CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20221/S012

ADMINISTRATIVE DOCUMENTS

ONCOLOGY DIVISION MEETING MINUTES

MEETING DATE: 10.05.98 TIME: 1:30p.m. LOCATION: Conf. G, rm 6002

IND/NDA: 20-221
DRUG: Ethyol®
SPONSOR/APPLICANT: U.S. Bioscience, Inc.

TYPE of MEETING:
1. Pre-SNDA
2. Proposed Indication: to reduce the incidence and severity of radiation-induced xerostomia.

Meeting Request Submission Date: July 13, 1998
Briefing Document Submission Date: September 16, 1998
Additional Submission Dates:

FDA PARTICIPANTS:
Robert Temple, ODE1 Office Director
Robert Justice, Division Director
Grant Williams, Medical Team Leader
Isagani Chico, Medical Reviewer
Robert Barron, Chemistry Reviewer, Invited
Atiq Rahman, Biopharm Team Leader
Gang Chen, Statistics Team Leader/Reviewer
Helgi van de Velde, Visiting Fellow
Mala Bahl, Visiting Fellow
Linda McCollum, CSO w/ Concurrence

INDUSTRY PARTICIPANTS:
Wolfgang Oster, Sr. V.P., Worldwide Clinical Research
Martha Manning, Sr. V.P., Regulatory Affairs
Lesley Russell, Sr. Director, Clinical Research
Jay Zhang, Head Biostatistician
Eve Damiano, Director, Regulatory Affairs
Deborah Skrocki,
Martin Stogniew, V.P., Pharmaceutical Sciences
David Brizel, Consultant, Duke University Medical Center, Durham, NC
Todd Wasserman, Consultant, Clinical Sciences Research Center, St. Louis, MO
Frances LeVeque, Consultant, Karmanos Cancer Institute, Detroit, MI
Tom Pajak, Consultant, RTOG Group Statistician, Philadelphia, PA
Irving Huang, Consultant, Irving Consulting Group, Pluckemin, NJ
John Mackowiak, Consultant, Center for Outcomes Research, Chapel Hill, NC
Robert Capizzi, Consultant, Jefferson Medical College
George Ohye, Consultant

MEETING OBJECTIVES:

1. Use of study WR-38 to support an efficacy supplement.
2. Properly word the indication to submit Ethyol as a radioprotective agent.
3. Discuss whether an Ethyol supplemental NDA would qualify for a priority review.

QUESTIONS for DISCUSSION, FDA RESPONSE and DECISIONS REACHED:

1. Does the agency agree with the sponsor that the results from the WR-38 study, along with the confirmatory evidence from other studies, constitute substantial evidence for the purpose of supporting a Supplemental application for the proposed indication; i.e., Ethyol® is indicated to reduce the incidence and severity of radiation-induced xerostomia?

   - Possibly, if confirmed upon review. In addition, only one of the two tests of salivary function (the unstimulated test) was supportive. If these questions are resolved upon review, data from WR-38 may support a supplemental application. However, the strength of evidence from other studies confirming the findings in WR-38 is not as clear. For which trial are you planning to submit primary data and case report forms?

   - Please identify the studies that you feel are confirmatory and whether primary data is available for them. Review your evidence documents and determine reasons why these are to be classified as confirmatory.

   - Please account for all patients under study. At the time of submission (December 1998) there will be one year follow-up data from all patients (approximately 300), and more than 200 patients will be available for late follow-up (approximately 20 months).

   - FDA would be interested in seeing the final analysis of acute xerostomia of the 120 patients in the Head and Neck trial (WR-38).

   - The exact indication will be determined after review of the application.

   - See US Bioscience slides used in support of the discussion: WR-38, and Saliva Production Correlations.

2. In accordance with standard methodology for measuring tumor control in head and neck cancer treated by local radiation therapy, locoregional control, disease free survival and overall survival will be assessed in study WR-38. At the time of the interim analysis,

with a median follow-up of 13 months, antitumor activity in the two treatment arms were equal. At the proposed time of submission (December 1998), 1 year follow-up data will be available on all patients enrolled into study WR-38 and the median follow up will be approximately 20 months. Does the agency concur that these data, in conjunction with information from other studies, will provide sufficient evidence to demonstrate preservation of antitumor efficacy?

- Patients' pretreatment characteristics seem to be balanced in Study WR-38; including the delineation of "risk groups" for disease recurrence. This probably provides sufficient evidence to demonstrate preservation of antitumor efficacy in this study. Evidence presented from the other studies should be summarized to support the findings of this study.

- Data from the other studies (i.e., Liu, Use of radiation with or without WR-2721 in advanced rectal cancer) may be needed for approval and to provide supportive evidence that Ethyol® is not tumor protective.

- See US Bioscience slides used to support the discussion: Antitumor Efficacy at 1 year....

3. The sponsor would like to discuss with the Agency, the results obtained from WR-38 and additional studies with respect to mucositis.

   - The data do not appear to support a claim for preventing clinically significant mucositis.

4. Does the Agency agree with the Sponsor that the results obtained with the Patient Benefit Questionnaire, which correlate with the clinical results for xerostomia, would be considered to support appropriate language in the prescribing information on increased clinical benefit to patients?

   - This is a question that would be decided during review.

   - See also the comments in Question 5.

5. Does the Agency have any comments on the WR-38 Statistical Analysis Plan?

   - Intent to treat population should be used in primary analysis.

   - Incidences should be compared between the treatment groups using Fisher's exact test because of the small sample size.

- Time to event (acute xerostomia or mucositis) analysis (logrank test) should be performed to confirm the incidence analysis.

- Proposed longitudinal analysis of PBQ data is acceptable. However, mean score method used in the briefing package is questionable.
  - Due to high percentage of missing data points, simple mean score comparison at each time point may be biased.
  - Longitudinal nature of the data can not be captured.
  - P-values need to be adjusted for multiple comparisons.

- If the submission is based on the interim data, alpha=0.001 should be used as the significance level.

- For antitumor efficacy analysis:
  - How will those patients who were followed up shorter than 1 year be handled in the ratio (1 year) of no evidence of disease (NED) analysis.
  - Time to evidence of disease should also be analyzed (logrank).
  - Survival and disease free survival analyses should be analyzed using logrank test and Cox model analysis should be considered as secondary.

6. Does the Agency agree that the proposed sNDA would be eligible for Priority Review status, with a 6-month PDUFA review and action goal?

   - Possibly. This decision would be made after preliminary examination of the NDA package. Please make your case for priority review in the application.

7. Does the Agency agree with the Sponsor that the new clinical investigations included in the proposed sNDA are essential to the approval of the application thereby conferring extended exclusivity?

   - If this application is approved, the new clinical investigations included will confer 3 years of exclusivity for that claim.

8. Will an Oncology Drugs Advisory Committee (ODAC) meeting be required as part of the regulatory review process of the proposed sNDA? If so, the sponsor believes that the most appropriate experts would be radiation oncologists. Does the Agency agree, and will the Agency add such expertise to the Committee for the review?

   - We plan to take the application to an ODAC meeting and to invite radiation oncologists experienced in head and neck cancer.

- See US Bioscience slide used to support the discussion: List of Radiation Oncologists with Expertise in Head and Neck Cancer.

9. Although the Sponsor is not aware of any outstanding issues, does the Agency have any questions relating to other matters relative to the proposed application?

   - Please submit the Table of Contents of the proposed supplemental NDA as soon as it is available.

   - We recommend that you submit the primary data electronically with adequate documentation. Attached are suggestions on electronic data submissions.

   - Regarding biopharm requirements you should respond to the issues that were raised in the review dated December 06, 1995 (submission dated October 27, 1995.)

     a. You should evaluate any gender differences in the clearance of amifostine given as 910 mg/m^2 dose and recommend any necessary dosage adjustment that may be required in the package insert.

     b. You should evaluate any possible effect of amifostine and its active metabolite on the pharmacokinetics of anticancer agents, such as, cisplatin, carboplatin, paclitaxel, 5-FU, and methotrexate should also be considered in this group.

     c. The plasma protein binding of amifostine and WR-1065 should be evaluated under an appropriate condition and over the therapeutic concentrations observed in patients.

UNRESOLVED ISSUES or ISSUES REQUIRING FURTHER DISCUSSION: NONE

ACTION ITEMS: NONE

The meeting was concluded at 3:00p.m. There were no unresolved issues or discussion points.

10.16.98
Linda McCollum, Project Manager

Concurrence: 10/16/98
Isagani Chico, Meeting Chair

MEETING MINUTES
POST ODAC

MEETING DATE: June 10, 1999 **TIME:** 12:00 PM **LOCATION** : Conf Room A

NDA: 20-221/ S-#012

DRUG: ETHYOL (amifostine) for Injection

APPLICANT: US Bioscience

TYPE OF MEETING: Post ODAC Plan

FDA PARTICIPANTS:

Grant Williams, MD	Medical Team Leader
Isagani Chico, MD	Medical Reviewer
Wendy Schmidt, PhD	Pharm/Tox Reviewer
Gang Chen, PhD	Biometrics Team Leader
Clara Chu, PhD	Biometrics Reviewer
Atiqur Rahman, PhD	OCBP Team Leader
Ms. Maureen Pelosi	Project Manager

MEETING TOPICS :

1. Draft Labeling Initial Considerations–Accepted by sponsor 6/10/99

   A. CLINICAL PHARMACOLOGY section

- Pharmacokinetics, Lines 60 – 64: Remove.

B. INDICATIONS AND USAGE section

- Lines 139 – 147: strike-outs should be put back into the text.
- Line 147 & 148: The following is acceptable - ETHYOL is indicated to reduce the incidence and severity of radiation induced xerostomia.

C. WARNINGS

- Lines 158 – 172: Text removed should be put back in. There is not sufficient data to remove this historical text. Possibly a question for ODAC?

D. PREGNANCY section – okay as written, lines 269-276

2. Goal Dates: User Fee Date = 6/24/99

Division Goal Date (Package completed ready to circulate) 6/14-18/99

Draft Labeling to USB by Tuesday/Wednesday
Comments back on Thursday 6/17
Package circulates on 6/18
Package to Temple on 6/22

Action Performance Goal Date (letter signed) 6/24/99
Who will sign letter – Dr. Temple

3. Discussion – Timeline for labeling reviews:

Labeling changes should be made using WORD. Select TOOLS, then TRACK CHANGES, then HIGHLIGHT CHANGES, the check all three boxes so that we can see the strike outs (deletions) and changes (underlined). Send your sections to Maureen for insertion into the label.

4. CMC Nomenclature Issue:

The CMC reviewer has recommended that the sponsor use the univerted CAS name as the chemical name. The sponsor has agreed to make the change.

Subsequent Labeling Meeting **June 14th (Monday) from 2-3pm in Conf Rm A.**

/S/
Maureen Pelosi 6/11/99
Project Manager, Recorder

TELECON MINUTES

TELECON DATE: 28 MAY 99 TIME: 1 PM LOCATION: Conference Rm B (2064)

NDA 20-221/S-012 Telecon Request Submission Date: 5/25/99
Briefing Document Submission Date: 5/28/99

DRUG: Ethyol (amifostine) for Injection

SPONSOR/APPLICANT: US Bioscience

TYPE of TELECON:

1. pre-ODAC presentation

2. Proposed Indication: Radioprotective Agent: Reduction of the incidence and severity of radiation-induced xerostomia

FDA PARTICIPANTS:

Grant Williams, M.D., Team Leader
Gani Chico, M.D., Medical Reviewer
Gang Chen, Ph.D., Biometrics Team Leader
Clara Chu, PhD, Biometrics reviewer
Care Gnecco, Ph.D.,Secondary Biometrics reviewer
Maureen Pelosi, R.Ph., Project Manager

INDUSTRY PARTICIPANTS:

Eve Damiano, Regulatory Affairs
Martha Manning, Regulatory Affairs
Wolfgang Oster, M.D., Clin. Research
Lesley Russell, M.D., Clin Research
Jay Zhang, Ph.D., Biostatistics
Bob Myers, Database Management
John Mackowiak, PhD, PBQ Consultant
Irving Hwang, PhD, Statistical Consult

TELECON OBJECTIVES:

1. To discuss substantial differences between the FDA and sponsor's analysis of late xerostomia.

2. Methodologies used by FDA for the PBQ asssment

3. Methodologies used for saliva quantitation analysis.

QUESTIONS for DISCUSSION with FDA RESPONSE and DECISIONS REACHED:

1. Saliva Production Analysis:

    - Retrospectively, the sponsor selected a threshold of 0.1 gm but the analysis is acceptable to the FDA..
    - The FDA chose to do an analysis from baseline as a different analysis to confirm/support the robustness of USB's findings.

2. Late xerostomia:

    - Regarding the difference in the numbers -the sponsor will send the data needed by the FDA is order to perform the protocol defined analysis of late xerostomia.

3. Patient Benefit Questionaire:

    - The clinical significance of lumping items together is unclear. This was the reason why the FDA looked at individiual scales. .
    - USB would like to work further with this issue, directly with the FDA biometrics reviewers.

4. Longitudinal Analysis:

    - USB used a mixed model with sline functions whereas the FDA used a GEE quadratic model.
    - Regarding the choice of cut-off time points to distinguish completeters from drop-outs, all the choices are subjective.

5. FDA will consider the new data (SAS transport files)on xerostomia which was ongoing during the 9-12 months windows defining the time of data collection for the primary endpoint and will update the Medical Officer review as appropriate.

6. The statistical reviewers may look at PBQ again before ODAC. It depends on the re-analysis and representation of the data.

7. Questions for ODAC will be faxed as soon as they are ready.

Slides/Overheads will also be exchanged as time permits.

UNRESOLVED ISSUES:

1. Sponsor would like to discuss the PBQ with the Statistical reviewers.

2. The issue of tumor protection was not fully discussed.

ACTION ITEM:

- Eva Damiano will FedEx the new data and SAS transport files as soon as possible
- FDA to provide ODAC questions as soon as possible.
- Exchange of overheads/slides if time permits.

The teleconference concluded at 2:45 PM

/S/ 10/9/99
Maureen Pelosi
Project Manager
Minutes preparer

Concurrence Chair: /S/ 6/10/99
Isagani Chico, M.D.
Medical Officer

MEETING MINUTES
120+ DAYS

MEETING DATE: May 3, 1999 **TIME:** 12:00 PM **LOCATION** : Conf Room B

NDA: 20-221/ S-#012

DRUG: ETHYOL (amifostine) for Injection

APPLICANT: US Bioscience

TYPE OF MEETING: 120+ day team meeting (draft label changes)

FDA PARTICIPANTS:

Julie Beitz, MD	Acting Deputy Division Director
Grant Williams, MD	Medical Team Leader
Isagani Chico, MD	Medical Reviewer
Wendy Schmidt, PhD	Pharm/Tox Reviewer
Paul Andrews, PhD	Pharm/Tox Team Leader
Gang Chen, PhD	Biometrics Team Leader
Clara Chu, PhD	Biometrics Reviewer
Atiqur Rahman, PhD	OCBP Team Leader
Robert Barron, MS	CMC Reviewer
Ms. Maureen Pelosi	Project Manager

MEETING TOPICS :

1. Draft Labeling: Initial Considerations –

   A. CLINICAL PHARMACOLOGY section

   - Lines 23-40 have been changed to read:

- Pharmacokinetics, Lines 60 – 64: Remove.

B. INDICATIONS AND USAGE section

- Lines 139 – 147: strike-outs should be put back into the text.
- Line 147 & 148: The following is acceptable - ETHYOL is indicated to reduce the incidence and severity of radiation induced xerostomia.

C. WARNINGS

- Lines 158 – 172: Text removed should be put back in. There is not sufficient data to remove this historical text. Possibly a question for ODAC?

D. PREGNANCY section – okay as written, lines 269-276

2. ODAC : Tentative date is either June 7th or 8th, 1999

3. Goal Dates: User Fee Date = 6/24/99
Division Goal Date (Package completed ready to circulate) 6/14-18/99
Action Performance Goal Date (letter signed) 6/24/99
Who will sign letter? Bob Justice will follow-up with Dr. Temple

Discussion – Timeline for labeling reviews according to priority review process.

- The MO will not be able to address labeling until closer to ODAC.
- Project Manager will compile labeling changes and Email to sponsor.
- If needed, a labeling meeting is set for May 24th (5month meeting).

Subsequent Meetings **Tentative Schedule. Individual dates may be cancelled if meeting is not required**

	DATE	DAY	TIME	ROOM	MEETING TYPE
a.	Mar 25	Thur	11 AM	WOC2-cr A	90 day-meeting / plan labeling timeline
b.	May 3	Mon	2 PM	WOC2-cr B	4-Mo plus 1 week team meeting/labeling
d.	June 3	Thur	1-3 PM	WOC2-cr A	ODAC Practice /***Temple has confirmed***
e.	June 10	Thur	12	WOC2-cr A	Post ODAC issues/**Label to Temple**
	June 14	Mon	2 - 3	WOC2-cr A	Wrap it up or revise label prn

CC: NDA 20-221
HFD-150/ Div File
Reviewers
Pease
Vaccari
Pelosi

Meeting Minutes 120 day

MEETING MINUTES
90 DAYS

MEETING DATE: March 25, 1999 **TIME:** 11:00 AM **LOCATION** : Conf Room A

NDA: 20-221/ S-#012

DRUG: ETHYOL (amifostine) for Injection

APPLICANT: US Bioscience

TYPE OF MEETING: 90 day team meeting

FDA PARTICIPANTS:

Robert Justice, MD	Acting Division Director
Grant Williams, MD	Medical Team Leader
Isagani Chico, MD	Medical Reviewer
Wendy Schmidt, PhD	Pharm/Tox Reviewer
Gang Chen, PhD	Biometrics Team Leader
Clara Chu, PhD	Biometrics Reviewer
Atiqur Rahman, PhD	OCBP Team Leader
Ms. Maureen Pelosi	Project Manager

MEETING TOPICS :

1. Potential Review Problems/ Consults Needed and/or Sent -
   A. Medical -

- The application has been designated priority (reduction in incidence of radiation induced xerostomia as well as previously treated patients with acute and late xerostomia.

- Regarding the dental consult discussed previously - Consult was sent on 3/12/99 with a suspense date of 4/20/99.

- US Bioscience is asking about the use of a Radiation Oncologist for the ODAC. They refer to their list in the pre-sNDA meeting package. Dr. Chico will send an Email with 3-4 names for consideration. He would like to have at least two consultants for ODAC.

- Sponsor has indicated that they will be unable to meet the 120 day deadline (April 22, 1999) for the safety update. They request that the Division grant an extension of one week (April 29, 1999). The Team agreed that this was acceptable.

A. Medical, continued:

- Mary Mease has 8 incident reports, 2 of which report deaths at higher doses levels. Dr. Chico is evaluating the reports.

- The medical review is proceeding.

B. Statistics

- Requested SAS programs and references for the methods that were used have been received.

- The longitudinal analysis programs for patient benefit involve problems and difficulties. For example, if a patient came in twice on the same day with different scores, USB selected the minimum scores. Treatment is once per week, but some patients came in twice a week, with 2 results. The last day was selected with arbitrary exclusion of certain visits. If this process is balanced, perhaps it may be ignored. If not balanced, it may cause a problem. Perhaps the using the average score would produce a more realistic treatment effect. The reviewer will consider the maximum versus the average versus the minimum score and look at the difference for bias.

C. Pharmacology/Toxicology –

- There is a 90 day rat study involving the effects on reproduction. It is useless because there is only a single time point at 6 hours.

- The major concern involves the labeling. Tumor protection language will be removed.

- Draft review is with Paul Andrews. There is concern over the labeling. All references to tumor protection have been removed. There is minimum new data which is not of much value. Dr. Chico agrees that the sponsor needs to show evidence of no tumor protection.

D. Clin. Pharmacology –

- There is one biopharm study involving 12 subjects to determine the PK of Ethyol at recommended doses.

- The Table of Contents was not acceptable. It should indicate what appendix relates to what and be clearly indexed and paginated. A revised version was submitted.

- Unique situation in that the PK supports a 200 mg dose (prior to radiation) versus the approved 900 mg dose. The regimen involves different dosing – daily for 5 days.

E. Chemistry -

- This is an approved drug. The EA impact statements show no change in manufacturing. The production estimate is 2 million vials, <1ppb. The sponsor has requested a categorical exclusion which will be granted.

- No inspections are required.

2. ODAC : Tentative date is either June 7th or 8th, 1999

3. Goal Dates: User Fee Date = 6/24/99
Division Goal Date (Package completed ready to circulate) 6/14-18/99
Action Performance Goal Date (letter signed) 6/24/99
Who will sign letter? Bob Justice will follow-up with Dr. Temple

Discussion – Timeline for labeling reviews according to priority review process.

- The MO will not be able to address labeling until closer to ODAC.
- Other disciplines will get whatever labeling changes they have to Project Manager by April 23rd. Project Manager will compile and distribute.
- If needed, a labeling meeting is set for May 3rd.

Subsequent Meetings **Tentative Schedule. Individual dates may be cancelled if meeting is not required**

	DATE	DAY	TIME	ROOM	MEETING TYPE
a.	Mar 25	Thur	11 AM	WOC2-cr A	90 day-meeting / plan labeling timeline
b.	May 3	Mon	2 PM	WOC2-cr B	4-Mo plus 1 week team meeting/labeling
c.	May 24	Mon	2:15 PM	WOC2-cr B	5th Month labeling
d.	June 3	Thur	1-3 PM	WOC2-cr A	ODAC Practice */Temple has confirmed*
e.	June 10	Thur	12	WOC2-cr A	Post ODAC issues/Label to Temple
	June 14	Mon	2 - 3	WOC2-cr A	Wrap it up or revise label prn

CC: NDA 20-221
HFD-150/ Div File
Reviewers
Pease
Vaccari
Pelosi

Meeting Minutes 90 day

MEETING MINUTES

MEETING DATE: February 2, 1999 **TIME:** 2:30 pm **LOCATION** : Conf Room B

NDA: 20-221/ S-#012

DRUG: ETHYOL (amifostine)

APPLICANT: US Bioscience

TYPE OF MEETING: 45 day Filing Meeting

FDA PARTICIPANTS:

Robert Justice, MD	Acting Division Director
Grant Williams, MD	Medical Team Leader
Isagani Chico, MD	Medical Reviewer
Paul Andrews, PhD	Pharm/Tox Team Leader
Wendy Schmidt, PhD	Pharm/Tox Reviewer
Gang Chen, PhD	Biometrics Team Leader
Clara Chu, PhD	Biometrics Reviewer
Atiqur Rahman, PhD	OCBP Team Leader
Rebecca Wood, PhD	CMC Team Leader
Robert Barron,MS	CMC Reviewer
Ms. Maureen Pelosi	Project Manager

FDA INVITEES PRESENT:

Gus Turner, PhD	DSI
M. Misocky,	DDMAC
D. Haggerty, MD	Orphan Drug

MEETING TOPICS :

1. **Fileability: Day 60 = 2/22/99**

   A. Medical - Application in fileable.

   - Reviewer requested information on the electronic database and sponsor has responded, but not completely – still need data on eligibility.

   - The DSI memo has been sent and faxed to Gus Turner. It requests an audit for the North Carolina and California sites, accounting for about 9% of the patients. If the inspections are not satisfactory, we may ask for an audit of some of the German sites.

   - The application has been designated priority (reduction in incidence of radiation induced xerostomia as well as previously treated patients with acute and late xerostomia.

- Regarding a dental consult - Reviewer needs to progress with his review in order to narrow what questions he will ask, such as the endpoint or special concerns about the acceptability of standards used.

B. Statistics - Application may be filed.

- Reviewer has requested SAS programs and references for the methods used.

C. Pharmacology/Toxicology - Fileable

- There is a 90 day rat study involving the effects on reproduction.
- The major concern involves the labeling. Tumor protection Language will be removed.

D. Clin. Pharmacology - NOT FILEABLE for content.

- There is one biopharm study involving 12 subjects to determine the PK of Ethyol at recommended doses.
- The Table of Contents in not acceptable. It should indicate what appendix relates to what and be clearly indexed and paginated.
- Unique situation in that the PK supports a 200 mg dose (prior to radiation) versus the approved 900 mg dose.

E. Chemistry - Fileable

- This is an approved drug. The EA impact statements show no change in manufacturing. The production estimate is vials, <1ppb. The sponsor has requested a categorical exclusion which will be granted.
- No inspections are required.

2. Potential Review Problems/Consults Required:

A. Medical -

- May send a dental consult and need remained of requested information.

B. Biometrics - none .

C. Pharmacology/Toxicology – nothing at this time.

D. Clin. Pharmacology – see comments above regarding index.

E. Chemistry -. No problems.

3. ODAC Date : Tentative date is either June 7th or 8th, 1999

4. Set Goal Dates: User Fee Date = 6/24/99
Division Goal Date (Package completed ready to circulate) 6/14-18/99
Action Performance Goal Date (letter signed) 6/24/99
Who will sign letter? Bob Justice will follow-up with Dr. Temple

Discussion - At the 90 day meeting, we will begin discussing labeling reviews and set a timeline.

Subsequent Meetings **Tentative Schedule. Individual dates may be cancelled if meeting is not required**

	DATE	DAY	TIME	ROOM	MEETING TYPE
a.	Mar 25	Thur	11 AM	WOC2-cr A	90 day-meeting / plan labeling timeline
b.	May 3	Mon	2 PM	WOC2-cr B	4-Mo plus 1 week team meeting/labeling
c.	May 24	Mon	2:15-3:15 PM	WOC2-cr B	ODAC PRACTICE
d.	June 3	Thur	1-3 PM	WOC2-cr A	Team Meeting/resolve final issues
e.	June 10	Thur	noon	WOC2-cr A	Post ODAC issues
	June 17	Thur	12-1	WOC2-cr A	Wrap it up!

CC: NDA 20-221
HFD-150/ Div File
Reviewers
Pease
Vaccari
Pelosi

Meeting Minutes 45 day

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20221	**Trade Name:**	ETHYOL (AMIFOSTINE) FOR INJ 500 MG/VIAL.
Supplement Number:	12	**Generic Name:**	AMIFOSTINE
Supplement Type:	SE1	**Dosage Form:**	FIJ
Regulatory Action:	PN	**Proposed Indication:**	Reduction of the incidence of moderate to severe radiation induced xerostomia in patients undergoing post-operative radiation treatment for head and neck cancer.

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?
NO, No waiver and no pediatric data

What are the INTENDED Pediatric Age Groups for this submission?

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

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

.here any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
This drug nis not expected to be used for this indciation (head and neck cancer) in pediatric patients.

Not indicated in pediatric patients

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

/S/ _____ 6-21-99

Signature Date

US BIOSCIENCE

Debarment Certification Statement
NDA#20-221
Supplement #012

U.S. Bioscience, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306, Subsections (a) or (b), of the Federal Food, Drug, and Cosmetic Act, in connection with this application.

Eve Damiano

21 Dec 98

Eve Damiano, M.S.
Director
Regulatory Affairs

Date

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One Tower Bridge
100 Front Street • West Conshohocken, PA 19428
(610) 832-0570 • FAX (610) 832-4500

FEB 17 1999

45 Day Meeting Overview / Statistics

NDA #:	20-221 / S-012
Sponsor:	U.S. Bioscience, Inc.
Name of Drug:	Ethyol (amifostine) for injection
Indication:	Treatment of radiation-induced Xerostomia in head and neck cancer
Documents Reviewed:	volumes 1, 33
Date Received:	1/19/99
Medical Reviewer:	Dr. Chico

Ethyol (amisfostine) has been evaluated for its ability to protect against toxicities associated with radiation treatment. The sponsor has submitted a phase III, open-label trial (WR-0038), which constitutes the primary analyses. Two additional randomized studies in patients with head and neck tumors conducted by independent investigators were submitted as supporting evidence. Reports from two additional controlled clinical trials have also been included in this submission to provide further evidence of amifostine's ability to protect epithelial-like tissues other than salivary glands from radiation-induced toxicities. These studies have been previously submitted to NDA#20-221 during the review of the original application. The SAS programs related to the SAS data sets for WR-0038 are available.

This supplementary NDA application is sufficiently complete for statistical review and is fileable from a statistical standpoint.

/S/
Clara Chu, Ph.D
Mathematical Statistician

CC:
HFD-150/Division File
HFD-150/Ms. Pelosi, CSO
HFD-150/Dr. Chico
HFD-710/Dr. Chen
HFD-710/Dr. Chi
HFD-710/Dr. Chu
HFD-710/Chron

C:\My Documents\review\ethyol\eth45dy.doc
This review consists of 1 page of text.

PELOSI

FEB 2 1999

Memo:	**45-day filing review**
Subject:	CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW
NDA:	20,221/S#012
Submission Date:	December 23, 1998
Drug Name:	Ethyol (amifostine)
Formulation & Strength:	500 mg Lyophilized Powder
Sponsor:	U.S. Bioscience, Inc. One Tower Bridge West Conshohocken, PA 19428
Reviewer:	Atiqur Rahman, Ph.D.
Type of Submission:	Supplemental NDA

BACKGROUND

This review evaluates the filing issues of the supplemental NDA 20,221/S#012 from the Clinical Pharmacology and Biopharmaceutics perspective. Ethyol is an Organic thiophosphate cytoprotective agent currently approved for use to reduce the cumulative renal toxicity associated with repeated administration of cisplatin in patients with advanced ovarian cancer or non-small cell lung cancer. The recommended starting dose is 910 mg/m^2 administered once daily as a 15 minute intravenous infusion. In this supplemental NDA (sNDA) the sponsor provides safety and efficacy data to seek approval of Ethyol to reduce the incidence and severity of radiation induced xerostomia. The recommended dose of Ethyol for this indication is 200 mg/m^2 administered once daily as a 3-minute intravenous infusion, starting 15-30 minutes prior to radiation therapy.

In item 6, Human Pharmacokinetics and Biopharmaceutics section of the sNDA the sponsor provided a Phase I three-way crossover study in 12 healthy male volunteers comparing relative bioavailability of intravenous (200 mg/m^2), oral (500 mg), and subcutaneous (500 mg) administration of amifostine. The sponsor also provided literature information to address drug-drug interactions.

COMMENTS

1. The submission index is inadequate to direct the reviewer to the specific subsections of item 6. The sponsor should list each appendix of the pharmacokinetic study report in the table of content, identifying the title or contents of each appendix and the page numbers.

2. The sponsor should identify the specific subsection containing the assay methodology used for the pharmacokinetic study and the assay validation report. Inadequate information regarding the assay validation will constitute a non-filing issue from the Clinical Pharmacology and Biopharmaceutics perspective.

RECOMMENDATION

The Human Pharmacokinetics and Bioavailability section of this NDA appears to be inadequate for filing from Clinical Pharmacology and Biopharmaceutics perspective at this time. The comments should be forwarded to the sponsor.

/S/ 2/2/99

Atiqur Rahman, Ph.D.
Team Leader
Division of Pharmaceutical Evaluation I

CC: NDA 20221 original
HFD-150 Division File
HFD-150 [redacted]
HFD-850 LLesko
HFD-860 MMehta, ARahman,
CDR Barbara Murphy

RECORD of TELEPHONE CONVERSATION

Between Eve Damiano
Director, Regulatory Affairs
U.S. Bioscience, Inc

and

Robert P. Barron RB 5/26/99
FDA

Date: May 26, 1999

Re: N 20-221/Se-012 Ethyol (amifostine) for Injection

I called Ms. Damiano to inform her that the CFR for categorical exclusion cited in the supplement was incorrect. The supplement cited 21 CFR 25.31(a) when it should be section 21 CFR 25.31(b) which covers an efficacy supplement, i.e. new indication. Section 21 CFR 25.31(b) states an EA may not be required if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 ppb.

I indicate to her that it was possible that the CFR used to prepare the supplement was issued in 1997 and that the section could have been relettered in the current CFR which was revised as of April 1, 1998. I felt there was no need to amend the application and that I would indicate in my review of the discrepancy and that the calculations supporting the supplement appeared to be in order.

Ms. Damiano apologized for the error and thanked me for pointing it out.

cc: Orig. NDA 20-221
HFD-150/Div File
HFD-150/RPBarron/RHWood
HFD-150/MPelosi

ETHYOL® (amifostine) for Injection NDA#20-221; Supplement #012

Claim for Categorical Exclusion under 21CFR§25.31(a)

The subject of this supplemental new drug application (SNDA) covers a new indication for the previously approved drug, which if approved, would increase the use of the active moiety (amifostine). However, **a claim is made for Categorical Exclusion under 21CFR§25.31(a) from the requirement to prepare an Environmental Assessment (EA)**, on the basis that the estimated concentration of the substance at the point of entry into the aquatic environment is **less than 1 ppb.** Following is the basis of this claim.

As described in the FDA Guidance for Industry on Environmental Assessments of Human Drug and Biologics Applications, dated July 1998, certain classes of actions are subject to categorical exclusion. Although approval of the subject SNDA which covers a new indication for previously approved drug, would increase the use of the active moiety, the estimated concentration of amifostine at the point of entry into the aquatic environment will be below 1 part per billion (ppb). In accordance with the FDA Guidance, following are the calculations to support this claim.

Based on the currently approved Environmental Assessment (submission dated February 20, 1996), approximately vials were calculated as a maximum usage in Year 5 of marketing. This is equivalent to 1000kg of amifostine. Current sales (1998) of Ethyol in the USA are equivalent to less than 100kg of amifostine. Therefore, the previous estimate is still valid.

If Ethyol is approved for use as described in the current application, the following calculation shows the additional amount of amifostine which could theoretically be introduced into the aquatic environment.

Head and neck cancer patient population = 60,810
[as shown in the statistics contained in our application for Orphan Drug Designation, dated February 25, 1998]

As described in the current application, if every patient received the complete course of Ethyol for 35 days at 200mg/m^2 (approximately 1 vial (0.5g) per day), the following calculation will determine the total amount of amifostine used in kilograms:

60,810 patients X 35 days X 0.5g = 1,064,175g = 1,064kg

plus

Calculated amount of amifostine as currently approved = 1,000kg

equals 2,064kg

Thus, using the equation:

Expected Introduction Concentration (EIC)-Aquatic (ppb) = A x B x C x D

where: A = kg/year produced for direct use (as active moiety) = 2,064kg/year
B = $1/1.214 \times 10^{11}$ L/day entering publicly owned treatment works
C = 1 year/365 days
D = 10^9 μg/kg (conversion factor)

EIC (ppb) = (2,064) X ($1/1.214 \times 10^{11}$) X (1/365) X (10^9) = **0.056 ppb**

In conclusion, the amount of amifostine that could potentially be present at the point of entry into the aquatic environment, is much lower than the allowed maximum limit of 1 ppb, thus substantiating the claim for categorical exclusion from the requirement to prepare an EA.

Signed: _____ Dated: Dec. 21, 1998

Martin Stogniew, Ph.D.
[see attached curriculum vitae]

MEDICAL OFFICER REVIEW FOR THE 21 DAY MEETING
(sNDA 20-221)

FILING DATE: December 23, 1998
DATE OF REVIEW: January 19, 1999
SUBJECT: Day 21 Report for NDA 20-221(Ethyol/Amifostine)
FROM: Isagani Chico, MD, Medical Officer

Proposed Indication: "To reduce the incidence and severity of radiation-induced xerostomia".

Primary clinical data on the following studies were submitted:

Adequate and Well-Controlled Study		
Study (Investigator)	Title	N (Ethyol)
WR-0038	Phase III Trial of Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer	315 (157)
Supportive Studies		
Investigator Protocol (Antonadou)	Randomized Trial of the Prophylactic Use of Amifostine in the Prevention of Chemoradiation Induced Mucositis and Xerostomia in Head and Neck Cancer	45 (22)
Investigator Protocol (Bohuslaviski)	Randomized Double-Blind, Placebo-Controlled Trial of High-Dose Radioiodine (HD-RIT) ± Ethyol in Patients with Thyroid Cancer	50 (29)
WR-9001 (Liu)	Randomized Trial of Fractionated Radiation Therapy ± Amifostine in Patients with Rectal Cancer	104 (49)

- The incidence of Grade 2 or higher acute and late xerostomia as assessed by the RTOG Acute and Late Morbidity Scoring Criteria, was significantly reduced in patients receiving Ethyol.

Incidence of Grade 2 or Higher Xerostomia			
	Ethyol + RT	**RT**	**p-value**
Acute	51% (75/148)	78% (120/153)	<0.0001
Late (>1 yr)	34% (33/97)	57 (60/106)	0.0019

COMMENTS:

1. **Designation: P (Priority)**

   According to the FDA Guidance for Industry on Standards for the Prompt Review of Efficacy Supplements, a priority review will be granted if the product, if approved , would be a significant improvement compared to marketed products in the treatment, diagnosis or prevention of disease.

   Salagen® (pilocarpine) is approved therapy for the treatment of symptoms of xerostomia from salivary gland hypofunction caused by radiotherapy for cancer of the head and neck. The proposed indication for ethyol is not as a palliative treatment; but for salivary gland tissue protection in order to "prevent" the incidence and severity of radiation induced xerostomia and its unwanted complications. This could potentially improve patients' quality of life significantly.

2. **Fileability:** The clinical section of the submission appears to be adequate for filing.

   There were 33 volumes of text, with 27 volumes for the clinical reviewer (one volume for overall summary, 10 volumes of clinical data and 17 volumes of CRT's and CRT tabulations). Primary data was provided to the Electronic Document Room in accordance to agency requirements for electronic submissions. Annotated CRF's were provided with a detailed explanation of each of the datasets included. Information not provided in the initial submission will be requested.

3. **DSI Consult:**

   The sites chosen for audit (after discussion with Gus Turner) were #0012 (Sacramento, CA: 16 patients) and # 0008 (Durham, NC: 11 patients) where most U.S. patients were enrolled. These patients only comprise 9% of the total population but should provide some preliminary information on the quality of the data. Forty-nine percent of the patients were enrolled in 14 study sites in Germany. Upon Gus Turner's suggestion, audit of the largest German sites will be arranged if the U.S. sites audit is unsatisfactory or if there are compelling reasons to do so after some in-depth review of the data.

COUNTRY	# Study Sites (N=40)	Accrual (%) N=315	Site Code/ #Patients Enrolled	Investigator Name	Location
Germany	14	153 (49)	0018/34 0038/30 0013/26	Wanenmacher Henke Sauer	Heidelberg Freiburg Erlangen
France	5	43 (14)	0042/20	Monnier	Cedex
Other European	3	9 (3)			
U.S.A.	14	72 (23)	0012/16 0008/11 0051/9	Jones Brizel Machtay	Sacramento, CA Durham, NC Philadelphia, PA
Canada	4	38 (12)	002/16 003/12	Gelinas Fortin	Montreal Quebec

Action Items:

1. **Please send a request for a DSI Consult to perform a scientific audit of the two U.S. sites highlighted in the table above.**

2. **Please send the following requests to the applicant by facsimile:**

   Please refer to volume 33 of sNDA 20-221 supp.12 (Case Report Tabulations-Electronic Archive Documentation for Study WR-0038).

   - Please provide the Agency with the following pages missing from the Annotated Case Report Forms: 73-75, and 77-110.

   - Ideally, electronic submissions should contain all primary data entered in the CRFs. Please make a list of all entries in the annotated CRF's that were labeled as, "not captured on database" (e.g. Inclusion Criteria and Exclusion Criteria), and clarify the reason/s for non-inclusion.

3. **Consult to HFD-540 (to be discussed during the meeting)**

/S/ 2/2/99

Isagani Mario Chico, M.D.
Medical Officer
Division of Oncology
HFD-150

cc:
NDA #20-571
HFD-150/Division File
HFD-150/I.M. Chico, MD
HFD-150/Pelosi

1. **Designation: P (Priority)**

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