosing differences between the new oral formulation and the currently marketed intravenous formulations. See Section 6 for complete details of these recommendations.

## 1 BACKGROUND

### 1.1 INTRODUCTION

This review is in response to a request from the Division of Oncology Products to evaluate the labels and labeling for Fludarabine Phosphate 10 mg tablets. This is a new oral dosage formulation for Fludarabine Phosphate, which is currently only available as an parenteral intravenous product from several manufacturers.

### 1.2 REGULATORY HISTORY

Currently, the only approved dosage form of Fludarabine Phosphate is the intravenous formulation, which is available as the reference listed drug product, Fludara, and as generic therapeutic equivalents from multiple manufacturers. The chart below summarizes the information about currently marketed Fludarabine Phosphate.

Proprietary Name	Strength	Dosage Form	Usual Adult Dose	Usual Frequency of Administration	Manufacturer
Fludara	50 mg/vial	Lyophilized powder for injection	25 mg/m <sup>2</sup>	Infused intravenously over 30 minutes daily for five days and repeated every 28 days	Bayer Healthcare
Fludara	50 mg/2 mL (25 mg/mL)	Injectable solution	25 mg/m <sup>2</sup>	Infused intravenously over 30 minutes daily for five days and repeated every 28 days	Ebewe Pharma
Fludarabine Phosphate	50 mg/vial	Lyophilized powder for injection	25 mg/m <sup>2</sup>	Infused intravenously over 30 minutes daily for five days and repeated every 28 days	Multiple
Fludarabine Phosphate	50 mg/2 mL (25 mg/mL)	Injectable Solution	25 mg/m <sup>2</sup>	Infused intravenously over 30 minutes daily for five days and repeated every 28 days	Multiple

### 1.3 PRODUCT INFORMATION

Fludarabine phosphate is an antineoplastic agent indicated for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating-agent containing regimen. The usual recommended dose is 40 mg/m<sup>2</sup> administered once daily for five consecutive days by the oral route. Each five-day course of treatment should commence every 28 days. The proposed package insert shows the number of tablets to be administered based on body surface area in Table. It is recommended that the dose be reduced by 20% in adult patients with moderate renal impairment (creatinine clearance 30 mL/min/1.73 m<sup>2</sup> – 70 mL/min/1.73 m<sup>2</sup>).

Fludarabine phosphate will be supplied in 10 mg tablets that are film-coated, capsule shaped, salmon pink in color, and marked on one side with 'LN' in a regular hexagon, and will be packaged in containers holding blister strips containing 5 tablets per strip in packages of 15 and 20 tablets.

## 2 METHODS AND MATERIALS

This section describe the methods and materials used by the Division of Medication Error Prevention and Analysis medication error staff to conduct a label, labeling, and/or packaging risk assessment (see 2.2 Container Label, Carton Labeling, and Insert Labeling Risk Assessment). The primary focus of the assessments is to identify and remedy potential sources of medication error prior to drug approval. The Division of Medication Error Prevention and Analysis defines a medication error as any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer.<sup>4</sup>

The label and labeling of a drug product are the primary means by which practitioners and patients (depending on configuration) interact with the pharmaceutical product. The carton labels and container labeling communicate critical information including proprietary and established name, strength, form, container quantity, expiration, and so on. The insert labeling is intended to communicate to practitioners all information relevant to the approved uses of the drug, including the correct dosing and administration.

Given the critical role that the label and labeling has in the safe use of drug products, it is not surprising that 33 percent of medication errors reported to the USP-ISMP Medication Error Reporting Program may be attributed to the packaging and labeling of drug products, including 30 percent of fatal errors.<sup>5</sup>

Because the Division of Medication Error Prevention and Analysis staff analyze reported misuse of drugs, the DMEPA staff are able to use this experience to identify potential errors with all medication similarly packaged, labeled or prescribed. The Division of Medication Error Prevention and Analysis uses FMEA and the principles of human factors to identify potential sources of error with the proposed product labels and insert labeling, and provided recommendations that aim at reducing the risk of medication errors.

For this product the Applicant submitted on May 19, 2008, the following labels and insert labeling for the Division of Medication Error Prevention and Analysis review (see Appendix B, C and D for images):

- Container: 10 mg (15 tablet and 20 tablet package)
- Carton: 10 mg (15 tablet and 20 tablet carton)

---

<sup>4</sup> National Coordinating Council for Medication Error Reporting and Prevention. <http://www.nccmerp.org/aboutMedErrors.html>. Last accessed 10/11/2007.

<sup>5</sup> Institute of Medicine. Preventing Medication Errors. The National Academies Press: Washington DC. 2006. p275.

- Blister strip label (5 tablets per strip)
- Package insert (no image)

## **2.1 ADVERSE EVENT REPORTING SYSTEM (AERS) SELECTION OF CASES**

Because Fludarabine Phosphate is currently marketed as an injectable product, on July 16, 2008, DMEPA conducted a search of the Adverse Event Reporting System (AERS) to identify post-marketing safety reports of medication errors that could relate to the proposed labels and labeling of this product. Analysis of these reports is used to identify areas of improvement related to the label and labeling of the proposed Fludarabine Phosphate film-coated tablets.

The MedDRA High Level Group Term (HLGT) "Medication Errors" and the tradename "Fludara", verbatim term 'Flud%', and active ingredients "Fludarabine Phosphate" were used as search criteria.

## **3 RESULTS**

### **3.1 AERS SEARCH**

Our search of AERS identified thirteen cases of medication errors involving the intravenous dosage form of Fludarabine Phosphate. Four cases were wrong drug errors involving name confusion. In three cases, Fludara was confused with the two other oncology drug products: FUDR (n = 2), and 5FU (n = 1). Acronyms and abbreviations for chemotherapy agents are known to cause confusion in oncology practice settings<sup>6</sup>, and we are limited in our ability to prevent name confusion with currently employed naming acronyms and Fludarabine Phosphate. In the fourth case, Fludara was confused with flumadine (n = 1) due to a knowledge deficit on the part of the prescriber.

One actual and six potential medication error cases involve look-alike packaging between generic Fludarabine Phosphate manufactured by Teva Pharmaceuticals and other chemotherapy agents manufactured by Teva Pharmaceuticals. However, Fludarabine Phosphate tablets will be manufactured by Bayer, which minimizes the look-alike packaging concerns with the tradename of the Teva product line. The six potential medication error cases involving look-alike packaging within the Teva product line, are being monitored as part of our routine postmarketing surveillance within the Division of Medication Error Prevention and Analysis.

The final two medication errors involved improper doses of Fludara but did not provide enough detail to determine causality. However, the dosing and administration labeling instructions for Fludarabine Phosphate are clear and comprehensible, and we do not anticipate similar dosing errors to occur.

### **3.2 CONTAINER LABEL**

1. No comments at this time.

### **3.3 CARTON LABELING**

1. No comments at this time.

### **3.4 BLISTER STRIP LABEL**

1. No comments at this time.

---

<sup>6</sup> M. Cohen, et. al., Preventing medication errors in cancer chemotherapy. American Journal of Health System Pharmacists, 53 (7):737-746.

### **3.5 PACKAGE INSERT LABELING**

1. The presentation of the information in Table 1 under Section 1 'Dosage and Administration' is ambiguous and difficult to interpret.
2. The usual recommended adult dose is  $40 \text{ mg/m}^2$ , which is different from the usual recommended dose of the approved intravenous dosage formulations currently on the market.
3. There are numerical values throughout the package insert which are not immediately followed by their corresponding unit of measure.

## **4 DISCUSSION**

### **4.1 LABELS AND LABELING RISK ASSESSMENT**

Our review noted that the usual recommended dose of the intravenous products is  $25 \text{ mg/m}^2$ , whereas the usual recommended dose for the oral dosage form is  $40 \text{ mg/m}^2$ . It is therefore important for healthcare providers to be educated about this dosing difference when the product is introduced into the marketplace, in order to avoid medication errors related to incorrect dosing of the oral tablets.

We also note that the dosing information presented in Table 1 is confusing and provides unnecessary information to practitioners who only need to correlate the body surface area of their patient to the correct dose to be administered (in milligrams) (see Appendix E). Including a dosage range in the middle column entitled 'Calculated Total Dose Based on BSA' is not useful in a clinical practice setting. In our opinion, it is also confusing to present both the number of tablets to be administered beside the corresponding dose. Presenting only the dose in milligrams is a more optimal presentation since Fludarabine Phosphate tablets are only available in one strength (10 mg), which facilitates easy calculation of the number of tablets based on the milligram dose provided.

Additionally, we identified several sections which present numerical data that is not immediately followed by the corresponding unit of measure. Numerical values immediately followed by their corresponding unit of measure provides clarity and makes the data easier to understand.

## **5 CONCLUSIONS**

Our analysis of the container labels, carton, and package insert labeling for Fludarabine Phosphate tablets noted several areas of concern with respect to the presentation of important information. Specifically, with respect to the package insert labeling, we found that the presentation of the dosing information in Table 1 is confusing and provides unnecessary information for practitioners. Clear presentation of dosing information is particularly important due to the difference in the usual recommended dose of the oral tablets ( $40 \text{ mg/m}^2$ ), and the intravenous dosage formulation ( $25 \text{ mg/m}^2$ ) which is currently marketed. Based on the difference in dosing between the two dosage forms, we believe it is important for the Applicant to implement an educational plan to explain to practitioners the dosing differences between the new oral formulation and the currently marketed intravenous formulations. See Section 6 for complete details of these recommendations.

## 6 RECOMMENDATIONS

### 6.1 COMMENTS TO THE DIVISION

We note that the dose of Fludarabine Phosphate tablets (40 mg/m<sup>2</sup>), and the dose of Fludarabine Phosphate intravenous solution (25 mg/m<sup>2</sup>) differ, which presents the potential for confusion that may lead to medication errors involving improper dosing. In addition to the package insert labeling changes described in this review, we are recommending the Applicant implement an educational campaign to minimize the the potential for confusion after this product is introduced into the market.

We believe the risks we have identified can be addressed and mitigated prior to drug approval, and provide recommendations in section 6.2 that aim at reducing the risk of medication errors.

We would appreciate feedback of the final outcome of this review. We would be willing to meet with the Division for further discussion, if needed. Please copy the Division of Medication Error Prevention and Analysis on any communication to the Applicant with regard to this review. If you have any questions or need clarification, contact Sandra Griffith, Project Manager, at 301-796-2445.

### 6.2 COMMENTS TO THE APPLICANT

Overall, our Risk Assessment is limited by our current understanding of medication errors and causality. The successful application of Failure Modes and Effect Analysis depends upon the learning gained for a spontaneous reporting program. It is quite possible that our understanding of medication error causality would benefit from unreported medication errors; and, that this understanding could have enabled the Staff to identify vulnerability in the proposed name, packaging, and labeling that was not identified in this assessment. To help minimize this limitation in future assessments, we encourage the Applicant to provide the Agency with medication error reports involving their marketed drug products regardless of adverse event severity.

#### 6.2.1 Carton Labeling

1. No comments at this time

### 6.3 PACKAGE INSERT LABELING

1. Delete the second column in Table 1 entitled \_\_\_\_\_ under Section 2 'Dosage and Administration'. The information in the second column is unnecessary and separates the body surface area from the corresponding dosage in milligrams, which is the most important information practitioners need to know.
2. \_\_\_\_\_ Greater clarity would also be provided if the milligram unit of measure followed each numerical dose in the table.
3. Include border lines for each row of Table 1 to make it easier for practitioners to read.
4. Present all numerical data throughout the package insert with the units of measure immediately following the corresponding numerical value to increase comprehensibility of important information and to minimize confusion.
5. Implement an educational plan to inform healthcare providers about the difference in the usual recommended dose of the oral tablets (40 mg/m<sup>2</sup>) compared to the intravenous formulations currently marketed (25 mg/m<sup>2</sup>), in order to minimize the risk of medication errors related to incorrect dosing.

b(4)

b(4)

## 7 REFERENCES

### 1. *Adverse Events Reporting System (AERS)*

AERS is a database application in CDER FDA that contains adverse event reports for approved drugs and therapeutic biologics. These reports are submitted to the FDA mostly from the manufacturers that have approved products in the U.S. The main utility of a spontaneous reporting system that captures reports from health care professionals and consumers, such as AERS, is to identify potential postmarketing safety issues. There are inherent limitations to the voluntary or spontaneous reporting system, such as underreporting and duplicate reporting; for any given report, there is no certainty that the reported suspect product(s) caused the reported adverse event(s); and raw counts from AERS cannot be used to calculate incidence rates or estimates of drug risk for a particular product or used for comparing risk between products.

### 2. *Micromedex Integrated Index (<http://weblern/>)*

Contains a variety of databases covering pharmacology, therapeutics, toxicology and diagnostics.

### 3. *Phonetic and Orthographic Computer Analysis (POCA)*

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. This is a database which was created for The Division of Medication Error Prevention and Analysis, FDA.

### 4. *Drug Facts and Comparisons, online version, St. Louis, MO (<http://weblern/>)*

Drug Facts and Comparisons is a compendium organized by therapeutic Course; contains monographs on prescription and OTC drugs, with charts comparing similar products.

### 5. *AMF Decision Support System [DSS]*

DSS is a government database used to track individual submissions and assignments in review divisions.

### 6. *Division of Medication Errors Prevention and Analysis proprietary name consultation requests*

This is a list of proposed and pending names that is generated by the Division of Medication Error Prevention and Analysis from the Access database/tracking system.

### 7. *Drugs@FDA (<http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm>)*

Drugs@FDA contains most of the drug products approved since 1939. The majority of labels, approval letters, reviews, and other information are available for drug products approved from 1998 to the present. Drugs@FDA contains official information about FDA approved brand name and generic drugs and therapeutic biological products; prescription and over-the-counter human drugs and therapeutic biologics, discontinued drugs and "Chemical Type 6" approvals.

### 8. *Electronic online version of the FDA Orange Book (<http://www.fda.gov/cder/ob/default.htm>)*

Provides a compilation of approved drug products with therapeutic equivalence evaluations.

9. **WWW location** <http://www.uspto.gov>.

Provides information regarding patent and trademarks.

10. **Clinical Pharmacology Online** (<http://weblern/>)

Contains full monographs for the most common drugs in clinical use, plus mini monographs covering investigational, less common, combination, nutraceutical and nutritional products. Provides a keyword search engine.

11. **Data provided by Thomson & Thomson's SAEGIS™ Online Service, available at [www.thomson-thomson.com](http://www.thomson-thomson.com)**

The Pharma In-Use Search database contains over 400,000 unique pharmaceutical trademarks and tradenames that are used in about 50 countries worldwide. The data is provided under license by IMS HEALTH.

12. **Natural Medicines Comprehensive Databases** (<http://weblern/>)

Contains up-to-date clinical data on the natural medicines, herbal medicines, and dietary supplements used in the western world.

13. **Stat!Ref** (<http://weblern/>)

Contains full-text information from approximately 30 texts. Includes tables and references. Among the database titles are: Handbook of Adverse Drug Interactions, Rudolphs Pediatrics, Basic Clinical Pharmacology and Dictionary of Medical Acronyms Abbreviations.

14. **USAN Stems** (<http://www.ama-assn.org/ama/pub/category/4782.html>)

List contains all the recognized USAN stems.

15. **Red Book Pharmacy's Fundamental Reference**

Contains prices and product information for prescription, over-the-counter drugs, medical devices, and accessories.

16. **Lexi-Comp** ([www.pharmacist.com](http://www.pharmacist.com))

A web-based searchable version of the Drug Information Handbook.

17. **Medical Abbreviations Book**

Contains commonly used medical abbreviations and their definitions.

Appears This Way  
On Original

## APPENDICES

### Appendix A:

The Medication Error Staff consider the spelling of the name, pronunciation of the name when spoken, and appearance of the name when scripted. The Division of Medication Error Prevention and Analysis also compare the spelling of the proposed proprietary name with the proprietary and established name of existing and proposed drug products because similarly spelled names may have greater likelihood to sound similar to one another when spoken or look similar to one another when scripted. The Medication Error Staff also examine the orthographic appearance of the proposed name using a number of different handwriting samples. Handwritten communication of drug names has a long-standing association with drug name confusion. Handwriting can cause similarly *and* dissimilarly spelled drug name pairs to appear very similar to one another and the similar appearance of drug names when scripted has led to medication errors. The Medication Error Staff apply their expertise gained from root-cause analysis of such medication errors to identify sources of ambiguity within the name that could be introduced when scripting (i.e. "T" may look like "F," lower case 'a' looks like a lower case 'u,' etc), along with other orthographic attributes that determine the overall appearance of the drug name when scripted (see detail in Table 1 below). Additionally, since verbal communication of medication names is common in clinical settings, the Medication Error Staff compare the pronunciation of the proposed proprietary name with the pronunciation of other drug names. If provided, the Division of Medication Error Prevention and Analysis will consider the Applicant's intended pronunciation of the proprietary name. However, because the Applicant has little control over how the name will be spoken in practice, the Division of Medication Error Prevention and Analysis also considers a variety of pronunciations that could occur in the English language.

**Table 1.** Criteria used to identify drug names that look- or sound-similar to a proposed proprietary name

Type of similarity	Considerations when searching the databases		
	Potential causes of drug name similarity	Attributes examined to identify similar drug names	Potential Effects
Look-alike	Similar spelling	Identical prefix Identical infix Identical suffix Length of the name Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may appear similar in print or electronic media and lead to drug name confusion in printed or electronic communication</li> <li>Names may look similar when scripted and lead to drug name confusion in written communication</li> </ul>
	Orthographic similarity	Similar spelling Length of the name Upstrokes Downstrokes	<ul style="list-style-type: none"> <li>Names may look similar when scripted, and lead to drug name confusion in written communication</li> </ul>

		Cross-strokes Dotted letters Ambiguity introduced by scripting letters Overlapping product characteristics	
Sound-alike	Phonetic similarity	Identical prefix Identical infix Identical suffix Number of syllables Stresses Placement of vowel sounds Placement of consonant sounds Overlapping product characteristics	<ul style="list-style-type: none"> <li>Names may sound similar when pronounced and lead to drug name confusion in verbal communication</li> </ul>

**Appendix B: Container Labels (15 tablet and 20 tablet bottles)**

**b(4)**

**Appendix C: Carton Labeling (15 tablet and 20 tablet bottles)**

T

7

b(4)

C

U

**Appendix D: Blister Labels**

**b(4)**

**Appendix E : Table 1 from Section 2, 'Dosage and Administration' form package insert of Fludarabine Phosphate 10 mg film-coated tablets.**

**b(4)**

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

/s/  
-----

Walter Fava  
8/4/2008 09:08:54 AM  
DRUG SAFETY OFFICE REVIEWER

Linda Kim-Jung  
8/4/2008 09:43:19 AM  
DRUG SAFETY OFFICE REVIEWER

Denise Toyer  
8/4/2008 10:27:23 AM  
DRUG SAFETY OFFICE REVIEWER

Appears This Way  
On Original

## ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION		
NDA # 22-273 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Fludarabine phosphate Established/Proper Name: Fludarabine phosphate Dosage Form: film-coated tablet		Applicant: Antisoma, Inc. Agent for Applicant (if applicable):
RPM: James M. Saunders		Division: DDOP
<p><b>NDA:</b>            NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:    <input type="checkbox"/> 505(b)(1)    <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		
<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</b></p> <p><input type="checkbox"/> No changes                      <input type="checkbox"/> Updated            Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>		
❖ User Fee Goal Date Action Goal Date (if different)		December 19, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application <sup>2</sup> Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):  <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC	
NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies  <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC	BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41) <input type="checkbox"/> Restricted distribution (21 CFR 601.42) Subpart H <input type="checkbox"/> Approval based on animal studies
Comments:	
❖ Application Integrity Policy (AIP) <a href="http://www.fda.gov/ora/compliance_ref/aip_page.html">http://www.fda.gov/ora/compliance_ref/aip_page.html</a>	
<ul style="list-style-type: none"> <li>Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>This application is on the AIP               <ul style="list-style-type: none"> <li>If yes, exception for review granted (<i>file Center Director's memo in Administrative/Regulatory Documents section, with Administrative Reviews</i>)</li> <li>If yes, OC clearance for approval (<i>file communication in, Administrative/Regulatory Documents section with Administrative Reviews</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input type="checkbox"/> No  <input type="checkbox"/> Yes  <input type="checkbox"/> Yes <input type="checkbox"/> Not an AP action
❖ Date reviewed by PeRC ( <i>required for approvals only</i> ) If PeRC review not necessary, explain: <input checked="" type="checkbox"/>	Orphan
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM ( <i>approvals only</i> )	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 ( <i>approvals only</i> )	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications ( <i>approvals only</i> )	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Press Office notified of action</li> </ul>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<input checked="" type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input type="checkbox"/> Other

<sup>2</sup> All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLA: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date exclusivity expires: _____
<ul style="list-style-type: none"> <li>NDA only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? (Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # _____ and date 10-year limitation expires: _____
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire _____
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For each <b>paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). (If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for each paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
---	--

**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	December 18, 2008
--	-------------------

**Officer/Employee List**

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/nonconsent by officers/employees	<input type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Accelerated Approval December 18, 2008
---	--

**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	December 11, 2008
❖ Original applicant-proposed labeling	November 15, 2007
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/29/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	December 5, 2008
❖ Original applicant-proposed labeling	May 19, 2008
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) (write submission/communication date at upper right of first page of each submission)	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	July 31, 2008
❖ Labeling reviews (indicate dates of reviews and meetings)	<input type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input checked="" type="checkbox"/> DRISK November 17, 2008 <input checked="" type="checkbox"/> DDMAC August 28, 2008 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DMEPAA August 4, 2008
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews (e.g., RPM Filing Review <sup>4</sup> /Memo of Filing Meeting) (indicate date of each review)	October 3, 2008
❖ NDAs only: Exclusivity Summary (signed by Division Director)	<input checked="" type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page (approvals only, must be reviewed by PERC before finalized)	<input checked="" type="checkbox"/> Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (include certification)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing communications (if located elsewhere in package, state where located)</li> </ul>	Outgoing Communication August 20, 2008, September 8, 2008, December 12, 2008
<ul style="list-style-type: none"> <li>• Incoming submissions/communications</li> </ul>	September 8, 2008, December 12, 2008
❖ Postmarketing Commitment (PMC) Studies	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (if located elsewhere in package, state where located)</li> <li>• Incoming submission documenting commitment</li> </ul>	
❖ Outgoing communications (letters (except previous action letters), emails, faxes, telecons)	
❖ Internal memoranda, telecons, etc.	December 18, 2008 December 3, 2008
❖ Minutes of Meetings	
<ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (indicate date; approvals only)</li> </ul>	<input type="checkbox"/> Not applicable December 15, 2008
<ul style="list-style-type: none"> <li>• Regulatory Briefing (indicate date)</li> </ul>	<input checked="" type="checkbox"/> No mtg

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.

• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input checked="" type="checkbox"/> No mtg
• EOP2 meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg
• Other (e.g., EOP2a, CMC pilot programs)	Pre-IND July 30, 2007
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None December 18, 2008
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	concur with MOR December 10, 2008
• Clinical review(s) ( <i>indicate date for each review</i> )	December 10, 2008
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	See MOR dated December 10, 2008
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See MOR dated December 10, 2008
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not needed
❖ REMS • REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> ) • Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate location/date if incorporated into another review</i> )	<input checked="" type="checkbox"/> None
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	September 29, 2008(from January 12, 2001)
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None concur with review June 9, 2008

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None concur with review December 4, 2008
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None December 4, 2008 QT November 14, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary	<input type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Supervisory Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 25, 2008
• Pharm/tox review(s), including referenced IND reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None August 25, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer <i>(indicate date for each review)</i>	<input type="checkbox"/> None Maternal Health December 9, 2008
❖ Statistical review(s) of carcinogenicity studies <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input checked="" type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None July 31, 2008
• CMC/product quality review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None July 31, 2008
• BLAs only: Facility information review(s) <i>(indicate dates)</i>	<input type="checkbox"/> None
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i>	<input checked="" type="checkbox"/> Not needed
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	See CMC review dated July 31, 2008
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i>	Date completed: July 10, 2008 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation

<ul style="list-style-type: none"><li>• BLAs:<ul style="list-style-type: none"><li>➤ TBP-EER</li> <li>➤ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li></ul></li></ul>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold
❖ NDAs: Methods Validation	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input checked="" type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed

Appears This Way  
On Original

### Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

## REQUEST FOR CONSULTATION

TO (Office/Division): Sandra Griffith  
ORDER OSE  
WO 22 Rm:  
(301)796-0675

FROM (Name, Office/Division, and Phone Number of Requestor):  
James M. Saunders  
Division of Oncology Drug Products  
WO22 RM 2369

DATE 05-19-2008	IND NO.	NDA NO. 22-273	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT 05-19-2008
--------------------	---------	-------------------	-------------------------	--------------------------------

NAME OF DRUG Fludarabine Phosphate	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE As time permits
---------------------------------------	------------------------	------------------------	--

NAME OF FIRM: Xanthus Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |   |  |
|--|---|--|
| <input type="checkbox"/> NEW PROTOCOL<br><input type="checkbox"/> PROGRESS REPORT<br><input type="checkbox"/> NEW CORRESPONDENCE<br><input type="checkbox"/> DRUG ADVERTISING<br><input type="checkbox"/> ADVERSE REACTION REPORT<br><input type="checkbox"/> MANUFACTURING CHANGE / ADDITION<br><input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> PRE-NDA MEETING<br><input type="checkbox"/> END-OF-PHASE 2a MEETING<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> RESUBMISSION<br><input type="checkbox"/> SAFETY / EFFICACY<br><input type="checkbox"/> PAPER NDA<br><input type="checkbox"/> CONTROL SUPPLEMENT | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER<br><input type="checkbox"/> FINAL PRINTED LABELING<br><input type="checkbox"/> LABELING REVISION<br><input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE<br><input type="checkbox"/> FORMULATIVE REVIEW<br><input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
|--|---|--|

#### II. BIOMETRICS

- |   |  |
|---|--|
| <input type="checkbox"/> PRIORITY P NDA REVIEW<br><input type="checkbox"/> END-OF-PHASE 2 MEETING<br><input type="checkbox"/> CONTROLLED STUDIES<br><input type="checkbox"/> PROTOCOL REVIEW<br><input type="checkbox"/> OTHER (SPECIFY BELOW): | <input type="checkbox"/> CHEMISTRY REVIEW<br><input type="checkbox"/> PHARMACOLOGY<br><input type="checkbox"/> BIOPHARMACEUTICS<br><input type="checkbox"/> OTHER (SPECIFY BELOW): |
|---|--|

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION<br><input type="checkbox"/> BIOAVAILABILITY STUDIES<br><input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE<br><input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS<br><input type="checkbox"/> IN-VIVO WAIVER REQUEST |
|--|--|

#### IV. DRUG SAFETY

- |   |   |
|---|---|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL<br><input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES<br><input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)<br><input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY<br><input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE<br><input type="checkbox"/> POISON RISK ANALYSIS |
|---|---|

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the container and carton label mock-ups for labelling issues. PDUFA date is 09-19-08.

Clinical Reviewer: Martin Cohen, M.D.  
Project Manager: James M. Saunders

SIGNATURE OF REQUESTOR  
James M. Saunders, Project Manager, (301)796-0621

METHOD OF DELIVERY (Check one)  
 DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

-----  
James Saunders  
5/19/2008 04:20:54 PM

Appears This Way  
On Original

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Friday, August 15, 2008 3:10 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273

**Attachments:** HighlightsofClinicalPharmacology.doc

Hi Kris,

In addition to the material you have already submitted, we are going to need the additional material from the Clinical Study report, 0004B1-100-GL/0004B1-400-GL:

- Electronic or hard copy of the Investigator's Brochure
- Annotated CRF
- A Define file which describes the contents of the electronic data sets
- Electronic data sets as SAS transport files
- SAS code for the primary statistical analysis
- Data set whose QT/QTc values are the average of the replicates
- Statistical programs with analysis datasets that were used to analyze the study endpoints as well as to perform exposure-response analysis
- Related ECG waveforms submitted to the ECG warehouse ([www.ecgwarehouse.com](http://www.ecgwarehouse.com))
- A completed Highlights of Clinical Pharmacology Table (Attached)



HighlightsofClinicalP  
harmacolo...

James

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

### Highlights of Clinical Pharmacology

Therapeutic dose	Include maximum proposed clinical dosing regimen.	
Maximum tolerated dose	Include if studied or NOAEL dose	
Principal adverse events	Include most common adverse events; dose limiting adverse events	
Maximum dose tested	Single Dose	Specify dose
	Multiple Dose	Specify dosing interval and duration
Exposures Achieved at Maximum Tested Dose	Single Dose	Mean (%CV) C <sub>max</sub> and AUC
	Multiple Dose	Mean (%CV) C <sub>max</sub> and AUC
Range of linear PK	Specify dosing regimen	
Accumulation at steady state	Mean (%CV); specify dosing regimen	
Metabolites	Include listing of all metabolites and activity	
Absorption	Absolute/Relative Bioavailability	Mean (%CV)
	T <sub>max</sub>	<ul style="list-style-type: none"> <li>• Median (range) for parent</li> <li>• Median (range) for metabolites</li> </ul>
Distribution	V <sub>d</sub> /F or V <sub>d</sub>	Mean (%CV)
	% bound	Mean (%CV)
Elimination	Route	<ul style="list-style-type: none"> <li>• Primary route; percent dose eliminated</li> <li>• Other routes</li> </ul>
	Terminal t <sub>1/2</sub>	<ul style="list-style-type: none"> <li>• Mean (%CV) for parent</li> <li>• Mean (%CV) for metabolites</li> </ul>
	CL/F or CL	Mean (%CV)
Intrinsic Factors	Age	Specify mean changes in C <sub>max</sub> and AUC
	Sex	Specify mean changes in C <sub>max</sub> and AUC
	Race	Specify mean changes in C <sub>max</sub> and AUC
	Hepatic & Renal Impairment	Specify mean changes in C <sub>max</sub> and AUC
Extrinsic Factors	Drug interactions	Include listing of studied DDI studies with mean changes in C <sub>max</sub> and AUC
	Food Effects	Specify mean changes in C <sub>max</sub> and AUC and meal type (i.e., high-fat, standard, low-fat)
Expected High Clinical	Describe worst case scenario and expected fold-change in C <sub>max</sub> and	

Exposure Scenario	AUC. The increase in exposure should be covered by the supra-therapeutic dose.
-------------------	--

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
12/9/2008 08:12:46 PM  
archived email from August 15, 2008

Appears This Way  
On Original

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Tuesday, August 12, 2008 9:38 AM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273 Clin Pharm

Good morning Kris,

**The clinical pharmacology reviewer cannot find analytical methods quality control data (inter- and -intra run accuracy and variability for QC samples) for the following three studies in the NDA:**

**Protocol TB-03-1105 Report A891**

**Protocol 94615 Report AU92**

**Protocol 94615 Report AW74 -- references AW69 which the reviewer cannot locate**

**If these data are available please indicate their location in the NDA. Currently, these are the only studies for which this issue has arisen. However, similar requests for other studies may follow if the analytical methods data is difficult to locate in the NDA.**

*Sincerely,*

*James*

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/12/2008 01:48:12 PM  
Clin Pharm Information needed

Appears This Way  
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		<b>REQUEST FOR CONSULTATION</b>			
TO (Office/Division): Interdisciplinary Review Team for QT dies, Devi Kozeli, PM			FROM (Name, Office/Division, and Phone Number of Requestor): James Saunders, PM/DDOP/796-0621/HFD-150		
DATE August 11, 2008	IND NO.	NDA NO. 22-273	TYPE OF DOCUMENT Protocol Submission for review by IRT	DATE OF DOCUMENT August 1, 2008	
NAME OF DRUG Fludarabine Phosphate Oral tablets		PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Cytotoxic	DESIRED COMPLETION DATE September 8, 2008	
NAME OF FIRM: Antisoma					
<b>REASON FOR REQUEST</b>					
<b>I. GENERAL</b>					
<input checked="" type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION <input type="checkbox"/> MEETING PLANNED BY		<input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> END-OF-PHASE 2a MEETING <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY / EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT		<input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):	
<b>II. BIOMETRICS</b>					
<input type="checkbox"/> PRIORITY P NDA REVIEW <input type="checkbox"/> END-OF-PHASE 2 MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):			<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
<b>III. BIOPHARMACEUTICS</b>					
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE 4 STUDIES			<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
<b>IV. DRUG SAFETY</b>					
<input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP			<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
<b>V. SCIENTIFIC INVESTIGATIONS</b>					
<input type="checkbox"/> CLINICAL			<input type="checkbox"/> NONCLINICAL		
<b>COMMENTS / SPECIAL INSTRUCTIONS:</b> Please evaluate the study 0004B1-100-GL/0004B1-400-GL, "Phase 1 and Phase 4 Study of a Single Fixed Dose of Oral Fludarabine Phosphate in Adult Patients with B-cell Malignancies". for consult review ( to evaluate any potential affects of Fludarabine Phosphate on QT/QTc prolongation) by the Interdisciplinary Review Team (IRT).					
SIGNATURE OF REQUESTOR James M. Saunders			METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS <input checked="" type="checkbox"/> EMAIL <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
PRINTED NAME AND SIGNATURE OF RECEIVER			PRINTED NAME AND SIGNATURE OF DELIVERER		

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

/s/  
-----

James Saunders  
8/11/2008 03:31:59 PM  
IRT Consult request

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Monday, August 11, 2008 1:55 PM  
**To:** 'Kris Piper'  
**Subject:** NDS 22-273 Genotoxicity Studies

Hi Kris,

Please send the following genotoxicity studies as soon as possible:

1. Ames assay
2. Chromosome aberration Assay in CHO cells
3. HGPRT mammalian cell mutagenesis Assay in CHO cells
4. Mouse micronucleus assay
5. Dominant lethal test in male mice

Thank,

*James*

CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 01:59:08 PM

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, August 06, 2008 4:21 PM  
**To:** 'Kris Piper'  
**Subject:** N 22-273

**Attachments:** Oral Fludarabine Phosphate PI3.1\_8.06.08.doc

Hi Kris,

Please see the following comments and the attached file which contain comments from our latest labeling meeting.

In addition, do you have Word version of the carton, container, and blister *mockups*? I have them in PDF in an email from you dated July 31, 2008. One of our reviewers is also asking for a Patient Package Insert as well from you.

1. 



2. 



**Greater clarity would also be provided if the milligram unit of measure followed each numerical dose in the table. (We have done this in our editing)**

3. **Include border lines for each row of Table 1 to make it easier for practitioners to read.**

4. **Present all numerical data throughout the package insert with the units of measure immediately following the corresponding numerical value to increase comprehensibility of important information and to minimize confusion.**

5. **Implement an educational plan to inform healthcare providers about the difference in the usual recommended dose of the oral tablets (40 mg/m<sup>2</sup>) compared to the intravenous formulations currently marketed (25 mg/m<sup>2</sup>), in order to minimize the risk of medication errors related to incorrect dosing.**

As usual, feel free to call or email in you have questions or need clarification.



Oral Fludarabine  
Phosphate PI3...

*James*

b(4)

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

# 23 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

-----  
James Saunders  
8/11/2008 12:33:46 PM  
Archived email from August 6, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Monday, July 28, 2008 4:17 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273 Fludarabine Phosphate Tablets - PI and Container, Carton, ad Blister Labels

**Follow Up Flag:** Follow up  
**Flag Status:** Completed

**Attachments:** Revised Comments from JUL 23 2008 Mtg - Fludarabine Phosphate (2).doc

**Hi Kris,**

**Please see the attached file which contains labeling revisions from our CMC review team.**



Revised  
Comments from JUL 2

**Sincerely,**

*James*

**CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621**

Appears This Way  
On Original

Comments:

General Comments:

1. Revise the storage statement to read: "Store under normal lighting conditions at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP controlled room temperature]."
2. Correct the applicant name appearing on all labeling.

Package Insert Labeling:

1. Revise " \_\_\_\_\_ " to "fludarabine phosphate". b(4)
2. Revise " \_\_\_\_\_ found on the top of page 1 to \_\_\_\_\_ " b(4)
3. Change " \_\_\_\_\_ found on page 1 to \_\_\_\_\_ " b(4)
4. Under DOSAGE FORMS AND STRENGTHS, page 2, revised " \_\_\_\_\_ " to "10 mg film-coated tablets". (See 3).
5. Under DESCRIPTION, move the second paragraph, beginning with "The chemical name ..." to the beginning and place the (current) first paragraph following the chemical structure of fludarabine phosphate.
6. In the DESCRIPTION section, the number of atoms in the molecular formula should be in subscript form.
7. HOW SUPPLIED/STORAGE AND HANDLING, page 21:
  - i. Remove \_\_\_\_\_
  - ii. Revise " \_\_\_\_\_ " to "Fludarabine phosphate is supplied in 10 mg tablets..." b(4)
  - iii. Provide the pertinent NDC numbers for each of the corresponding container sizes,
  - iv. Add "16.2 STORAGE" and "16.3 HANDLING AND DISPOSAL" as headings.
  - v. Correct the spelling of the word "package" found under the 15 – 10 mg film-coated tablets container.
  - vi. Under STORAGE, remove 20- and 68-.
  - vii. The information regarding "Manufactured for" and "Manufactured by" should not be in bolded.

Blister Labels:

1. Delete the established name, ' \_\_\_\_\_ ' since the product name is the same as the established name.

Container Labels:

1. Provide the pertinent NDC numbers for each container size (i.e., 15 or 20 tablets).
2. \_\_\_\_\_  
(Does this apply to the container labels?)
3. Change ' \_\_\_\_\_ ' to \_\_\_\_\_
4. Relocate Rx Only to be under "xx tablets (3x 5 tablet blister strips)" preferably in a center position.
5. Delete \_\_\_\_\_ from the from the storage statement.
6. Move the Caution Statement toward the center. **b(4)**

Carton Labels:

1. Provide the pertinent NDC numbers for each container size (i.e., 15 or 20 tablets).
2. \_\_\_\_\_
3. Change ' \_\_\_\_\_ ' to \_\_\_\_\_
4. On the front label, relocate Rx Only to be under "15 tablets (3x 5 tablet blister strips)" preferably at the center.
5. On the front and back labels, delete \_\_\_\_\_ from the storage statement.
6. Move the Caution Statement toward the center and the word. **b(4)**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 12:27:32 PM  
Archived email from July 28, 2008

Appears This Way  
On Original

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Wednesday, July 23, 2008 2:45 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273

Hi,

I wanted to thank you for the recent labeling files you sent and to let you know I have not forgotten about your question regarding "accelerated approval" and post-approval trials. I have another request though from our Non Clinical Reviewer.

Can you resubmit the reproductive/teratogenic studies in rats and rabbits that were submitted in the original NDA?

Thanks,

*James*

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 12:21:30 PM  
Archived emial from July 23, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Friday, July 18, 2008 5:41 PM  
**To:** 'Kris Piper'  
**Subject:** Labeling Comments

**Attachments:** NDA 22-273 LABELING REVIEW FOR JUL 23 2008 Mtg.doc; Fludarabine Phosphate Container Labels Review.doc

**Hi Kris,**

**See the attached files from one of our reviewers concerning labeling. I know it is after hours on a Friday, but the reviewer wanted as quick a response as possible, by Tuesday if you can?**



NDA 22-273 Fludarabine  
LABELING REVIEW Phosphate Containe

*James*

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

# 31 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/  
-----

James Saunders  
8/11/2008 12:16:45 PM  
Archived emial from July 18, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, July 16, 2008 3:15 PM  
**To:** 'Kris Piper'  
**Subject:** Question

Hi Kris,

One of our reviewers had asked me to inquire about the carton container mock-ups you sent. Specifically the question was which panel was the primary display model. As he was looking at it, it appeared that when folded one side would be upside down.

*James*

**CDR James M. Saunders**  
**Senior Regulatory Management Officer**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On the

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

/s/

-----  
James Saunders  
8/11/2008 11:56:42 AM  
Archived email from July 16, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Monday, July 14, 2008 5:32 PM  
**To:** 'Kris Piper'  
**Subject:** N 22-273

**Hi Kris,**

**I need to have a Word version of the package insert. I am unsure if you have already submitted it, but all I have found thus far is the labeling that was submitted in SPL format and the carton and container mockups and labels. I can call you in the morning to discuss if you like.**

**James**

**CDR James M. Saunders  
Senior Regulatory Management Officer  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:59:25 AM  
Archived email from July 14, 2008

Appears This Way  
On 8/11/08

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Tuesday, May 27, 2008 10:09 AM  
**To:** 'Kris Piper'  
**Subject:** Additional question from the stat reviewer

Good morning Kris,

In addition to your response dated 4/18/2008, please also provide results for the following:

- (1) Comparison between IV and oral Fludara in CR+nPR+PR rate
- (2) Descriptive statistics (n, mean, median, stdev, min, max) for duration of response in CR+nPR+PR responders separately for IV Fludara treated or oral Fludara treated patients

Thanks,

*James*

**LCDR James M. Saunders**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:51:36 AM

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Friday, May 23, 2008 12:27 PM  
**To:** 'Kris Piper'  
**Subject:** NDA 22-273 Stat Reviewer request

Hi Kris,

I am sending this request from our Stat reviewer. We would like to have a response in the next week or two if possible.

1. **The p-values presented in clinical study report AZ84 text table 21 may not be correct as they indicated that a response rate of 34.6% is closer than 51.3% to the background rate of 45% ( $p=0.32$  for response rate=51.3%, while  $p=0.35$  for response rate=34.6%). Please verify your results.**
2. **In clinical study report AZ84 text table 25, there were 7 subjects had their responses listed as ND/UNK/NA. Please provide the reasons for not being to determine response to treatment in these subjects.**

Thanks,

*James*

**LCDR James M. Saunders  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:42:53 AM  
Archived email from May 23, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James

**Sent:** Monday, March 03, 2008 11:28 AM

**To:** 'Kris Piper'

**Subject:** I received the FEDEX package today

**Good morning Kris,**

**Thanks for the copies of the studies. Another question though. Can you tell me when you think you will have the carton/container labels available in mock ups with full color? Will there be a tradename you will be using?**

**Sincerely,**

*James*

**LCDR James M. Saunders**

**OND/OODP**

**Division of Drug Oncology Products**

**10903 New Hampshire Avenue**

**WO-22 Room 2369**

**Silver Spring, Maryland 20993**

**(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
12/9/2008 07:35:51 PM  
Arched email from March 3, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Tuesday, February 26, 2008 11:50 AM  
**To:** 'Kris Piper'  
**Subject:** Status

Hi,

I hope this email finds you well. Are we still waiting on the efficiency database for study LRF CLL4? I assume so, but do you know when we should expect to receive it? The stat reviewer is asking me, and I want to give an accurate date.

*James*

**LCDR James M. Saunders**  
**OND/OODP**  
**Division of Drug Oncology Products**  
**10903 New Hampshire Avenue**  
**WO-22 Room 2369**  
**Silver Spring, Maryland 20993**  
**(301) 796-0621**

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
12/9/2008 07:29:43 PM

Appears This Way  
On Original

**Saunders, James**

---

**From:** Kris Piper [kris.piper@xanthus.com]  
**Sent:** Wednesday, February 20, 2008 4:41 PM  
**To:** Saunders, James  
**Subject:** RE: Additional Information needed

Hello James,

I'm not certain I understand your request. If "manuscript" refers to the publication of the studies, all those are in the NDA. We can send you the exact locations or we can send you additional copies if you want. The details regarding response rates, duration of response, PFS and the criteria used are detailed in the publications when those data are available.

Results broken down by IV vs PO, worst-case/best-case scenarios and NCI/IWCLL criteria are presented in the efficacy summary in Module 2.7.

Please let me know what you would like us to provide.

Thanks,  
Kris

J. Kris Piper  
Senior Vice President  
Clinical Operations & Regulatory Affairs  
Xanthus Pharmaceuticals, Inc.  
300 Technology Square  
Cambridge, MA 02139  
phone: 617-225-0522, ext 130  
fax: 617-225-0525  
e-mail: kris.piper@xanthus.com  
web: www.xanthus.com

---

**From:** Saunders, James [mailto:James.Saunders@fda.hhs.gov]  
**Sent:** Wednesday, February 20, 2008 2:26 PM  
**To:** Kris Piper  
**Subject:** Additional Information needed

Hi Kris,

We need copies of manuscripts of studies 303080, LRF CLL4, CALGB and \_\_\_\_\_, with attention to:

1. The total response rate (Crts, nPRs and PRs?)
2. The CR rate
3. The duration of response

b(4)

8/8/2008

4. PFS results

Survival results broken down by whether the patient received oral or IV fludarabine would also be of interest. Also it would be useful to know if analyses were best case or worst case scenarios, and who did the analyses that were submitted. Were the responses reported by the studies by NCI and/or IWCLL criteria?

Thanks again

*James*

LCDR James M. Saunders

OND/OODP

Division of Drug Oncology Products

10903 New Hampshire Avenue

WO-22 Room 2369

Silver Spring, Maryland 20993

(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:36:01 AM  
Archived email from February 20, 2008

Appears This Way  
On Original

**Saunders, James**

**From:** Saunders, James  
**Sent:** Wednesday, February 20, 2008 9:53 AM  
**To:** 'Kris Piper'  
**Subject:** Request for information.

Good morning Kris,

I have a request from one of our reviewers for you to provide all correspondence related to \_\_\_\_\_ Thanks.

**b(4)**

*James*

LCDR James M. Saunders  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:22:47 AM  
Archived email from February 20, 2008

Appears This Way  
On Original

**Saunders, James**  
**From:** Saunders, James  
**Sent:** Tuesday, February 19, 2008 11:45 AM  
**To:** 'kris.piper@xanthus.com'  
**Subject:** NDA 22-273

Good morning Kris,

I trust things are going fine with you. I wonder if you could officially submit an electronic copy of the draft carton and container labels, and any other pertinent labeling information not previously submitted. I was able to get the SPL of the prescribing information. I am sure I will be in touch if I need anything else. As always, you may call or email if you have questions. Thanks.

Sincerely  
*James*

LCDR James M. Saunders  
OND/OODP  
Division of Drug Oncology Products  
10903 New Hampshire Avenue  
WO-22 Room 2369  
Silver Spring, Maryland 20993  
(301) 796-0621

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:17:59 AM  
Archived from email dated February 19, 2008

Appears This Way  
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR CONSULTATION

TO (Office/Division):

Janet Anderson  
DMETS/DSRCS  
WO22 Rm:  
(301)796-0675

FROM (Name, Office/Division, and Phone Number of Requestor):

James M. Saunders  
Division of Oncology Drug Products  
WO22 Rm. 2369

DATE  
02-15-08

IND NO.

NDA NO.  
22-273

TYPE OF DOCUMENT  
NDA

DATE OF DOCUMENT  
11-15-07

NAME OF DRUG  
fludarabine phosphate

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
As time permits

NAME OF FIRM:

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP         |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the new NDA for labelling issues. Submission received 11-19-07, filing date 1-16-08, midcycle currently scheduled for 4-7-08, PDUFA due date 09-19-08. The submission can be found in the EDR \\Cdsesub1\nonectd\N22273\N\_000\2007-11-15\SPL.

Clinical Reviewer: Martin Cohen, M.D.

Project Manager: James M. Saunders

SIGNATURE OF REQUESTOR

James M. Saunders, Project Manager, 3010-796-0621

METHOD OF DELIVERY (Check one)

- DFS     EMAIL     MAIL     HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

-----  
James Saunders  
2/14/2008 05:17:29 PM  
Consult from DMETS/DSRCS

Appears This Way  
On Original

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION

## REQUEST FOR CONSULTATION

TO (Office/Division):  
ODMAC  
Attention: JuWon Lee  
WO22 RM: 1493

FROM (Name, Office/Division, and Phone Number of Requestor): PM  
James Saunders  
Division of Drug Oncology Products

DATE  
February 14, 2008

IND NO.

NDA NO.  
22-273

TYPE OF DOCUMENT  
Labelling

DATE OF DOCUMENT  
November 15, 2007

NAME OF DRUG  
fludarbine phosphate

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE  
As time permits

NAME OF FIRM: Xanthus Pharmaceuticals, Inc.

### REASON FOR REQUEST

#### I. GENERAL

- |  |  |  |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL                    | <input type="checkbox"/> PRE-NDA MEETING         | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER     |
| <input type="checkbox"/> PROGRESS REPORT                 | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING            |
| <input type="checkbox"/> NEW CORRESPONDENCE              | <input type="checkbox"/> END-OF-PHASE 2 MEETING  | <input type="checkbox"/> LABELING REVISION                 |
| <input type="checkbox"/> DRUG ADVERTISING                | <input type="checkbox"/> RESUBMISSION            | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE       |
| <input type="checkbox"/> ADVERSE REACTION REPORT         | <input type="checkbox"/> SAFETY / EFFICACY       | <input type="checkbox"/> FORMULATIVE REVIEW                |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA               | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY              | <input type="checkbox"/> CONTROL SUPPLEMENT      |  |

#### II. BIOMETRICS

- |   |   |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW  | <input type="checkbox"/> CHEMISTRY REVIEW       |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY           |
| <input type="checkbox"/> CONTROLLED STUDIES     | <input type="checkbox"/> BIOPHARMACEUTICS       |
| <input type="checkbox"/> PROTOCOL REVIEW        | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): |   |

#### III. BIOPHARMACEUTICS

- |  |  |
|--|--|
| <input type="checkbox"/> DISSOLUTION             | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE  |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES         | <input type="checkbox"/> IN-VIVO WAIVER REQUEST      |

#### IV. DRUG SAFETY

- |  |  |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL                | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE                       |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below)           | <input type="checkbox"/> POISON RISK ANALYSIS                                |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP -       |  |

#### V. SCIENTIFIC INVESTIGATIONS

- |                                   |                                      |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: Please review the proposed product labeling and any relevant advertising for this NDA. It is available in the EDR at the following link: \\Cdsub1\nonectd\N22273\N\_000\2007-11-15\SPL. PDUFA date 09/19/08.

Clinical Reviewer: Martin Cohen, M.D.

Project Manager: James M. Saunders, (301) 796-0621

SIGNATURE OF REQUESTOR  
James M. Saunders

METHOD OF DELIVERY (Check one)  
 DFS  EMAIL  MAIL  HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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

/s/

-----  
James Saunders  
2/14/2008 05:09:54 PM  
Consult for DDMAC

Appears This Way  
On Original

**Saunders, James**

**From:** Hemingway, Nicholette  
**Sent:** Wednesday, February 06, 2008 12:18 PM  
**To:** 'Kris Piper'  
**Cc:** Saunders, James  
**Subject:** NDA 22-273 Investigator Information

Hi Kris,

Can you please provide a list of investigators and their addresses for Study MD96029 and the number of patients that the investigators accrued. If I can have this by the end of the week, that would be great. Please contact James Saunders starting on Monday (2/11/08) exclusively regarding the NDA- he will be the project manager, but include him on this response.

Thanks,  
Nicholette

Nicholette Y. Hemingway, M.P.H.  
CDR, USPHS  
Sr. Regulatory Management Officer  
FDA/CDER/OODP/DDOP  
301.796.1365 Office  
301.796.9845 Fax

Appears This Way  
On Original

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

/s/

-----  
James Saunders  
8/11/2008 11:13:31 AM  
Archived email from February 6, 2008

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-273

Xanthus Pharmaceuticals, Inc.  
Attention: J. Kris Piper, Senior Vice President  
300 Technology Square, 5<sup>th</sup> Floor  
Cambridge, MA 02139

Dear Mr. Piper:

Please refer to your new drug application (NDA) dated November 15, 2007, received November 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Fludarabine Phosphate tablets for oral use.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is September 19, 2008.

During our filing review of your application, we identified the potential review issues listed below, and request that information addressing the following issues be submitted:

1. Please submit all of the raw human pharmacokinetic data contained in the NDA in electronic format (i.e., as SAS transport files).
2. In your Letter of Authorization (LOA) in the NDA submission, the status of Type II DMF 14924 appeared as "Inactive". Please clarify the status of DMF 14924, and submit the update as an amendment to the NDA.
3. The following comment is reproduced from the minutes of the July 30, 2007 meeting:

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

We note that Module 2.7.2 Clinical Summary - Clinical Pharmacology does not include a summary of what is known regarding the ability of fludarabine to alter the QT interval.

We request that you submit a summary of what is known regarding the ability of fludarabine to alter the QT interval.

Please clarify whether a study of the effect of fludarabine on QT interval is being planned or is underway. If the study is ongoing, please let us know whether the results will be available during the NDA review cycle.

We are providing the above comments and requests to give you preliminary notice of potential 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. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Nicholette Hemingway, Regulatory Project Manager, at (301) 796-2330.

Sincerely,

{See appended electronic signature page}

Robert L. Justice, M.D.  
Division Director  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Appears This Way  
On Original

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

/s/

-----  
Robert Justice  
1/31/2008 02:56:59 PM

Appears This Way  
On Original



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

NDA 22-273

NDA ACKNOWLEDGMENT

Xanthus Pharmaceuticals, Inc.  
Attention: J. Kris Piper, Senior Vice President  
300 Technology Square, 5<sup>th</sup> Floor  
Cambridge, MA 02139

Dear Mr. Piper:

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: fludarabine phosphate tablets for oral use

Date of Application: November 15, 2007

Date of Receipt: November 19, 2007

Our Reference Number: NDA 22-273

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 January 18, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Oncology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

NDA 22-273

Page 2

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call Nicholette Hemingway, Regulatory Project Manager, at (301) 796-2330.

Sincerely,

{See appended electronic signature page}

Nicholette Y. Hemingway, M.P.H.  
Regulatory Project Manager  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

Appears This Way  
On Original

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

/s/

-----  
Nicholette Hemingway  
1/17/2008 02:47:37 PM

Appears This Way  
On Original

**Pease, Dorothy W**

---

**From:** Pease, Dorothy W  
**Sent:** Wednesday, August 08, 2007 8:09 AM  
**To:** 'Kris Piper'  
**Subject:** Minutes of oral fludarabine meeting

**Attachments:** fludarabine oral minutes.pdf



fludarabine  
minutes.pdf

Dotti Pease  
Chief, Project Management Staff  
Division of Drug Oncology Products  
Office of Oncology Drug Products  
301 796-1434 fax 301 796-9845

Appears this is  
On

# MEETING MINUTES

**MEETING DATE:** July 30, 2007      **TIME:** 12:00      **LOCATION:** 1309

**IND:** 78,335      **Meeting Request Receipt Date:** May 31, 2007  
**FDA Response Date:** June 12, 2007  
**Briefing Document Receipt Date:** June 29, 2007

**DRUG:** Oral fludarabine      **INDICATION:** CLL

**SPONSOR:** Xanthus      **TYPE of MEETING:** pre-IND

**FDA PARTICIPANTS:** Ann Farrell, M.D., Dep. Dir., DDOP  
John Johnson, M.D., Medical Team Leader, DDOP (Chair)  
Martin Cohen, M.D., Medical Officer, DDOP  
Sarah Pope, Ph.D., PAL/Oncology, Br V, ONDQA (pre-meeting)  
Haleh Saber, Ph.D., Acting Pharm. Supervisor, DDOP (pre-mtg)  
Brian Booth, Ph.D., Clin. Pharm. Team Leader, OCP (pre-mtg)  
Gene Williams, Ph.D., Clin. Pharm. Reviewer, OCP  
Janet Jiang, Ph.D., Statistician, OB  
Nancy Boocker, ORP 505(b)(2) issues (pre-meeting)  
Dotti Pease, Project Manager, DDOP

## **SPONSOR:**

Constance Berghs-Clairmont, Ph.D., Xanthus Pharm. Inc., Asst. Director, Regulatory Affairs  
Robert L Capizzi, M.D., Xanthus Pharm. Inc., Chief Medical Officer  
Richard T. Dean, Ph.D., Xanthus Pharmaceuticals Inc., Chief Executive Officer

---

John Lister-James, Ph.D., Xanthus Pharmaceuticals Inc., VP Development  
J. Kris Piper, Xanthus Pharmaceuticals Inc., VP Regulatory Affairs

Maude Tessier, Ph.D., Xanthus Pharmaceuticals Inc., Project Manager  
Wei Yin, Ph.D., Xanthus Pharmaceuticals Inc., Assoc. Director, Development

**MEETING OBJECTIVES:** Discuss proposed IND and sponsor's questions

**BACKGROUND:** Xanthus proposes submitting an IND for a bioequivalence study of their oral formulation vs IV fludarabine

---

b(4)

b(4)

**QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:**

1. Clinical Pharmacology - Equivalence of systemic exposure

Please refer to section 9.3.2 of this briefing document for supporting information.

Xanthus has performed a new and more extensive analysis of the data from study ME95101 which is presented in this briefing document in section 9.3.2.4 and as Appendix 5, a report by \_\_\_\_\_ entitled 'Investigation of the Systemic Exposure Equivalence of Orally and Intravenously Dosed Fludarabine Phosphate'. This analysis shows that a 90 mg oral dose resulted in comparable systemic exposure (based on the AUC of 2F-ara-A, the primary metabolite of fludarabine phosphate) to a 50 mg intravenous dose. However, the new analysis also shows that a 40 mg/m<sup>2</sup> oral dose of fludarabine phosphate will result in a systemic exposure of 2F-ara-A equivalent to that resulting from a 25 mg/m<sup>2</sup> intravenous dose (point estimates for comparisons of AUCs near unity and 90% confidence intervals falling within 80% to 125%).

Although the aforementioned results predict systemic exposure equivalence, the ME95101 study was not conducted using the approved 25 mg/m<sup>2</sup> intravenous dose and the proposed 40 mg/m<sup>2</sup> oral dose. Consequently, Xanthus proposes to conduct a new confirmatory clinical PK study comparing these two doses. Details of the proposed clinical study are presented in section 9.3.2.5 of this briefing document and in the clinical protocol synopsis attached (Appendix 1). The new study is designed to detect a 20% difference in systemic drug exposure based on 2F-ara-A AUC with an 80% power. It is expected that the new study will confirm that a 40 mg/m<sup>2</sup> oral dose of fludarabine phosphate results in equivalent systemic drug exposure to that from a 25 mg/m<sup>2</sup> intravenous dose.

Does FDA concur that results of a new clinical PK study demonstrating that, with 80% power to detect a 20% difference, the 90% confidence intervals of a comparison of systemic 2F-ara-A AUCs fall within 80 to 125% will demonstrate that a 40 mg/m<sup>2</sup> oral dose of fludarabine phosphate is equivalent to a 25 mg/m<sup>2</sup> intravenous dose?

**FDA - If a confidence interval within 80-125% for AUC of 2F-ara-A was demonstrated, we would conclude that the 40 mg/m<sup>2</sup> oral dose provides a similar extent of exposure to 2F-ara-A as does a 25 mg/m<sup>2</sup> intravenous dose. We would not conclude that the rate of exposure was similar between the two routes of administration unless**

b(4)

b(4)

**equivalence of Cmax was demonstrated in a bioequivalence-type comparison.**

**DISCUSSION:** Sponsor presented 3 slides which they felt demonstrated that AUC is more relevant than rate of exposure.

2. Clinical Pharmacology – Metabolism

While 2F-ara-AMP is dephosphorylated virtually immediately upon intravenous infusion to its principal metabolite, 2F-ara-A, this conversion has not been empirically determined for orally administered fludarabine phosphate. Xanthus plans to include analysis of 2F-ara-AMP in the proposed clinical PK study (see section 9.3.2.5 and Appendix, Protocol Synopsis, Appendix 1). In the proposed study, systemic levels of 2F-ara-AMP as well 2F-ara-A and second metabolite, 2F-ara-Hx will be measured over time, subsequent to IV administered and orally administered fludarabine phosphate.

Will the planned new clinical PK study address the FDA concern over the lack of information on circulating levels of the drug 2F-ara-AMP following oral administration of fludarabine phosphate?

**FDA - Perhaps. What is of interest is not only the concentrations of the moieties but their equivalence between the regimens. We recommend that bioequivalence-type comparisons of the AUC and Cmax be performed for each moiety measured.**

**DISCUSSION:** none needed.

3. Clinical Pharmacology – Metabolism and Excretion

The Agency commented \_\_\_\_\_ that the fate of IV and orally administered fludarabine phosphate is largely unknown (less than 50% of the mass administered has been recovered in excreta), which leaves open the possibility that as much as 50% of the administered dose is metabolized to moieties that are pharmacologically active but have not been elucidated. Furthermore, the Agency stated that there are no data to support that circulating drug-derived moieties other than 2F-ara-A are not present.

Please refer to section 9.3.3 of this briefing document for supporting information. The results of a careful inspection of the literature \_\_\_\_\_

\_\_\_\_\_ with regard to metabolism and mass balance are described in section 9.3.3. Only 3 metabolites are known to occur in humans (2F-ara-A, 2F-ara-ATP and 2F-ara-Hx). In the proposed new clinical PK study, plasma, urine and feces will be assayed for parent 2F-ara-AMP as well as 2F-ara-A and 2F-ara-Hx. In addition, essentially all systemically available drug can be accounted for in either excreta or in tumor. Confirmation that non-systemically available drug is indeed excreted in the feces will be obtained from the proposed

new PK study.

Does FDA agree that the accounting of metabolites and mass balance described in section 9.3.3, in addition to the information expected to be obtained from the proposed new clinical PK study, address the Agency's concerns regarding metabolism and mass balance?

**FDA - In order to assure equivalent efficacy and safety using concentration data alone, it would be necessary to demonstrate that the extent and rate of absorption of all active moieties are equivalent. The planned studies are unlikely to demonstrate such equivalence.**

**DISCUSSION:** none needed.

4. Clinical Pharmacology – PK/PD Relationship

┌ 7  
└ J

b(4)

Please refer to section 9.3.4 of this briefing document for supporting information. It is now well established that 2F-ara-ATP, formed intracellularly and accumulated in tumor cells, is the only cytotoxic form of the drug and is therefore responsible for the cytotoxic activity observed following administration of 2F-ara-AMP<sup>1</sup>. 2F-ara-ATP is incorporated into both DNA and RNA, where it leads to disruption of DNA synthesis and repair and interference with RNA transcription leading to cell death. Consequently, the intracellular concentration of 2F-ara-ATP may be considered to be reflective of drug pharmacodynamics, since it is the most proximate cytotoxic metabolite of 2F-ara-A. However, the measurement of this metabolite in tumor cells, commonly collected during cycles 1 and 2 of treatment, is difficult to relate to the pharmacodynamic effect of fludarabine, especially efficacy, which is typically assessed after Cycles 3 to 8 (i.e. months later). Attempts have been made to correlate the pharmacokinetics of intracellular 2F-ara-ATP with those of 2F-ara-A. Unfortunately, extensive intra and interpatient variability have been observed in measurements of intracellularly accumulated 2F-ara-ATP (this phenomenon has been observed also with other nucleoside drugs). Therefore Xanthus feels that it would be extremely difficult to show a meaningful PK/PD relationship through correlation of the systemic PK of 2F-ara A and cellular PK of 2F-ara-ATP.

Nevertheless, it would seem reasonable to expect that administration of drug by any route that leads to equivalent systemic exposure and similar systemic PK profiles would lead to equivalent efficacy.

Does FDA agree that, absent an accessible PD marker with which to conduct a PK/PD correlation, it is reasonable to expect that administration of fludarabine phosphate, by either oral or intravenous routes at doses that result in equivalent systemic exposure and similar

systemic PK profiles would lead to equivalent efficacy?

**FDA - Proof that all moieties that contribute to efficacy have been identified, together with equivalent rate and extent of exposure for all such moieties, would be needed to make regulatory conclusions regarding efficacy.**

**Your question regards only efficacy; safety is also an issue.**

**DISCUSSION:** none needed

5. Clinical Pharmacology – Drug-Drug Interactions (DDI)

\_\_\_\_\_

Please refer to section 9.3.5 of this briefing document that summarizes the results of two studies: \_\_\_\_\_ The first study evaluated the inhibitory potential of fludarabine phosphate on CYP450 enzymes in vitro (CYP inhibition study). The second study evaluated the effects of known CYP450 inhibitors on fludarabine phosphate metabolism in vitro (CYP mapping study). Both studies indicate that 2F-ara-A is not metabolized by or inhibits CYP450 liver enzymes.

b(4)

\_\_\_\_\_ In addition, over \_\_\_\_\_ patients have been treated with oral fludarabine phosphate worldwide and thus far, there is no indication of any significant drug-drug interactions of fludarabine phosphate with co-administered drugs in clinical practice.

b(4)

Does FDA agree that results of the newly conducted CYP450 studies, together with the experience of \_\_\_\_\_ patients in clinical practice since EU approval as well as the clinical experience from the 160 subjects in the US trials reported previously in the earlier NDA lead to the conclusion that oral administration of fludarabine phosphate does not lead to significant drug-drug interactions?

b(4)

**FDA - A definitive conclusion regarding whether fludarabine or its metabolites are inhibitors or substrates of CYP450 enzymes requires review of the *in vitro* experiments and literature evidence.**

**You should also address whether the drug is an inducer of CYP450, a substrate of transporters, or an inhibitor of transporters.**

**DISCUSSION:** none needed.

6. Clinical – Safety and Efficacy

During the review of NDA 21-293, FDA commented on the insufficiency of the single arm efficacy study, Study ME96029, where the only measure of activity was response rates.

\_\_\_\_\_ oral fludarabine phosphate has been approved in 75 countries worldwide. Launched initially in the United Kingdom (UK) in 2001, over \_\_\_\_\_ patients have been exposed to oral fludarabine phosphate over the past 6 years in clinical practice. The current safety database confirms the safety profile for fludarabine phosphate that was established at launch, with serious adverse drug reactions mainly in the system organ classes of “Blood and lymphatic disorders” and “Infections and Infestations”. This safety profile is identical to the IV formulation, maybe with exception of occurring GI effects like diarrhea, which seem to occur more frequently in the oral study. The worldwide experience of the approved use of oral fludarabine phosphate demonstrates the widespread use of the drug and further supports its safety.

b(4)

In the US, the use of IV fludarabine phosphate has dramatically broadened over the past few years, as indicated by Oncology treatment guidances such as the NCCN guidelines, where fludarabine phosphate is recommended for use as single agent and in combination as standard of care for CLL patients \_\_\_\_\_

b(4)

two studies were identified where oral fludarabine phosphate was used in combination with other chemotherapeutics<sup>iii,iv</sup>. While Xanthus is not aware of any other study conducted with oral fludarabine phosphate in second line CLL, several clinical trials have been conducted in other indications, including first line CLL, indolent Non-Hodgkin’s lymphoma and myeloma.

b(4)

Does FDA agree that the new information Xanthus proposes to have available at the time of submission of its NDA, including the results of a new clinical PK study showing equivalent exposure between oral fludarabine phosphate at the proposed dose of 40 mg/m<sup>2</sup> with IV fludarabine phosphate at 25 mg/m<sup>2</sup>, results of new preclinical studies regarding metabolism, worldwide pharmacovigilance and reported studies of oral fludarabine phosphate, would be sufficient to support approval of oral fludarabine phosphate for the treatment of adult patients with B-cell chronic lymphocytic leukemia (CLL) who have not responded to or whose disease has progressed during treatment with at least one standard alkylating-agent containing regimen?

**FDA – Please see above. In addition, the extent to which clinical studies will provide information on whether IV and oral fludarabine in the proposed doses will have comparable safety and efficacy will be a review issue.**

**DISCUSSION:** The FDA indicated that the NDA must qualify for approval based on either clinical evidence of safety and efficacy or bioequivalence. A situation where the NDA does not qualify on either alone, but meets 50% or some higher proportion needed to qualify for each will not suffice. The FDA emphasized again that good data on complete response and

complete response duration are essential.

FDA noted that this application will be based primarily on clinical data but that there are still outstanding clinical pharmacology issues that will need to be addressed, such as QT/QTc. Xanthus summarized the available clinical data (first line and second line single arm studies), including literature and recently completed studies. The sponsor proposes that the first-line studies could support the second-line indication if there is demonstrated duration in the first-line indication. With response rate as the primary endpoint, an approval would be accelerated approval. The Agency briefly discussed that a trial would be needed to confirm and convert the approval to regular approval.

If the clinical data are adequate, a BE study would not be needed.

#### FDA ADDITIONAL COMMENTS

##### 1. QT Evaluation

In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). In oncology, alternative proposals to the "TQT" study may be appropriate. Please plan to address this issue early in development.

**DISCUSSION:** It was agreed that the ICH E14 TQT study would not be appropriate for this drug. This data may be collected during the proposed PK study or in a new study with QTc as a primary outcome.

2. 

 b(4)

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 C.F.R. 314.54, and the October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/cder/guidance/guidance.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions challenging the agency's interpretation of this statutory provision. See Dockets 2001P-0323, 2002P-0447, and 2003P-0408.

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for a listed drug, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug. In this case, you should establish a "bridge" between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is appropriate. If you intend to rely on literature or other studies for which you have no right of reference but

that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

**DISCUSSION:** None needed \_\_\_\_\_

**b(4)**

**ACTION ITEMS:**

Xanthus will consider our comments and submit IND \_\_\_\_\_ when ready.

\_\_\_\_\_  
Dotti Pease  
Chief, Project Management Staff

**Concurrence Chair:** \_\_\_\_\_  
John Johnson, M.D.  
Medical Team Leader

Appears This Way  
On Original

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

/s/

-----  
John Johnson

8/7/2007 09:20:34 AM

Appears This Way  
On Original

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

/s/

-----  
Dotti Pease  
8/8/2007 08:14:53 AM

Appears This Way  
On Original