CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:NDA 20221/S012

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 18 1997

N 020221
US Bioscience, Inc.
Attention: Barbara Scheffler
Senior V.P. for Clinical Operations
and Regulatory Affairs
One Tower Bridge, 100 Front Street
West Conshohocken, PA 19428

Dear Representative:

This is in reference to the above-approved NDA for Amifostine and to your commitment(s) to conduct the following phase 4 studies.

Attached is our most current report listing the applicable study commitments and subsequent activity by the firm and the review division.

To update our records, please provide, in Section G of your next annual report, the following information on your phase 4 commitment(s):

1. Any corrections or updates to our report.

2. IND and Protocol Number under which each commitment was, or is being, conducted, and the dates of all submissions.

3. Status of the commitment.

4. Expected completion date for each commitment.

If you believe the commitment(s) is no longer needed to fulfill its original purposes, e.g., because alternative data has become available that obviates the need for the additional information, please provide justification.

All future annual reports should include the information listed above until we notify you that you have fulfilled the commitments. The status of any future commitments for phase 4 studies for any other drug products should always be provided in the annual report for the respective NDA.

M. PELOSI

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-221/S-012

U.S. Bioscience, Inc.
One Tower Bridge, Suite 400
100 Front Street
West Conshohocken, PA 19428

DEC 28 1998

Attention: Eve Damiano
Director, Regulatory Affairs

Dear Ms. Damiano:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Ethyol (amifostine) for Injection

NDA Number: 20-221

Supplement Number: 012

Date of Supplement: December 23, 1998

Date of Receipt: December 24, 1998

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on February 22, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

(if via U.S. Postal Service)

FDA/CDER
Division of Oncology Drug
Products, HFD-150
5600 Fishers Lane
Rockville, Maryland 20857

(if via courier)

FDA/CDER
Division of Oncology Drug Products,
HFD-150
1451 Rockville Pike
Rockville, Maryland 20852

Sincerely,

TSI 12/24/98

for

Dotti Pease
Chief, Project Management Staff
Division of Oncology Drug Products, HFD-150
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-221/012
HFD-150/Div. Files
HFD-150/CSO/M. Pelosi

filename: C:\WPWIN61\TEMPLATE\FDA\20221S12.WPD

SUPPLEMENT ACKNOWLEDGEMENT

BIOSCIENCE

COPY

December 23, 1998

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
Park Building, Room 2-14
12420 Parklawn Drive
Rockville, MD 20857

RE: PATENT INFORMATION
NDA #20-221; Ethyol® (amifostine) for Injection, 500mg
Supplemental Application #012

Dear Sir/Madam:

Reference is made to our approved New Drug Application #20-221, and to Supplemental Application #012, adding a new indication for Ethyol, which was submitted to the Division of Oncology Drug Products on December 23, 1998.

Attached here is Patent Information submitted in accordance with 21CFR§314.53.

Please contact me by telephone at (610) 832-4580 if you have any questions regarding this information.

Kindly acknowledge receipt hereof by date-stamping the enclosed copy of this letter and returning it to me in the envelope provided.

Sincerely,

Eve Damiano
Director, Regulatory Affairs

Submitted in Duplicate

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

BIOSCIENCE

Ethyol® (amifostine) for Injection
PATENT INFORMATION

U.S. Patent No:	5,424,471
Expiration Date:	July 31, 2012
Type of Patent:	Drug product
Patent Owner:	U.S. Bioscience, Inc., West Conshohocken, Pennsylvania, USA

AND

U.S. Patent No:	5,591,731
Expiration Date:	July 31, 2012
Type of Patent:	Drug product
Patent Owner:	U.S. Bioscience, Inc., West Conshohocken, Pennsylvania, USA

ORIGINAL DECLARATION

The undersigned declares that U.S. Patent Nos. 5,424,471 and 5,591,731 cover the formulation, composition and/or method of use of Ethyol® (amifostine) for Injection. This product is the subject of Supplemental Application #012 to NDA #20-221 for which approval is being sought.

Signed: _____ Date: Dec. 21-98

Martin Stogniew, Ph.D.
Vice President, Pharmaceutical Sciences

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

EXCLUSIVITY SUMMARY FOR NDA # 20-221 SUPPL # 012

Trade Name Ethyol for Injection Generic Name amifostine

Applicant Name US Bioscience, Inc HFD # 150 DODP

Approval Date If Known Pending

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it an original NDA?

YES /___/ NO /X/

b) Is it an effectiveness supplement?

YES /X/ NO /___/

If yes, what type? (SE1, SE2, etc.) SE-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 /X/ NO /___/

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

N/A

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:

N/A

Form OGD-011347 Revised 10/13/98

cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /X/

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

- orphan drug (#98-1116)

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

no

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

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

YES /___/ NO /X/

If yes, NDA #_____. Drug Name _____.

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

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

YES /___/ NO /X/

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

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved.

Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

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

NDA# 20-221 _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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

YES /___/ NO /X/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

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

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

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

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

YES /X/ NO /___/

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

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

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

YES /X/ NO /___/

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

_____

_____

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

YES /___/ NO /X/

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 /_X_/

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:

WR-38 Phase 3 Trial of Radiation Therapy ± Amifostine in Patients with Head and Neck Cancer

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

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

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

Investigation #1 YES /X/ NO /__/

Investigation #2 YES /___/ NO /___/

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

WR-0038 _____ _____

_____ _____

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

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

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

_____ _____

_____ _____

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

NA _____ _____

_____ _____

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

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

Investigation #1

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

_____

Investigation #2

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

_____

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

Investigation #1

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

_____ _____

_____ _____

Investigation #2

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

_____ _____

_____ _____

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

YES /___/ NO /X/

If yes, explain: _____

_____

/S/ 6-16-99

Signature Date

Title: Project Manager

/S/ 6/17/99

Signature of Office/ Date

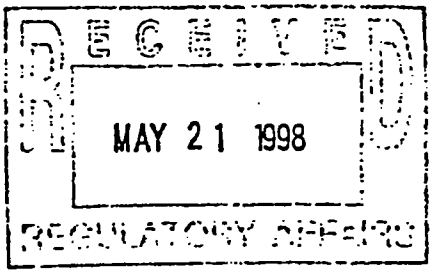
Division Director

cc: Original NDA 20-221 / Division File HFD-150 / HFD 93 Mary Ann Holovac

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

May 12, 1998



U.S. Bioscience, Inc.
One Tower Bridge
100 Front Street, Suite 400
West Conshohocken, PA 19428

Attention: Eve Damiano
Director, Regulatory Affairs

Dear Ms. Damiano:

Reference is made to the orphan drug application of February 25, 1998, submitted pursuant to Section 526 of the Federal Food, Drug and Cosmetic Act (FFDCA) for the designation of Ethyol (amifostine) as an orphan drug (application #98-1116).

We have completed the review of this application and have determined that Ethyol qualifies for orphan designation for the reduction of the incidence and severity of radiation induced xerostomia. Please note that it is Ethyol and not its formulation that has received orphan designation.

Please be advised that if Ethyol were approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA. Therefore, prior to final marketing approval, sponsors of designated orphan products are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of Ethyol as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved [21 CFR 316.30]. If you need further assistance in the development of your product for marketing, please feel free to contact Donald R. Haggerty, MD, MPH at (301) 827-0986.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan drug designation.

Sincerely yours,

/S/

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

US BIOSCIENCE

January 12, 1999

Dr. Gus Turner
FDA
Division of Scientific Investigations
7520 Standish Place
Rockville, MD 20855

RE: NDA #20-221; Ethyol® (amifostine) for Injection
Supplement #012

Dear Dr. Turner:

Per your request, please find enclosed a copy of the WR-0038 Study Protocol, along with a list of all participating investigators and the number of patients enrolled at each investigational site.

Please feel free to reach me by telephone at (610) 832-4580 or by fax at (610) 832-4571, if you require further information.

Sincerely,

Eve Damiano
Director, Regulatory Affairs

cc: Maureen Pelosi, Project Manager, CDER, Oncology Division
via fax.(301) 827-4590

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

US BIOSCIENCE

January 21, 1999

Dr. Gus Turner
FDA
Division of Scientific Investigations
7520 Standish Place
Rockville, MD 20855

RE: NDA #20-221; Ethyol® (amifostine) for Injection
Supplement #012

Dear Dr. Turner:

Per your request, please find enclosed copies of the case report forms for the eleven patients enrolled in Study WR-0038 at Site #8 (Duke University Medical Center, Durham, NC) and the sixteen patients enrolled at Site #12 (Sutter Cancer Center, Sacramento, CA).

Also included herein are the Adverse Event listings from these two sites, as contained in the database submitted in the Application.

Please feel free to reach me by telephone at (610) 832-4580 or by fax at (610) 832-4571, if you require further information.

Sincerely,

Eve Damiano
Director, Regulatory Affairs

cc: Maureen Pelosi, Project Manager, CDER, Oncology Division
via fax.(301) 827-4590

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

BIOSCIENCE

cc: M. Pelosi, Project Manager

January 27, 1999

Division of Oncological Drug Products
Food and Drug Administration (HFD-150)
1451 Rockville Pike
Rockville, MD 20852

RE: NDA #20-221; Ethyol® (amifostine) for Injection
Efficacy Supplement #012: Response to Request for Information

Dear Sir/Madam:

Reference is made to Efficacy Supplement #012, submitted to the Division on December 23, 1998.

Reference is also made to a fax from the Division, dated January 21, 1999, which contained a request for additional information to support the Electronic Archive Documentation contained in Volume 33 of the SNDA. In response to the Division's request, the following information is included herein:

- ATTACHMENT 1: Copies of pages 73-75 and 77-110 of the WR-0038 Case Report Form. It should be noted that these pages were not included in the Annotated CRF portion of Volume 33 because they are redundant pages used for collecting the same type of follow-up information at months 3, 5, 7, 9, 11, 17 and 23.

- ATTACHMENT 2: List of data not captured on the database, along with a reason(s).

Please feel free to contact me by telephone at (610) 832-4580 or by fax at (610) 832-4571, if you have any questions or require additional information.

Sincerely,

Eve Damiano
Director, Regulatory Affairs

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